PUBLICATION AND DISCLOSURE ISSUES IN ANTIDEPRESSANT PEDIATRIC CLINICAL TRIALS

HEARING

BEFORE THE

SUBCOMMITTEE ON
OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND
COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

SEPTEMBER 9, 2004

Serial No. 108–121

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PUBLICATION AND DISCLOSURE ISSUES IN ANTIDEPRESSANT PEDIATRIC CLINICAL TRIALS

THURSDAY, SEPTEMBER 9, 2004

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
Washington, DC.

The subcommittee met, pursuant to notice, at 11 a.m., in room 2123, Rayburn House Office Building, Hon. Joe Barton (chairman) presiding.

Members present: Representatives Stearns, Bass, Walden, Ferguson, Rogers, Barton (ex officio), Deutsch, DeGette, Allen, Schakowsky, Waxman, and Markey.

Also present: Representatives Stupak and Murphy.

Staff present: Mark Paoletta, majority counsel; Alan Slobodin, majority counsel; Bud Albright, majority staff director; Kelly Andrews, majority counsel; Toby Fortson, majority counsel; Bill Harvard, majority staff assistant; David Nelson, minority senior investigator; Jessica McNiece, minority research assistant; Ashely Grossbeck, minority research assistant; and Jeff Donofrio, minority research assistant.

Chairman BARTON. The subcommittee will come to order. Today's hearing is on the publication and disclosure issues in the antidepressant pediatric clinical trials.

As part of the committee's jurisdiction over public health, the subcommittee today will examine the publication and disclosure of clinical studies conducted on prescription drugs. What has raised public interest in the disclosure of clinical trial data has been the controversy over the use of antidepressants in children.

In reviewing this issue, the subcommittee will be focused on the 15 placebo-controlled randomized studies submitted to the FDA for an indication in children with depression. The FDA found that in 12 out of the 15 studies there was no efficacy that was shown. I would also note that only 3 out of the 15 studies have been published as stand-alone articles in peer review journals. Therefore, many people want to know what was in the other 12 studies? What do those studies show? Why haven't those other 12 studies been published in peer review journals? Was there sufficient information available to the public about these unpublished studies to make informed decisions? These are some of the questions the subcommittee will attempt to find answers to today.

Given the highly visible public health question over disclosure of clinical studies and the use of antidepressants in children, under the leadership of the former subcommittee chairman of this subcommittee, the Honorable Jim Greenwood of Pennsylvania, the committee launched an investigation 7 months ago. As the central repository of the 12 unpublished studies and with its own regulatory role in the matter of antidepressants, the committee looked to the Food and Drug Administration, or FDA, to obtain much of the information for this investigation.

In March of this year, the committee requested records from the FDA and also requested interviews with key FDA officials. Unfortunately, over the last months, the committee has been met mostly with stonewalling, slow rolling, plain incompetency from the FDA. That is not acceptable. The FDA's lack of cooperation with the committee in obtaining relevant and responsive information in a timely fashion on a matter that involves the safety of our children leaves me wondering whether this is sheer ineptitude or something worse. The examples of the course of conduct extend for over 5 months of this committee attempting to do its job and oversee an agency on a topic of grave concern.

I am outraged to learn that an FDA employee in the Office of Legislation was tasked with handling the Agency's response to the committee; in other words, Congressional Affairs at FDA is supposed to be there to help the Congress get information from the FDA. This individual's response was to defy the document request contained in a letter that I signed, and this individual unilaterally decided to limit the document request to exclude drafts, internal notes or memos to the file. And I am reading this from an email from a Mr. Patrick McGarey to Anne Henig with re: line 8 is Barton question number 8 referring to question number 8 in the March 24 letter that we sent to the FDA.

The email states, "Here is my draft of instructions to the CDER employees who have to search for documents for question number 8." He goes on to say, "Please do not include draft documents, notes or memos to self or file." I don't understand this, because the question is provide copies of all records that raise a concern about the safety or efficacy of antidepressants in pediatric or adolescent populations. That was the question. And Mr. McGarey's response was, "Please do not include draft documents, notes, memos to self or file or incoming communications from non-FDA individuals, i.e. the public, business organizations, other HHS operations divisions, unless an FDA employee has forwarded such communication to others with additional questions or concerns." Well, that is not going to work, folks. Is Mr. McGarey in the room? Is he here? Okay. Let the record show that if he is here, he is not standing up and showing his face. We will get that changed. We will get that changed.

If you read this email, it is obvious why FDA's document production has been so minimal. The problem is that FDA either does not hear the wakeup call we have repeatedly—we, committee, on a bipartisan basis—have been trying to send or they are choosing to ignore it. We are going to fix that, folks. We are going to fix it beginning at this hearing. The conduct by the FDA has only reinforced my past sentiments that the Food and Drug Administration really stands for Foot Dragging and Alibis, and that is not acceptable.

[The e-mail follows:]

Dettelbach, Kim

From: McGarey, Patrick
Sent: Monday, May 03, 2004 2:46 PM
To: Henig, Anne M
Cc: Meister, Karen G; Katz, Donna; Dettelbach, Kim
Subject: Barton Q#8

Here is my draft of instructions to the CDER employees who have to search for documents for question#8:

Provide copies of all records that--

1. Raise a question or concern about the safety or efficacy of antidepressants in pediatric or adolescent populations.

Please be sure to forward only records that raise safety or efficacy in the body of the record.

Please do not include draft documents, notes, memos to self or file, or incoming communications from non-FDA individuals (i.e., the public, businesses, organizations, other HHS op divs) unless an FDA employee has forwarded such communications to others with additional questions or concerns.

Finally Ann, there were different timeframes for the two employees. For Dr. Avagan, we need to search back to 1/1/02. For Dr. Knudsen, they did not place a time frame on the documents, so we need to search back a far as possible.

Patrick McGarey
FDA Office of Legislation
Phone = 301 827-0088
FAX = 301 827-1955

Chairman BARTON. Today's witness for the FDA is Dr. Janet Woodcock, the acting Deputy Commissioner for Operations. I assume that she is here. I have a message for you to take back to the acting FDA Commissioner, Dr. Lester Crawford: If you folks can't fix it, we will fix it for you. Now, I have instructed my staff this morning in preparing for this that if we have to, we will send our staff people, if necessary, with the Capitol Police to the FDA and we will get enough individuals that are familiar with the files and we will go through the files ourselves. Do you understand that? Okay. Can you instruct Mr. McGarey his job is to cooperate with this committee, not to obstruct it? Do you understand that? Let the record show that she says she does understand it.

In addition to the problem of cooperation, this subcommittee will also review the FDA's spotty record on sharing results from clinical trial data with the public, as required under Section 9 of the Best Pharmaceuticals for Children Act. Although required by law since 2002, the FDA has not published any summaries of the pediatric antidepressants until this year, and almost all of them were just 3 weeks ago after I made a personal phone call to an individual at the FDA. Why did it take so long for the FDA to do its job? While I plan to ask the companies about their publication and disclosure practices, I am also interested in finding out from the FDA why they refused on several occasions to allow the companies to put additional labeling on their antidepressants indicating that the drug was tested in pediatric clinical trials and did not show efficacy. It would seem to me that the first place where disclosure of no efficacy in these pediatric clinical trials should be shown would be the product label itself. I would like to have the FDA explain its reasoning on this point.

This committee began its investigation for today's hearing on the publication of clinical trials based on news reports surrounding the possibility that there may be an increased risk of suicide related behavior in children and adolescents with major depressive dis-

order, MDD, that take antidepressants. And I would point out that on a bipartisan basis we passed—well, we had the debate on a bill last night on the House floor, a suicide prevention bill, for teenagers and young adults. That vote is going to occur sometime today. We have over 4,000 young people in our country that committed suicide last year. This potential increased risk of suicidal behavior in mostly undisclosed studies is what has raised questions regarding the safety and efficacy of antidepressants in the pediatric population and the release of data to that extent. And that is the reason we are having this hearing.

Late last year the Medical Health Regulatory Agency, the British equivalent of the FDA, pulled from public sale all antidepressants for people with depression under 18 years of age except for Prozac due to the risk/benefit analysis of safety concerns coupled with a weak showing of efficacy in all of the antidepressant pediatric clinical trials. Likewise, in our country, the FDA has approved Prozac made by Eli Lilly to treat MDD in children, yet the products of the other six companies present today have not been approved as of today.

Much of the controversy is over whether antidepressants really work in children at all. Only one drug, Prozac, has ever been judged by the FDA to be effective for depression in children and received approval for this use. Nevertheless, I note that four different antidepressant drugs not approved for children with depression use are prescribed to children at higher rates that Prozac, the only drug that has been approved. As a father of three and a grandfather of two and stepfather of two, I am especially concerned about advances in technology and medicine that can help young people better adapt to learning and to lie.

After this committee in the Congress passed the Best Pharmaceuticals for Children Act, a number of companies took advantage of the 6-month patent extension in the legislation granted to companies if they performed pediatric clinical trials. The incentives in this law have worked, as companies have performed new pediatric clinical trials. I am happy that Congress' actions have helped to protect and to promote children's health through the performance of such clinical trials. The companies here today all have drugs whose primary purpose is treating depression in adults. Thus, it was only natural to see if these antidepressants also had a pediatric use. This strikes at a major public health need: The development of more treatment options for teenagers and children diagnosed with depression. I am told that one out of six of our young people is under prescription for some sort of antidepressive drug. That is an amazing statistic—one of our every six of our children is under a doctor's prescription for some sort of an antidepressant drug.

Unfortunately, the increase in the number of trials undertaken by drug companies to try to find treatment options, as I have stated earlier, have so far met with meager results. Today, we will review the timeliness and disclosure of these companies in regards to the clinical trials that they have performed for these drugs. In addition, we will hear from them on what practices they have undertaken in regards to the publication of all clinical trial results for their company. Finally, we are going to hear from leading members

of the industry discuss their actions and suggestions regarding publication of clinical trials. We will also hear from them on other issues, such as co-prescribing and how we can better inform patients, doctors and the public of possible concerns and negative results of clinical trials.

The bottom line is that we need to ensure that the processes we undertake in our trials ensure that the drugs that the American people purchase are effective and are safe. I am pleased that this committee's investigation may have already played a role in the recent actions and policy announcements by both the FDA and the private sector. These announcements indicate that both will more freely disclose clinical data to the medical community, industry and the general public.

I want to thank our witnesses for attending today, and I look forward to hearing their testimony. With that, I would yield to the ranking member of the subcommittee, Mr. Deutsch, for an opening statement.

Mr. DEUTSCH. Thank you, Mr. Chairman. I have a statement by the ranking democrat of the full committee, which I would like to submit for the record.

Chairman BARTON. Without objection, so ordered.

[The prepared statement of Hon. John D. Dingell follows:]

PREPARED STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, thank you for initiating this investigation and holding the first of this Subcommittee's hearings into the safety and efficacy of anti-depressants in adolescents and related issues. Today's hearing focuses on efficacy. Specifically, whether parents, pediatricians, and other physicians who treat children with anti-depressant drugs should have been notified of the repeated failure of clinical trials to show that these medicines, with a single exception, are effective in adolescents and how such notice should have been provided.

We are told that the Food and Drug Administration (FDA) does not believe that these very potent drugs, which are labeled as a treatment for severe depression in adults, need to be labeled as clinical trial failures for children. Is withholding this information in the best interests of patients? Or is it in the best interest of the drug companies that are supposed to be regulated by the FDA? It becomes an even more relevant question when we know that those trials were paid for by billions of dollars from the pockets of consumers and taxpayers.

Today we will explore how the drug manufacturers and the FDA justify not providing to parents and doctors the evidence of the ineffectiveness and dangerous side effects of these powerful drugs on children. We will not only ask why the FDA and the manufacturers failed to provide this important information on the label, but why the FDA ignored the minimal public disclosure requirement in the pediatric exclusivity legislation.

I opposed giving drug companies additional monopoly profits in order to induce them to test their drugs on children when the "Best Pharmaceuticals for Children Act" was passed last Congress. During the debate a number of logical amendments were offered that would have mitigated the giveaway or at least imposed minimal labeling requirements upon the beneficiaries of that Act. The pharmaceutical industry opposed every amendment, as did their allies in the Administration.

Since enactment of the law, study after study of dubious design has been submitted and apparently approved by those responsible for protecting children and other citizens from products that are ineffective and cause dangerous side effects. The study designs were dubious because they apparently could never satisfy the FDA that drugs would not work for children and youth regardless of what the data showed. In other words, once the drug had been approved for adults the studies could never show ineffectiveness in children.

This hearing will demonstrate, with the exception of Eli Lilly, that the manufacturers and the FDA went to extraordinary lengths to keep vital information from the public regarding the ineffectiveness of these drugs in children. The hearing scheduled for September 23rd will further show how FDA attempted to hide critical

information about the increase in suicides or suicidal ideation by adolescents who were prescribed certain drugs. In both cases, crucial information was withheld by an agency responsible for providing public health information to the doctors and the parents who care for these troubled children.

We need prompt, accurate labeling of all drugs before any exclusivity is granted. I look forward to working with my colleagues on legislation to make sure doctors and parents have the information they need and expect, and that the FDA and drug manufacturers uphold their responsibilities to the public.

Mr. DEUTSCH. Thank you. Thank you, Mr. Chairman. Now, I recall the debate and the hearings that we had when we passed the legislation regarding pediatric exclusivity, and I wish we could play back some of those debates and videos at this time because there were many amendments that were offered that in fact were defeated at that time, which I think would have prevented the situation that we are in at this moment, specifically an amendment by Mr. Stupak at the time which would have not granted the exclusivity until labeling changes regarding pediatric use was approved by the FDA. Had that occurred we would not be sitting here with the situation that we find ourselves in.

As you are aware, and I think it is important to point out, effectively, consumers paid for this research literally in the billions of dollars, literally in the billions of dollars. And in terms of the value that was gotten by consumers, if anything, we have a negative value in terms of the lack of information provided, lack of efficacy provided. Specifically, I think in some ways the most disturbing information from this hearing and this research by our staffs is that prescriptions are being written today, literally today, and I mean hopefully we will talk about that and get some testimony about that, but as you mentioned in your testimony, the only efficacy that I am aware of is in the case of Prozac and yet that is the least prescribed of the antidepressants at this moment in time. So I look forward to the testimony and compliment our staffs, this is a bipartisan effort, and look forward to working with you to resolve this issue in a positive outcome for the consumers and people of the United States.

Chairman BARTON. We thank the gentleman from Florida. The gentleman from Oregon, the vice chairman of the subcommittee, Mr. Walden, is recognized for an opening statement.

Mr. WALDEN. Thank you, Mr. Chairman. This morning the subcommittee holds its first hearing to examine issues related to the use of antidepressants in children and adolescents. Today, we will focus on the disclosure and transparency of pediatric clinical trials of antidepressants.

Now, I know this is an extremely sensitive topic for many parents, caregivers and doctors in this country. Depression, especially in teenagers, is sometimes difficult to identify and even more difficult to treat. When a loved one is suffering, it is only natural to search for any possible solution. What is troubling, however, is that millions of antidepressant prescriptions are written for depressed kids when the facts show that 6 of the 7 antidepressants tested in pediatric trials do not show efficacy in kids.

In 2002 alone, more than 10 million American children were prescribed antidepressants, and that number is on the rise. So one has to ask, if pediatric clinical trials show that a sugar pill is about as effective as an expensive drug, is it appropriate for physicians to

write millions of off-label prescriptions for kids? Does this happen because physicians are aware of the studies showing these drugs were effective in adults but may not be as aware of the studies showing that with one exception they are not effective in children and adolescents? Even of more concern is this: In what I am sure are good faith efforts to help kids with depression, are physicians prescribing drugs that not only show little or no efficacy but also may show an increase in suicidal thought and action?

One of the issues that triggered this investigation into how the United States through the FDA manages these antidepressants was news that the United Kingdom last December moved to contraindicate virtually all of the antidepressants for children under 18 with major depressive disorder, MDD, due to the risk of suicide related behavior in children and adolescents. What does our own FDA know about such concerns, when did it know it, and what has it done? Well, we know that in one review of 22 studies involving more than 4,000 children suggested that children taking antidepressants were 1.89 times more likely to become suicidal than those given placebos, and a recently Columbia University seems to confirm that point. Yet every day these drugs are being swallowed by America's youth. These issues will be explored in greater detail at our second hearing later this month.

So it is time to ask the tough questions. Are America's kids being prescribed drugs for depression that are no better than sugar pills yet may nearly double their risk of suicidal behavior and thought? Are the companies who sell these drugs adequately disclosing the results of their trials in ways that allow parents and physicians to get all of the facts? Can and should the FDA do more to protect the public health in this area? Are adequate steps being taken by the companies and their trade association and the FDA to improve disclosure of trials and make warnings of risks available to those who prescribe and those who take these drugs? It is the responsibility of this committee to investigate and provide oversight, and today we will focus our bright light on this dark problem. Thank you, Mr. Chairman.

Chairman BARTON. Thank the gentleman. We now recognize the gentlelady of Colorado, Ms. DeGette. Then the gentlelady yields to Mr. Waxman of California.

Mr. WAXMAN. Thank you very much, Mr. Chairman, for this chance to make an opening statement. We are holding a hearing on the question of antidepressants for children, but I think it opens up a very much broader perspective for us than just that issue, because what we are seeing in fact is that the pharmaceutical industry has systematically mislead physicians and patients by suppressing important data on their drugs. At the same time, the industry has encouraged these physicians to use drugs that are ineffective and possibly even dangerous in one of the most vulnerable population groups, children, and as a result the industry has reaped literally billions of dollars in the process.

Let me give some background because I was the author of the legislation to try to encourage the drug companies to do the studies on children. Drug companies didn't want to do the studies on children; they were making drugs for adults. That was the population they expected to buy their drugs, but often kids use the same

drugs. So in order to get the companies to do studies on children, we bribed them by saying we would give them a 6-month additional exclusivity over that drug, not just for the sales to children but for everyone. That is worth a lot of money, hundreds of millions of dollars if it is a big-selling drug. And antidepressants are pretty big-selling drugs. Well, the drug companies did the studies on antidepressants for children and it turned out, as a result of their studies, there was no conclusive showing that, as someone has said, six out of the seven antidepressants were even effective in children. Only one study on Prozac showed some effectiveness for children.

Well, this is not a problem just as it relates to children that this information was withheld, it is a problem for all users of pharmaceuticals because oftentimes companies will do studies and if it is a negative study for the sale of their product, they will withhold the information. They will push the positive studies that will encourage people to use their drugs even though they know that they have negative studies that are contrary. But if you don't tell the whole story, people aren't getting the whole story, and the people we are talking about are physicians and patients.

So I think what we have to be concerned about is we have given this pediatric exclusivity in order to encourage the studies for children, but the companies are using that only to get a longer patent time or monopoly time over the drug that they are selling to adults, and they are not making the results of their studies that aren't positive known. They are making it known to FDA because they have to, and we want to ask why FDA has not done more to get this information out, but there is a clear responsibility for the companies, and I am pleased to be working with Congressman Ed Markey on legislation that he and I will be introducing to require a registry of information about all the studies done on pharmaceuticals so that we don't just hear about the positive ones but we hear about the negative ones and the inconclusive ones so that we can get the full picture to the medical professionals.

In this particular issue of antidepressants, we have, I think, learned that we need to go back and look at that pediatric exclusivity bill. That law, which we tried to amend, Congressman Stupak particularly, to make sure that there was a label requirement on the drug, would have then made all this information available to the public and we would have known whether the drug was going to work or not. The majority on this committee refused to go along with that amendment. So I think we need to change the pediatric exclusivity law, we need to require broad disclosure of the results of clinical trials, and I hope we can have legislation to do that.

We are going to hear from many people in the drug industry who are going to tell us we don't need legislation to set up a registry; they are going to do it voluntarily. Well, I don't accept the idea that voluntary solutions are the only way we can approach this problem, because if it is voluntary, it is also voluntary not to do it or it is not voluntary to make full disclosure. I think we owe the public and the medical profession the opportunity to get all the information, the negative and inconclusive tests as well as those that the

companies want us to hear about, which accentuate the positive in order to accentuate the profits.

I appreciate that the leadership of this committee has called this hearing. I hope my colleagues will agree on the need for data on drugs. It is not a partisan issue. Allowing the marketplace of medical information to be significantly distorted by those who have a financial interest in the results is devastating for good medical care. Access to important data is one prescription for health that Congress can and should write, and we ought to do it right away. Thank you.

Chairman BARTON. Thank the gentleman for his statement. Gentleman from New Jersey, Mr. Ferguson, is recognized for an opening statement.

Mr. FERGUSON. Thank you, Mr. Chairman. Thank you for holding this important hearing on an issue that is impacting children and their families in my district and throughout our country. Mr. Chairman, I also want to acknowledge and welcome a constituent of mine who is here with us today, who knows firsthand what it is like to suffer along with her child. Lisa Van Syckel is here in the second row. Lisa, can you raise your hand? Hi, Lisa. Lisa is from Raritan Township, New Jersey. She is here. She and her daughter, Michelle, have been through some harrowing and heartbreaking experiences, and their perseverance and hope I believe are an inspiration to parents and families who have dealt with the difficulties of childhood depressive disorders. I am happy to have Lisa here today to join us at this hearing, and I am also happy to report that her daughter, Michelle, is a happy and healthy student today at the University of Hartford.

Mr. Chairman, 6 weeks ago, my wife and I welcomed our fourth child, and like any parent it breaks my heart to see children and their families suffer from the effects of a major depressive disorder or any psychological disorder. As a parent, it must be torture to see the happy child that you know is somewhere deep down within deal with a disease with which they might not know how to cope, which them and their families to turn to outside help to find a cure. In order to help children cope with the effects of these illnesses, parents and doctors must have the most complete and accurate research and information readily available to them, because the lives of these children, quite literally, depend on it.

In my meetings with Lisa and others, it has become clear that there are several problems faced by parents who are looking for the right treatment for their child. Sometimes all the clinical research for a drug has not been made publicly available by the manufacturer. Sometimes doctors prescribe a drug for a child when it has not been approved for that particular use. And sometimes the FDA has not made enough of an effort to inform doctors about potential risks that a drug may have when taken by a child.

It is my hope that this hearing today will examine these points and will help all of us to do a better job of protecting our children. Pharmaceutical companies, because they do incredible work in researching and finding cures to diseases and afflictions of all kinds, also bear an enormous responsibility to make public any and all clinical research data which could potentially impact the decisions of doctors and parents when determining the right treatment for a

child. If that information has not been shared and made public up until this point, it damn well better be and soon, because children's quite literally depend on it.

Doctors, too, must examine their role in prescribing medicines for their children which might not necessarily have been proven safe and effective for them. This, I believe, is a weakness in the system, and it needs to be recognized. And the FDA must redouble its efforts to gather, analyze and publish clinical data on the effects of SSRIs since this will enhance their credibility and further their role in protecting children and their families from the tragedies like those which we are hearing about today.

In short, there is plenty of responsibility to go around, and this hearing will highlight the problems which exist and I hope will provide a blueprint for where we go together to address this most important issue. Thank you, Mr. Chairman. I yield back.

Chairman BARTON. Thank the gentleman from New Jersey. We now recognize the gentlelady from Colorado for an opening statement.

Ms. DEGETTE. Thank you, Mr. Chairman. Today's hearing delves into a complex and troubling issue which is well known to members of this subcommittee who have worked for many years to examine clinical trials and medications for children and also those in need of mental health services. For this vulnerable population, the ethical considerations are substantial and of course the two issues juxtapose here today.

I have been working for a long time to ensure the safety of clinical trials for American patients, and this investigation is deeply troubling. Data and results from clinical trials are not the most easily understood even by sophisticated observers. I remain concerned about the transparency of the data from these clinical trials that Mr. Waxman talked about a few minutes ago. I am encouraged that some pharmaceutical companies have put results of their trial data on the Internet, but I am also concerned whether these actions are sufficient, either to inform parents and consumers about the risks and the results of these clinical trials and even doctors of the same thing.

Beyond specific cases for specific drugs that I am sure will come up in the hearing today, this subcommittee's investigation has provided more evidence that our mental health system is hindered by inadequate funding and limited labeling information. It is simply unconscionable that parents seeking easy-to-understand information about mental health pharmaceuticals for their children somehow have to try to become experts as to what all this data means. NIH and our health care system must do more to show parents and patients the risks and benefits of the treatment and they also need to demonstrate this to physicians.

We are focusing today on the publication of clinical trial results, but I, like many of my colleagues here, are also looking forward to the next hearing which will focus on the FDA's ability and efforts to ensure that all approved pharmaceuticals are safe. The two hearings are truly interlocking pieces, because without transparency and improved labeling, patients and their physicians will not be assured of a drug's efficacy and without comprehensive stud-

ies and rigorous scientific inquiry, will never be sure if these medications are safe for the kids we are giving them to.

While we must approach this issue with sensitivity because it also has a wide-ranging effect on our mental health treatment, I don't believe that we can shirk our oversight duty. I am alarmed, like the chairman, about reports that the FDA has not adequately enforced provisions from the Best Pharmaceuticals for Children Act. FDA is supposed to be a watchdog agency, and I would like to remind them that this role is essential for America's health, especially when we are talking about unapproved uses of antidepressants for juvenile populations.

Finally, and most importantly, I think, we need to remember that we are here because we are all looking for better health for our children. I hope that the researchers here today are truly working on developing drugs that will benefit this population, and I hope that the physicians and their representatives who are here today are carefully prescribing and monitoring their pediatric patients, because truly it is about the patient and it is about the parents who are trying to find the best solution for their children. We cannot allow anyone in our system to take advantage of that hope, and we also cannot risk snuffing out that hope. We all have to work together to make sure our mental health system works and that it works not just for adults but for the children who increasingly are becoming enmeshed in that system. I yield back.

Chairman BARTON. We thank the gentlelady. The gentleman from Florida, Mr. Stearns, is recognized for an opening statement.

Mr. STEARNS. Thank you, Mr. Chairman, and I appreciate your leadership on this. Obviously, this is a question that all individuals who have children are concerned about in the efficacy of these drugs. You would think something simple like this, the data base of clinical trials, should it be voluntary or mandated, it would be something we could all agree upon. And if you go into the commercial world and you are a consumer, you want to buy something, let us say I want to buy a car or I want to buy a television or even food, I can always research whether I want to buy that car and how much it should cost and whether that product is recommended safe or not. The Consumer Report will list all the cars that are safe and all those cars that are not safe. In this same way, shouldn't American parents be able to access some sort of registry to see whether the drugs their children are being prescribed are efficacious and safe? I mean that seems to be a pretty basic point. I don't think many people would disagree on that.

But there are some things on the other side. For example, once you publish this information in a data base and you have these clinical trials, then when you get into litigation, you are going to have lawyers use that clinical information in a way against the drug companies that wasn't intended, and a lot of it becomes subject to the jury's interpretation. So from the standpoint of the pharmaceutical companies, I can see their concern that the litigation that might come about from this data base would harm them in such a way that they could not speculate. So that is probably one reason that some people are worried about publishing negative things about the drugs that they are putting on the market be-

cause that could come back to haunt them, and we don't have tort reform in this country, so I think it is a legitimate question.

Pharmaceutical companies in the United States have been a leader, a world leader in drug development and health care. We don't want to kill the golden goose here. I commend the industry for launching a voluntary clinical trial data base, and I commend those companies that go far and beyond what the industry requires. I think industry certainly should make every effort or Congress will come down with a registry. I think improvements need to be made and we can't be complacent with the efforts because in the end the American consumer deserves a rate, much like when he buys a car, a piece of food or a television or T.V. or toaster. He should be able to find out a little bit about how good this product is.

So I think the hearing we have today, Mr. Chairman, is very good, and hopefully we will be able to get more information so we can decide whether we should have mandatory prescription for the pharmaceutical companies. But I do leave the committee with this thought is that once you make this clinical information available, you are going to subject these drug companies to lawsuits on a very strong, tangible way that they are going to have to defend themselves. And in the end, it might be based upon specious information. So that with, I return.

Chairman BARTON. We thank the gentleman. And I believe Mr. Markey is next.

Mr. MARKEY. Thank you, Mr. Chairman. Thank you, Mr. Chairman. Let me begin by thanking you, Mr. Chairman, for holding this extremely important hearing. Today, we will explore the issue of disclosure of clinical trials on pediatric antidepressants and hear about several cases in which critical data about those drugs were not disclosed. But the problem of selective disclosure in publication is not limited to a specific type of drug or scenario. The same concern exists whether we are talking about drugs to treat depression, heart disease or high cholesterol.

Every day, in hospitals and clinics around the country, ordinary people are placing their health and their very lives into the hands of researchers who are testing these experimental drugs for safety and for effectiveness. In other words, the public places great faith in the judgment of the researchers and the institutions and companies for which they work. Recently, however, the public has had reason to question their judgment in certain cases where trials which provided important insights regarding a drug never saw the light of day. Some of these trials did not become part of the medical literature for innocent reasons, but we cannot ignore the possibility that some studies were and continue to be intentionally buried by companies worried about the impact of a negative trial on their bottom line.

I understand when companies are concerned about how bad news might lead their stockholders to suffer a monetary loss, but the alternative is that patients' health suffers as doctors research and sick people proceed on the basis of false assumptions. Regardless of the motivation, the fact remains that clinicians, patients, researchers and the general public do not have access to all the information currently available about the drugs that we use.

There are two major problems with this situation. The first is that in order for doctors to make good medical decisions and to provide their patients with the best possible care, they need to have access to complete and sound scientific data. Every student starting school this fall knows they can't pick and choose which tests will count and which won't. Likewise, drug companies can't be permitted to decide which trials to disclose and which to hide from the public. Doctors should never be put in the position of prescribing medications to a patient with only partial access to what is known about the drug's effects. Doctors should never be put in the position of making medical decisions based on misleading or inaccurate information.

In addition, there is a sacred yet unspoken contract that binds the participants in clinical trials and the drug companies that sponsor them. Participants give up control of their medical decisions, willingly take experimental drugs and subject themselves to potential harm, because they believe that their participation in the studies will add to the advancement of medical knowledge and potentially unlock the secrets of disease. But if a researcher or a company that sponsors a trial does not publicize the results, the knowledge gained from putting these participants at risk becomes forever buried in some Orwellian memory box locked up in the files of a researcher's computer.

In order to ensure that clinicians have all the information they need to make sound medical decisions and uphold the ethical responsibility to patients and protect public health, Congressman Henry Waxman and I will very soon introduce a bill to create a mandatory public Federal registry of all clinical trials. Congressman Waxman has already outlined the details of the legislation. The data base will expand on clinicaltrials.gov and will include both federally funded and privately funded clinical trials so that clinicians, patients and researchers will be able to know the universe of clinical trials on a particular drug and have access to the results of those trials.

Since we believe that companies and researchers have a moral and ethical responsibility to share their trials with the public, registration in this data base will be a condition of institutional review board approval, and failure to report results will have consequences, including civil penalties. The registry will meet all of the minimal criteria for a trial registry set out by the International Committee of Medical Journal Editors and will satisfy the American Medical Association's call for the results of all clinical trials to be publicly available to doctors and patients. The bill will require the posting of important results that are not published in the peer reviewed medical literature in a timely fashion. Although the bill will use the infrastructure put in place by clinicaltrials.gov, the bill will reserve patient access to enrollment information about clinical trials for serious and life-threatening diseases.

Some companies are now urging that we accept a renewed commitment to voluntary disclosure as a substitute for a mandatory enforceable system. Well, we tried that approach and it didn't work. Since 1997, trials involving serious and life-threatening diseases have been subject to mandatory registration, but since there is no enforcement mechanism, it is the equivalent of a voluntary

system. As a result, in 2002, the FDA found that only 48 percent of trials of cancer drugs had been registered. If the idea is to make sure that all the clinical trials are available, then it has to be mandatory. If it is not mandatory, then the good companies will disclose what they want to report, while the bad companies will hide what they believe they can get away with.

This is a very important hearing. Congressman Waxman and I are looking forward to working with the committee to pass legislation that will ensure the protection of the public. Thank you.

Chairman BARTON. We thank the gentleman. We have a series of three recorded votes on the floor. The first is 15 and then two 5s. If at all possible, I would like to get all the opening statements in before we go to the votes. Gentleman from Maine is recognized, Mr. Allen, for an opening statement.

Mr. ALLEN. Thank you, Mr. Chairman. Let me join others in thanking you for calling this hearing on a most troubling issue: The systematic withholding of negative clinical trial results with a particular focus on antidepressant pediatric clinical trials. This is a serious public health issue, and I commend your leadership in having the committee conduct an investigation into the use and promotion of antidepressants in children and the current lack of full disclosure of clinical studies, whether the results of positive, negative or in some case inconclusive.

The fact that clinical trials with positive results are used for promotional purposes while those with negative outcomes may be suppressed is likely to create a bias leading to an overprescribing of the newest and more expensive treatments regardless of whether they are safe and effective. Of course, in this case, illness and even death can be a more serious consequence.

I have a particular interest in the government's role in supporting evidence-based research on prescription drugs and the public disclosure of clinical trial results. Last June, I introduced a bipartisan bill, H.R. 2356, The Prescription Drug Comparative Effectiveness Act. This bill would essentially provide a consumer report for prescription drugs. It authorizes $50 million in funding to NIH and $25 million in funding to the Agency for Health Care, Research and Quality. The bill directs these agencies to examine existing research and if necessary conduct new research, including head-to-head clinical trials in order to develop valid scientific evidence regarding the comparative effectiveness, the cost effectiveness and comparative safety relative to other drugs and treatments for the same disease or condition. This legislation is designed to provide doctors and their patients with valid, evidence-based information on how drugs that treat a particular condition compare to one another.

The FDA deals essentially with the safety and efficacy of the drugs that they review, but the larger issue here is whether or not we can have a system that is broader than that. And what I mean by that, a functioning free market depends on good information broadly shared. A vital public health interest is at stake in this issue today. I believe we need to have a system where the companies producing the most effective drugs have a comparative advantage, not the companies which are best at manipulating information regarding clinical trials or the companies with the largest mar-

keting budget. That ought to be the goal that we are striving for here today. I don't see how you get there unless all companies are operating on a level playing field, all are required to provide the same information in the same timely manner, to the same agency. But that has to be the goal. We need a system that creates a level playing field where the result is the companies with the best drugs have the advantage, not the companies with the biggest marketing budget or the ones that are best at disclosing some studies and hiding others.

I look forward to the testimony of all of you today, and, Mr. Chairman, I yield back.

Chairman BARTON. We thank the gentleman, and the gentlelady from Illinois, Ms. Schakowsky, is recognized for an opening statement.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. I thank you for holding this hearing to look into the failure of some drug manufacturers and the FDA to disclose to pediatricians and the public the results of clinical trials aimed at determining the efficacy of antidepressants in children.

I would like to understand why the system that was supposedly put in place to protect children from the potential side effects of ineffective medications allowed for such a breach of trust to occur. And more specifically, I hope we will explore whether it makes sense to continue to give drug manufacturers 6 months of exclusivity in exchange for their conducting clinical trials when the results of those trials are not made available to physicians, patients or American taxpayers.

It is important that we all understand why when the FDA was informed that clinical trials of several antidepressants demonstrated no efficacy in children or worse, far worse, they did not make an attempt to inform both pediatricians and patients of this critical information. Why were parents not given the results of the studies which could very well have influenced their decisions to start their children on those medications?

When physicians discuss with parents the possibility of starting a child on a drug, an important part of that discussion involves the weighing of risks and benefits associated with taking that medication. If neither parents nor physicians possess information from these trials, they will be left in the dark and unable to make informed decisions regarding what is best for their children.

I support Congressmen Waxman's and Markey's effort to create a registry that contains the results of all clinical trials conducted by all drug manufacturers. I think history shows it would be a failure for us, in meeting our obligation to protect the public health, to rely on the drug industry to create that registry. And I hope that as a result of this hearing, we will have a better understanding of how American families who subsidize clinical trials through their tax dollars can most easily obtain the results which allow them to make the right decisions for their children.

Going further beyond the narrow scope of this particular hearing, as one of the perhaps millions of families facing a serious medical challenge and interested in the most up-to-date information on potential therapies, my family and I find it completely unacceptable that data from clinical studies that may have a really positive ef-

fect on outcomes are unavailable. I look forward to dealing with that situation in the near future. Thank you.

Chairman BARTON. Before we recognize Mr. Stupak for his opening statement, the Chair would ask unanimous consent that the hearing binder be put into the record that has all the documents that we have received from the FDA. Hearing no objections—and others—so ordered.

[The material appears at the end of the hearing.]

Chairman BARTON. The Chair would recognize the gentleman from Michigan for an opening statement.

Mr. STUPAK. Thank you, Mr. Chairman, and thank you for allowing me the opportunity to take part in this important hearing on the publication and disclosure of antidepressant pediatric clinical trials.

Every day brings new disturbing reports showing a link between suicidal behavior and antidepressants used by children. Physicians and parents deserve a full accounting of the research from both the FDA and drug companies about the risks and benefits of these drugs. The integrity of our drug safety system is being questioned and I believe rightfully so.

Right now, drug companies can cherry pick which studies they publish and which they don't. We all know that the negative ones rarely see the light of day, and the FDA has done a truly dismal job of enforcing the two laws on the books today that provide for a minimal amount of transparency. Next week, the FDA Advisory Committee will meet to address the latest analysis that as yet again seems to show a link between suicidal behavior and antidepressant use by children. And in 2 weeks we will hold a second hearing on the FDA's analysis and the Advisory Committee's recommendation, including labeling. I look forward to that hearing, but as we all know with Accutane, the Advisory Committee recommendations will most likely be ignored by the FDA.

There are a lot of concerns about the safety of these drugs. What is appalling is until very recently doctors and parents had no way of knowing that these concerns existed. Drugs companies, aided by FDA's complacency, gave them no reason to question the safety or effectiveness of these drugs. Congress will not sit back if the drug companies and the FDA ignore or are slow to implement those recommendations by the Advisory Committee. We cannot allow profits and stock prices to trump the safety of our children.

In 2002, almost 11 million antidepressant prescriptions were written for children and adolescents. Two point seven million of those prescriptions were for children under 12, to kids as young as 7 years old. Prozac has demonstrated some effectiveness today, but yet today there are new questions about its safety after an NIH study found an increased risk of suicidal behavior and thoughts when adolescents are treated with Prozac alone or in a combination with talk therapy when compared with placebos. This raises concerns about the safety of Prozac. We know these concerns and can address them today because it was a public study that was actually published. It is an example of how the system could work.

I want to touch on a way the system is not working. Since 1997, we have given pharmaceutical companies billions of dollars worth of patent extensions in exchange for testing the safety and efficacy

of drugs in children. Those patent protections cost taxpayers billions in increased prescription drug prices and increased costs to Medicare and Medicaid. Many believe this system is justified because of the new information we gain in return, but what are we really gaining in return? If positive results are shown from pediatric trials, the FDA will allow the drug to be marketed to children. However, if the efficacy results are inconclusive or negative, the drug companies still have their patent extensions, ensuring millions in profits and doctors can still prescribe off label.

I offered an amendment during the Best Pharmaceutical for Children Act, BPCA, debate to require results of the trials to be clearly outlined on the drug's label before patent extensions could be granted. Unfortunately, my amendment was defeated. My amendment would have given the pharmaceutical companies a powerful incentive to do good studies and to change their labels promptly. Remember, each patent extension often means hundreds of millions of dollars to the drug companies. This systematic flaw that rewards companies for doing a study, the results of which are not made public, which may show the drug is not effective and actually may harm young people and the consumers' notice, the package labeling is not immediately changed. We have it backwards. The patent extension should only occur if the drug is safe, effective and after the necessary label changes are fully implemented. Then, and only then, should a patent extension be granted.

We were successful, however, in including a provision in the Best Pharmaceutical Children's Act that the FDA must publish the summaries of each of these pediatric trials done in exchange for patent extensions. At the very least, the FDA could publish the summaries, but this is not being done. The committee has found that the FDA had only posted the summaries for one of the antidepressants, Effexor, before August 20 of this year. There is no room for this kind of incompetence. Now, when you go to the FDA web site, you can see the summaries, but, interesting, none of the summaries include any mention of suicidal thoughts or behavior.

Mr. Chairman, I have a lot more, and I know we are running out of time, but bottom line is let us get to the bottom of this, whether it is Accutane or whether it is the antidepressants, the FDA and the drug companies have let us down, they have not done their job. The complacency has got to end, and I look forward to asking questions, and I look forward to getting some answers to some of the letters I have written over the last couple of months to the FDA, to Ms. Woodcock just trying to get some of these studies produced and put out in the public.

Chairman BARTON. I thank the gentleman from Michigan. We will stand in recess until these series of votes, which will be approximately 12:20. All members not present or a member of the subcommittee will have the requisite number of days to put their opening statements in record. So we stand in recess until approximately 12:20.

[Brief recess.]

Chairman BARTON. The subcommittee will come to order. Before we recessed for the votes, we had heard opening statements from all members of the subcommittee. Now we want to hear our witnesses. The Chair would call forward Dr. Janet Woodcock who is

the Deputy Commissioner for Operations for the Food and Drug Administration.

Dr. Woodcock, you are aware that the committee is holding an investigative hearing and when doing so we have the practice of taking testimony under oath. Do you have any objection to testifying under oath?

Ms. WOODCOCK. No.

Chairman BARTON. Okay. The Chair would also advise you that under the rules of the House and the rules of the Energy and Commerce Committee, you are entitled to be advised by counsel. Do you desire to be advised by counsel during your testimony today?

Ms. WOODCOCK. No.

Chairman BARTON. Okay. Would you please raise your right hand?

[Witness sworn.]

Chairman BARTON. Be seated.

Ms. WOODCOCK. Thank you.

Chairman BARTON. Dr. Woodcock, your written is in the record in its entirety. We are going to give you 7 minutes or such time as you may consume to advise us of that testimony. Welcome to the subcommittee.

TESTIMONY OF HON. JANET WOODCOCK, DEPUTY COMMISSIONER FOR OPERATIONS, FOOD AND DRUG ADMINISTRATION

Ms. WOODCOCK. Thank you. Mr. Chairman and members of the subcommittee, I am Janet Woodcock, FDA's acting Deputy Commissioner for Operations. The agency appreciates the opportunity to participate in this important hearing.

Today, I will focus on disclosure and publication of information regarding clinical trials under the Food and Drug Administration Modernization Act and the disclosure and dissemination of pediatric information under the Best Pharmaceuticals for Children Act.

Now, it is generally agreed, and we have heard this morning already, and it is agreed upon in the biomedical community-at-large, that results of trials involving human subjects should be made available to the public after completion of the trial and data analysis. This is especially important for studies of marketed products, surgical interventions and other medical treatments where a bias toward publication of positive results may distort the community's overall understanding of an intervention's effectiveness or risk profile. Government, academic or industry groups may sponsor human clinical trials, and each of these sponsors has a role in making clinical results available.

Now, I would like to say that personally I have always had a strong commitment during my career at the FDA toward improving transparency of clinical trial results to the extent that was legal for the FDA. Starting in my tenure as Director of the Center of Drugs, I established web sites where the clinical results could be made available when drugs were approved. I established templates which are currently being used. I wrote those personally to provide summaries of reviews and get those results made public. I established procedures for redaction under Freedom of Information so that we would have a prompt process for making that information available

to prescribers and to patients once new drugs became available on the market. So I have always been involved in this issue, and I strongly support the goal of transparency and availability of information from human subjects.

When I took care of patients in clinical trials, I always tried to promise my patients I would send them the results or the published paper of the studies, because people who enroll in clinical trials are altruistic and they want to know that their efforts have gone into helping others and improving knowledge.

Now, the FDA Modernization Act required the Department of Health and Human Services, acting through NIH, in consultation with FDA and CDC, to establish, maintain and operate a data bank of information on clinical trials for treatment of serious and life-threatening diseases and conditions. The data bank must contain information about clinical trials whether federally or privately funded that are conducted under an IND if the drug under study is to treat a serious or life-threatening condition and the trial is testing the drug's effectiveness.

Now, the purpose of this data bank primarily was for access to clinical trials so that the existence of these trials would be posted and patients or families or physicians who had a serious and life-threatening illness they were dealing with could look at what trials were open.

NIH implemented Section 113 by establishing the clinical trials.gov web site in February 2000. The information in the data bank must include for each trial a description of the purpose of each experimental drug, patient eligibility criteria, location of the sites for the trial and a point of contact for patients seeking to enroll in the trial. Information about other clinical trials such as those for non-serious diseases or trials that aren't designed to assess effectiveness may be included but are not required to be submitted. Additionally, the law authorizes but does not require that the data bank include information about results of clinical trials. That is only voluntarily by the sponsor.

Currently, clinicaltrials.gov contains information on more than 11,000 publicly and privately funded trials of which about 4,000 are ongoing. Most of the trials are safety and efficacy studies for treatment of serious or life-threatening diseases or conditions; however, sponsors can and have voluntarily listed some early studies and studies for non-serious conditions. For some of the completed studies, links are also provided to abstracts or publications describing the study's outcome.

Recent public attention on increasing the availability of clinical trial information, some of which has been brought about by this committee's efforts, have made pharmaceutical companies more aware of their responsibility to list these clinical trials. Last month, non-Federal sponsors listed 80 new trials—2 times the average monthly listing than the year before.

Now, when Congress enacted the Food and Drug Modernization Act, it also provided incentives for manufacturers to conduct pediatric trials. The FDAMA authorized FDA to grant additional marketing exclusivity to pharmaceutical manufacturers that conduct studies of their drugs in pediatric populations, and that has already been alluded to this morning. To qualify for this exclusivity,

sponsors must conduct these studies according to the terms of a written request from the FDA and then submit the results of those studies in a new drug application or supplement. Congress renewed this authority in 2002 in the Best Pharmaceuticals for Children Act. Now, the change in the Best Pharmaceuticals for Children Act was it contained new disclosure requirements related to these clinical trials.

Outside of the Best Pharmaceuticals for Children Act, the agency generally may not publicly disclose information and INDs, unapproved new drug applications or unapproved supplemental new drug applications. Only after a new drug application or supplemental application is approved can we make certain summary information available on the safety and effectiveness of the product for the approved indication. And these were the efforts I have been talking about that we have been working on.

In contrast, the Best Pharmaceuticals for Children Act requires that no later than 180 days after submission of the studies in response to a written request the agency must publish a summary of FDA's medical and clinical pharmacology reviews of those studies. We must publish this information regardless of whether our action on the pediatric application is approvable or not approve. Since 2002, FDA has posted the summaries of 41 products submitted in response to written requests on FDA's web site.

FDA and NIH will continue to work with individual sponsors to put required information into the clinicaltrials.gov registry. Also, FDA is reviewing sponsor listing in this registry to assess whether additional FDA action is warranted, and FDA welcomes the continued dialog regarding the kind of information from clinical trials that would be most useful to providers, patients and families in making meaningful treatment decisions. Thank you.

[The prepared statement of Hon. Janet Woodcock follows:]

PREPARED STATEMENT OF JANET WOODCOCK, ACTING DEPUTY COMMISSIONER FOR OPERATIONS, U.S. FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Acting Deputy Commissioner for Operations at the U.S. Food and Drug Administration (FDA or the Agency). We appreciate the opportunity to participate in this hearing regarding publication and disclosure issues in pediatric clinical trials for anti-depressant drug products.

On September 23, 2004, the Committee will hold a hearing regarding FDA's process for review of anti-depressants for pediatric use. Today, I will focus on the disclosure and publication of information regarding clinical trials under the Food and Drug Administration Modernization Act (FDAMA) of 1997 and the disclosure and dissemination of pediatric information under the Best Pharmaceuticals for Children Act (BPCA) in general, and in the context of anti-depressant pediatric clinical trials in particular. I will also provide a status report on the Agency's review of selective serotonin reuptake inhibitors (SSRIs) for pediatric use.

It is generally agreed upon in the biomedical community that results of trials involving human subjects should be made available to the public after completion of the trial and data analysis. This is especially important for studies of marketed products, surgical interventions, and other medical treatments where a bias toward publication of positive results may distort the community's overall understanding of an intervention's effectiveness or risk profile. Government, academic, or industry groups, may sponsor human trials and each of these sponsors has a role in making clinical trial results available.

FDAMA: CLINICAL TRIALS DATA BANK

Section 113 of FDAMA amended the Public Health Service Act to require the Department of Health and Human Services (HHS or the Department), acting through the National Institutes of Health (NIH) and in consultation with FDA and the Centers for Disease Control and Prevention, to establish, maintain and operate a data bank of information on clinical trials for treatments for serious or life-threatening diseases and conditions. The goal of section 113 was to improve access to information that would enable the public to learn about opportunities to participate in clinical trials of promising new treatments. FDAMA specifies that the data bank must contain information about clinical trials, whether Federally or privately funded, that are conducted under an investigational new drug (IND) application if the drug under study is to treat a serious or life-threatening disease or condition and the trial is testing the drug's effectiveness.

Working together with FDA and other sister agencies in the Department, NIH implemented section 113 by establishing the ClinicalTrials.gov website in February 2000. The information in the data bank must include, for each trial, a description of the purpose of each experimental drug, patient eligibility criteria, the location of the clinical trial sites, and a point of contact for patients seeking to enroll in the trial. Information about other clinical trials, such as those treating non-serious diseases or for trials that are not designed to assess effectiveness, may be included, but sponsors are not required to submit this information. Additionally, the law authorizes but does not require that the data bank include information about the results of clinical trials of such treatments, but only with the consent of the sponsor.

CLINICAL TRIALS.GOV

Today, ClinicalTrials.gov contains information on more than 11,000 publicly and privately funded trials, of which over 4,000 are open for recruitment. Most of the trials are safety efficacy studies (Phase II, III, and IV) for treatments for serious or life-threatening diseases or conditions. However, sponsors can and have voluntarily listed some Phase I (safety) studies and studies for conditions not classified as serious. In addition, for some of the completed studies in ClinicalTrials.gov links are also provided to publications or abstracts describing the study's outcome. Information on studies that are no longer recruiting patients or that are completed is retained in the database and available to the public.

Recent public attention on increasing the availability of clinical trial information has made pharmaceutical companies more aware of their responsibility to list clinical trials in ClinicalTrials.gov. In fact, non-Federal sponsors listed 80 new trials last month—two times the average monthly listing for 2003. Additionally, companies that previously listed "pharmaceutical company" as the drug sponsor now list the specific company name.

Section 113 of FDAMA does not authorize NIH to require that sponsors submit all clinical drug trial information to ClinicalTrials.gov. However, NIH does include non-mandatory information in the database when the sponsor voluntarily provides this information. For example, sponsors can include information about trial design.

FDA DISCLOSURE OBLIGATIONS UNDER BPCA

When Congress enacted FDAMA in 1997, it also provided incentives to manufacturers to conduct pediatric clinical trials. Section 111 of FDAMA authorized FDA to grant additional marketing exclusivity (known as pediatric exclusivity) to pharmaceutical manufacturers that conduct studies of their drugs in pediatric populations. To qualify for pediatric exclusivity, sponsors must conduct pediatric studies according to the terms of a Written Request from FDA and submit the results of those studies in a new drug application or supplement. Congress renewed this authority in 2002, in the BPCA Act.

BPCA contains important, new disclosure requirements. Outside of the BPCA, the Agency generally may not publicly disclose information contained in investigational new drug applications, unapproved new drug applications, or unapproved supplemental new drug applications. Only after a new drug application or supplemental new drug application is approved can the Agency make public certain summary information regarding the safety and effectiveness of the product for the approved indication.

However, section 9 of BPCA regarding the dissemination of pediatric information gives the Agency additional disclosure authority and differs from FDA regulations that generally preclude the Agency from disclosing to the public information in an unapproved application. BPCA requires that, no later than 180 days after the submission of studies conducted in response to a Written Request, the Agency must

publish a summary of FDA's medical and clinical pharmacology reviews of those studies. Moreover, we must publish this information regardless of whether our action on the pediatric application is an approval, approvable, or not-approvable action. Thus, although under FDAMA information on pediatric studies conducted in response to Written Requests is not available until after the supplemental application is approved, under BPCA, a summary of FDA's medical and clinical pharmacology reviews of pediatric studies is publicly available irrespective of the action taken on the application. Since 2002, FDA has posted the summaries of these reviews of 41 products submitted in response to a Written Request on FDA's website at: http://www.fda.gov/cder/pediatric/Summaryreview.htm.

DISCLOSURE OF INFORMATIUON RELATED TO PEDIATRIC SSRI CLINICAL TRIALS

Prior to the enactment of BPCA, using the pediatric exclusivity authority of FDAMA, FDA issued seven Written Requests to manufacturers of drugs approved for the treatment of depression (Prozac, Zoloft, Remeron, Paxil, Celexa, Serzone, and Effexor). The sponsors of three of these drugs (Prozac, Zoloft, and Remeron) performed the studies and submitted the reports of their studies before FDAMA expired on January 1, 2002, (and thus, before BPCA took effect).— The manufacturers of two of these drugs, Prozac and Zoloft, received pediatric exclusivity for doing those studies. The third sponsor, the manufacturer of Remeron, did not receive pediatric exclusivity. Under FDA's general disclosure provisions regarding the availability of information in approved applications, pediatric anti-depressant data on Prozac are publicly available at: http://www.fda.gov/cder/foi/nda/2003/18936s064_Prozac.htm. Just as it has for other product approvals, FDA posted this information because we granted approval for Prozac for use in treating pediatric depression. The pediatric data for Zoloft and Remeron would not normally be available for public disclosure because their pediatric supplements have not yet been approved. However, FDA nonetheless asked the sponsors to allow us to make summaries of these studies public. The sponsors agreed to our request and summaries are now available on FDA's website at: http://www.fda.gov/cder/pediatric/Summaryreview.htm.

Following enactment of BPCA in January 2002, FDA determined that the provisions of this new law should apply as broadly as possible to outstanding Written Requests for which studies had not yet been submitted. In a July 2002 letter, the Agency notified drug sponsors with outstanding Written Requests issued under FDAMA that FDA also considered those Written Requests to be reissued under the BPCA. In its July 2002 letter, FDA further advised manufacturers that any studies submitted in response to the Written Requests would be subject to the terms of BPCA, including, among other things, the provisions governing public availability of study summaries. However, the Written Requests for three anti-depressants (Paxil, Celexa, and Serzone) were not considered as reissued under BPCA in July 2002 because the manufacturers had already submitted their pediatric studies to the Agency before FDA issued its July 2002 letter (albeit after BPCA was enacted). Therefore, FDA considered the studies for Paxil, Celexa, and Serzone, to have been submitted under FDAMA and did not consider their Written Requests to be reissued, and did not apply the public disclosure provisions of BPCA to these studies. Nonetheless, the Agency has received permission from the sponsors of these drugs to post summaries of the safety and effectiveness reviews of their pediatric studies on FDA's website, and this information appears at: http://www.fda.gov/cder/pediatric/Summaryreview.htm.

Only one of the outstanding and reissued Written Requests under BPCA was for studies relating to the treatment of pediatric depression. This Written Request was for Effexor. FDA granted pediatric exclusivity for this product and posted the study summaries on the FDA Pediatric Summary review website, according to the requirements of BPCA. No new Written Requests for anti-depressants have been issued since the passage of BPCA.

STATUS OF SSRIS AND SUICIDALITY IN THE PEDIATRIC POPULATION

FDA has been reviewing the results of anti-depressant studies in children since June 2003 after an initial report on studies with paroxetine (tradename, Paxil) appeared to suggest an increased risk of suicidal thoughts and actions in the children given Paxil, compared to those given placebo. Later reports on studies of other drugs supported the possibility of an increased risk of suicidal thoughts and actions in children taking these drugs. There were no suicides in any of the trials.

FDA has closely examined the studies of the anti-depressants because of the potential public health impact of a link between the drugs and suicidality and the importance of these drugs in treating depression and other serious mental health con-

ditions. After examining the initial reports of suicidality, it was unclear whether some of the identified suicidal behaviors reported in these studies represented actual suicide attempts or self-injurious behavior that was not suicide-related. FDA therefore arranged with Columbia University suicidality experts to review these reports.

Meanwhile, FDA brought available information on this issue to its Psychopharmacologic Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committees on February 2, 2004. The advisory committee members advised FDA that even before the Columbia analysis was complete, the labeling should draw more attention to the need to monitor patients closely when anti-depressant therapy is initiated. Based on this recommendation, FDA asked manufacturers to change the labels of ten drugs to include stronger cautions and warnings about the need to monitor patients for worsening of depression and the emergence of suicidality, whether such worsening represents an adverse effect of the drug or failure of the drug to prevent such worsening. The new warning language has now been added to the labels for seven of these products. Sponsors for the other three drugs have also agreed to adopt the language. The "Columbia" Study

Because of concerns about whether the varied events identified by sponsors under the broad category of "possibly suicide-related" could all reasonably be considered to represent suicidality, FDA asked Columbia University to assemble an international panel of pediatric suicidality experts to undertake a blinded review of the reported behaviors using a rigorous classification system. The Columbia group submitted its completed review to FDA in June 2004.

FDA has analyzed the pediatric suicidality data, based on the case classifications provided by Columbia University, and has posted the analysis on its website at http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-09-TAB07-Iyasu-Audit_report.pdf. While there are findings among these data suggestive of an increased risk of suicidality for some of these drugs, there remain inconsistencies in the results, both across trials for individual drugs and across drugs. Thus, an overall interpretation of these findings remains a substantial challenge.

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As a public health agency, FDA must weigh the possibility of an increased risk of suicidality in young patients taking these drugs against the known risk of suicide in patients whose depression goes untreated. FDA's next step, as we announced in March 2004, will be to update the Psychopharmacologic Drugs and the Pediatric Advisory Committees about the results of these reviews and to seek assistance from the committees in interpreting the data and in considering what additional regulatory actions may be needed to promote the safe use of these drugs. This meeting will be held in Bethesda, Maryland on September 13 and 14, 2004.

CONCLUSION

FDA and NIH will continue to work with individual sponsors to put required information into the registry. Also, FDA is reviewing sponsor listings in ClinicalTrials.gov to assess whether additional FDA action is warranted. FDA will continue to actively provide summaries of pediatric trials in a timely manner. FDA welcomes a continued dialogue regarding the kind of information from clinical trials that would be useful to providers, patients, and families so they can make more meaningful treatment decisions. Finally, FDA will carefully consider what further action may be required for the safe use of anti-depressant drugs in children.

Chairman BARTON. Thank you. Thank you, Dr. Woodcock. The Chair would recognize himself for 10 minutes of the first round of questions.

The purpose of our hearing today, the title of our hearing is, "Oversight Hearing on Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials." And as I said in my opening statement, for us to have a hearing, we need to have documents in which to base our questions and give our members of the subcommittee a chance to see what the facts are. We could have had a hearing on the disclosure of FDA to document requests by this subcommittee, and we have got seven or eight members here that are going to ask a lot of very specific questions on the policy issues. I am going to primarily limit my questions to a procedure issue.

I was subcommittee chairman of this subcommittee from 1995 through 1999, and one of my primary emphasis was the FDA under Dr. Kessler, and the FDA Reform Act that you referred to in your testimony was a bipartisan effort between myself, Mr. Bliley, Mr. Bilirakis, Mr. Dingell, Ms. Eshoo and Mr. Burr on this committee. So I have been away from doing active oversight and investigations for approximately 6 years. Now with Mr. Greenwood's resignation as subcommittee chairman, I have an excellent vice chairman in Mr. Walden, but for the remainder of this Congress I am serving kind of de facto as the acting subcommittee chairman of Oversight and Investigations. And I want to tell you straight up, as a senior representative from FDA, your agency's cooperation with this subcommittee and this investigation is as poor as it could possibly be and still be called cooperation.

Mr. Greenwood and I sent a letter on March 24 to Dr. McClellan when he was still Commissioner of the FDA, it is about a 6 or 7 page letter, but we had a number of questions that we asked that we get a timely response to. Question number 8, and I am going to read the question, "All records relating to communications by FDA employees that raise questions or concerns about the safety or efficacy of antidepressants in the pediatric adolescent population, we are asking for those records."

Now, as an addendum to the letter, we sent our standard attachment where we define the term, "records." "The term, 'records,' is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description consisting of the original and any non-identical copy, whether different from the original because of notes made on or attached to such copy or otherwise, and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, included but not limited to the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants' projections, statistical statements, draft contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinion logs, diaries, desk calendars, appointment books, tape recordings, video recordings, emails, voicemails, computer tapes or other computer stored material, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, mechanical means, charts, photographs, notes, drawings, plans, interoffice communications, interoffice or interdepartmental communications, transcripts, checks, canceled checks, bank statements, ledgers, books, records or statements of accounts and papers and things similar to any of the foregoing, however denominated." You got that. Not you, personally; Dr. McClellan.

Here is the answer. This is from Mr. Patrick McGarey who is in the Office of Legislation for the FDA. It was sent on Monday, May 3 to Anne Henig who is a CDER employee who is responsible for coordinating the response to this letter. And there were blind copies sent to Karen Meister who is also in Legislative Affairs at FDA, Donna Katz and Kim Dettelbach who are in the Legal Counsel's Office at FDA. And I am quoting verbatim from this email. "Here

is my draft of instructions to the CDER employees who have to search for documents for question 8: Provide copies of all records that, one, raise a question or concern about the safety or efficacy of antidepressants in the pediatric or adolescent populations. Be sure to forward only records that raise safety or efficacy in the body of the record. Please do not—please do not—include draft documents, notes, memos to self or file or incoming communications from non-FDA individuals, i.e., the public, business organizations, other HHS ops divisions unless an FDA employee has forwarded such communications to others with additional questions or concerns. Finally, Anne, there are different timeframes for the two employees. For Dr. Avagan, we need to search back to January 1, 2002; For Dr. Knudsen, they do not place a timeframe on the documents, so we need to search back as far as possible. Patrick McGarey, FDA Office of Legislation."

Now, I take this as a direct contradiction to what we were asking for. How do you take it?

Ms. WOODCOCK. I was not directly involved in this document search.

Chairman BARTON. I am not saying that you were.

Ms. WOODCOCK. My understanding is that, No. 1, that the subcommittee has the documents, all the documents, that have been requested.

Chairman BARTON. That is not a true statement.

Ms. WOODCOCK. And my other understanding is that there is a prioritization of what would be provided to the committee, because this was a very massive document request, and therefore those sets of documents that were mentioned in the email were the first types of documents that were produced.

Chairman BARTON. Well, I appreciate that answer, but it is nonresponsive. Now, I want this subcommittee to be able to conduct a full and fair investigation. That is not possible if we don't get the documents and we don't get true cooperation. Now I know that you are not the acting Commissioner. You are a Deputy Commissioner in charge of Operations, and you are here primarily to testify about the subject of disclosure of these clinical trials, but you are the senior ranking FDA person here. What can you tell me that gives me comfort that we are going to get cooperation? I do not want to have to subpoena records of the FDA. That is not the way this committee is operated under Chairman Dingell, it is not the way it operated under Chairman Bliley nor Chairman Tauzin, but we have got—this is a very important issue, and we have simply got to get the documents that we need to have so that members on both sides of the aisle have access to the proper information. We have never had a problem on either side of the aisle with proprietary information, with disclosure, leaks, things of this sort when we had an agreement with the agency that we are getting the documents from about how to handle those documents. So what do you think we can do to solve this problem?

Ms. WOODCOCK. The FDA will make every effort to cooperate with the committee. We recognize this is a very important investigation. My understanding is we have invited the investigators to come to the FDA and evaluate the records in situ but they have

declined. However, that offer is still open. But we also will cooperate fully in production of documents.

Chairman BARTON. Well, I could give you two or three more instances of information that we have requested that has not been received, and there has been some technical reason why it wasn't received. We didn't ask for it in just the right way or whatever. So I am going to ask—I have got a meeting at 2:30 with former Chairman Dingell. I am going to seek his counsel on this, but we are almost certainly going to ask for a senior principals meeting in the very near future, in my office, and we are going to come up with a protocol that not only is FDA comfortable with but the committee is comfortable with. Would you please take that message back?

Ms. WOODCOCK. Certainly.

Chairman BARTON. On the policy—my time is almost expired, but on the policy issue, do you feel there is any reluctance on behalf of the FDA to disclose negative clinical information—clinical trial information?

Ms. WOODCOCK. No. I believe that we have legal restraints on the amount of information we can disclose and when we can disclose that information. And we must follow the law as far as it pertains to information disclosure. As I said in my testimony, prior to approval of a drug, it is not possible for FDA to disclose information on clinical trials, clinical trial results and so forth until the drug would be approved for that particular indication.

Chairman BARTON. Well, what do you do when you have a situation, as apparently is the case with some of the clinical trials under discussion today, where the trials all appear to be fairly negative, if there is no showing of efficacy and yet some of those drugs are being prescribed off label even though the clinical trial data shows that they are not helpful? What do you do in that situation?

Ms. WOODCOCK. Well, as you probably know, the FDA has been criticized many times for not approving drugs, and in many cases that is because we have access to information about the drugs that would provide an explanation that we are not currently able to disclose. Now, as was said earlier, this has been remedied for pediatric clinical trials that are done under the Best Pharmaceuticals for Children Act provisions, because after submission of the information to the FDA, reviews are automatically disclosable after 180 days. So that gives FDA the permission to make those data available in summary form, and we have been doing that. We have done that with 41 products so far.

Chairman BARTON. My time has expired. I recognize the distinguished ranking member, Mr. Deutsch of Florida for 10 minutes.

Mr. DEUTSCH. Thank you, Mr. Chairman. Dr. Woodcock, I am trying to get to the timeline of reviews and analysis. Is it correct that an initial study completed last year by Dr. Andrew Mosholder at the FDA concluded that the pediatric use of certain antidepressants increased the risk of suicide?

Ms. WOODCOCK. Correct. Not suicide—excuse me for interrupting you—but suicidality; in other words, thoughts about suicide.

Mr. DEUTSCH. And if we explore the safety issue at length at the next hearing, if I wanted to be aware of the facts involved, is it further correct that the FDA wasn't prepared to allow Dr. Mosholder to present his findings to the Advisory Committee?

Ms. WOODCOCK. We presented Dr. Mosholder's analysis to the Advisory Committee. He did not present a recommendation to the Advisory Committee because we were seeking their advice on what to do.

Mr. DEUTSCH. Is it true that after Columbia University finished their study, which was analyzed outside of the Office of Drug Safety, that the results agreed with Dr. Mosholder's finding about the increased risk of suicidal thought in pediatric patients taking antidepressants?

Ms. WOODCOCK. Yes. The analyses were generally in agreement.

Mr. DEUTSCH. Is this going to be followed up on as well as the Advisory Committee meeting?

Ms. WOODCOCK. This will be discussed at an open public Advisory Committee meeting next week where the full analyses will be presented before an extensive panel of experts in pediatrics and depression, and we will seek advice of that committee on further steps.

Mr. DEUTSCH. So just to be clear, FDA aided and abetted the industry in helping to keep the findings of ineffectiveness from the public and in keeping information showing evidence of increased suicide risk hidden from the public through this Advisory Committee process. And if you can, again, I mean try to explain to us these drugs that make the agency believe that keeping the information at this point non-public, what were the policy reasons for that to be?

Ms. WOODCOCK. FDA made all information available that we were legally able to do, and although Dr. Mosholder's particular conclusions about those analyses were not presented to the committee, the full data were presented publicly at that committee meeting, so no information was withheld.

Mr. DEUTSCH. Could you cite a specific statute or regulation that would have prevented you from providing that information to the public?

Ms. WOODCOCK. Well, I am not counsel for the FDA, but this is—we have had numerous discussions of this within the FDA and provisions of freedom of information and provisions of statutes governing confidential commercial information.

Mr. DEUTSCH. Is counsel with you today who can present to us any specific——

Ms. WOODCOCK. We can get back to you on that.

Mr. DEUTSCH. Your testimony touches upon the subject of pediatric exclusivity. On average, how many proposed pediatric study requests has the FDA received?

Ms. WOODCOCK. We send them out. We send out written requests, and, I am sorry, I don't have that. We can provide—it has been hundreds, and we can provide the exact numbers to you.

Mr. DEUTSCH. So there is a difference between the proposed request and written request; is that accurate?

Ms. WOODCOCK. Under the Best Pharmaceuticals for Children's Act, FDA has a responsibility to request of a company that they perform these studies, whether or not they have sent a proposal in or not. And it is that request that governs the process.

Mr. DEUTSCH. And, specifically, how many labeling changes have occurred? Would you——

Ms. WOODCOCK. I don't know how many labeling changes.

Mr. DEUTSCH. Could you give us a relative sense between the number of requests, the number of studies and the labeling changes?

Ms. WOODCOCK. I don't have that information at my fingertips, I am sorry.

Mr. DEUTSCH. Okay. Our staff actually has some numbers that actually points out that, at least according to our staff, the numbers are 71 labeling changes based upon 678 requests, and I think that really highlights the statement that I made in my opening statement. There have been 678 requests for pediatric studies. I am not aware of exactly how many studies have been made, but, as you have said, in the hundreds, but only 71 actual labeling changes, which would clearly indicate that in many cases the studies are made without any operational changes, at least on the label. Is there any request that the FDA get the companies to change the labels on more of the drugs after the pediatric studies have been made?

Ms. WOODCOCK. We certainly make every attempt to get any relevant information that has been obtained from those studies into the label. Some of the studies that you referred to are still ongoing and therefore the information will not be available to go into the label or to be submitted to FDA. In other cases, and the pediatric depression example is a good one, where the studies are negative or inconclusive, there is currently no provision that that information would be in the label.

Mr. DEUTSCH. Now, it seems—again, it goes back to maybe the whole point of the pediatric exclusivity statute that if the point is—and, again, I raise it again because we are not talking about a small amount of money. On the antidepressant side, the amount that effectively taxpayers in this country have paid is close to $4 billion on the six drugs that are the topics of this hearing, yet in terms of actual benefit to consumers, without the information, where is that benefit shown? I guess, really, I pose that as a question. I mean this whole issue, which we raised previously, about without putting it on the labels, without making it a use, either negative or positive, saying that it has efficacy or doesn't have efficacy, where is the value? Where is the ultimate value?

And then could you respond to the amendment that was offered in committee by Mr. Stupak that I referred to earlier? Would you support that type of change that the exclusivity provision not be granted until—I mean that would be one way—you mentioned how you try to, I guess, jawbone the companies to change the labeling. Well, I can tell you that if that was a requirement for the increased exclusivity, you wouldn't have to jawbone. So maybe that is something that we should be looking at at this point in time. I mean could you respond specifically to that proposal?

Ms. WOODCOCK. Yes. Well, to step back, you asked what value for the BPCA in this situation. I think we need to take the big picture into account and remember without the provisions of this act, none of these studies would have been done probably, and we may not have had this information about side effects that the committee is now investigating. So more information, more studies about use of drugs in children, because they are being used already now, this

is very desirable and we will eventually buildup a knowledge base that will help us decide what drugs should be used in pediatric diseases. And this is a very positive step.

On the other hand, this issue of disclosure is something that has been identified, I think, as this program has unfolded, as we have done written requests, as studies have been done and we have gotten new information that we are discussing here today.

As far as amendments, I think we have to balance the issue of timeliness of information. I believe that the summary, the 180-day release of information by the FDA of review summaries is timely, and so many of these drugs that we are discussing today did not have the written requests done under the Best Pharmaceuticals for Children Act. They were done under the FDAMA provisions, which did not have a disclosure piece to it. So for further pediatric studies that are done under written request, we will have prompt disclosure at 180 days. But it is true, that is not the same as having information in the label.

Mr. DEUTSCH. All right. Thank you. My time has expired.

Mr. WALDEN [presiding]. Okay. Doctor, could you please turn to tab 41? This is a "Dear Health Care" letter dated August 22, 2003. It is tab 41, that Wyeth decided to send out the positions along with a labeling change that included a strong warning about hostility and suicide related events occurring in pediatric patients and recommending the product not be used in kids under the age of 18. The language was included in the section of the label called, "precautions-usage in children." FDA did not require that Wyeth put this stronger labeling on Effexor back in 2003, correct? The FDA didn't require them to do that?

Ms. WOODCOCK. Correct.

Mr. WALDEN. On March 19 of this year, the FDA issued letters to the antidepressant companies requesting a labeling change. It is my understanding this labeling change was not directed just at the pediatric population but was to, "kids and adults," correct?

Ms. WOODCOCK. That is correct.

Mr. WALDEN. So the FDA's warning would not appear under the pediatric use section, correct?

Ms. WOODCOCK. Right.

Mr. WALDEN. Now, if you would turn to tab 40. This is a letter sent from Russell Katz, the Director of the Neuropharm division to Wyeth, and it states, and I quote, "We note your agreement to our request," emphasis added, "to remove your proposed addition of hostility and suicide related adverse events from the precautions usage in children section." And then the letter goes on to say, "We continue to feel that it would not be helpful to include the language regarding reports of hostility and suicidality that you have proposed for the pediatric use sections." Why would FDA request that a company remove stronger labeling, that is labeling that would be more informative to parents and doctors about the risks that may be associated with children taking this drug?

Ms. WOODCOCK. The FDA attempts to make the language in the label factual and based on the scientific data that is available, and that includes not going beyond the data that are available scientifically on which those statements may be based. The FDA had developed a statement to be put in all drugs of this class, a very

prominent statement, a warning about development of some of these psychiatric side effects and potential association with these agents and was requesting that that be put in labels of all the drugs, and that has been done.

Mr. WALDEN. Is it FDA's position that if a company's own internal analysis of, for example, suicide-related events turns up a signal the company thinks practitioners and the public should be aware of, that they are prohibited from doing so because the FDA has found no causal connection?

Ms. WOODCOCK. I don't believe that we require causal connection. The FDA tries to make sure that labels are factual and based on the scientific data.

Mr. WALDEN. Well, under tab 40 in the letter from Dr. Katz, in part, down toward the bottom, it says, "As currently written, the language is uninterpretable since it notes there were increased reports but without noting with reference to what data. If a reference to placebo data were added, this would suggest a causal association. However, this suggestion would be contradicted by the new language that follows." I guess the question is it seems to me as a parent that if a company, Wyeth, sends out a letter to 400,000 or so health care professionals saying, "We think you need to be aware, alert to signs of suicidal ideation in children and adolescent patients prescribed Effexor or Effexor XR. You may need to reassess risk/benefit balance when treating individual patients with Effexor or Effexor XR." FDA would want to encourage a company to do this sort of thing, and you would want that sort of added to the label, especially is a company wanted it added. I mean we have heard a lot about companies maybe going the other direction. Here you have got one saying, "Warning, there may be suicidal and hostility increases." Wouldn't you want that on the label?

Ms. WOODCOCK. We want balanced information that really reflects what is known scientifically about the drug.

Mr. WALDEN. So you think what Wyeth found isn't based on science?

Ms. WOODCOCK. That is what we are talking about over the next week at our Advisory Committee. We will be discussing how much we know about the science right now of psychiatric adverse events in patients treated with SSRIs.

Mr. WALDEN. Their letter, I would just suggest, came out August 22, 2003. In fact, 12 of the 15 clinical trials for depressed kids showed no efficacy, according to the FDA, correct?

Ms. WOODCOCK. The other trials did not meet FDA standards for showing effectiveness. Some of them were completely negative; others did not reach statistical significance.

Mr. WALDEN. Is that a yes then?

Ms. WOODCOCK. That means they didn't meet FDA standards for——

Mr. WALDEN. Efficacy.

Ms. WOODCOCK. [continuing] approval, for efficacy, that is correct.

Mr. WALDEN. For approval for efficacy, correct? Why doesn't FDA mandate that the labeling for pediatric use state that clinical trials were done in depressed children and adolescents and they did not show efficacy?

Ms. WOODCOCK. Again, we are discussing how to relay this information. In general, the labels are only able right now to discuss approved indications, and this is not an approved indication.

Mr. WALDEN. So if a drug were going to do something really bad to somebody or do nothing at all, you don't think that needs to be defined in the label?

Ms. WOODCOCK. I am not saying what I think; I am saying the way the law is structured. We can add side effects even if they are seen for off-label uses, but we are not able to compel companies to put extensive information on negative trials within the labels.

Mr. WALDEN. Can you cite the legal barrier to that?

Ms. WOODCOCK. The law and the regulations. We can provide you that information.

Mr. WALDEN. Provide me that.

Ms. WOODCOCK. We would be glad to do that.

Mr. WALDEN. I just find that amazing. We are talking, what is it, 10 million kids taking these drugs, being prescribed off label, and you have got companies, some of them saying, "We think, by the way, Mr. and Mrs. Physician, look for hostility and suicidal." You have got internal studies that say suicide is maybe up 1.89 percent on Mosholder and Columbia says, I think, 1.78 times, right?

Ms. WOODCOCK. Suicidality, yes.

Mr. WALDEN. Okay. We have been told by various pharmaceutical companies that conducted these antidepressant pediatric trials they proposed labeling changes stating that their clinical trials did not show efficacy in depressed kids and that FDA told them they did not want that, the fact of the failed trials to be mentioned in the labeling. Can you explain why that is? Is this again the law in the rules?

Ms. WOODCOCK. I am sorry, I don't have knowledge of that exchange.

Mr. WALDEN. Why would FDA prevent a company from disclosing the fact that clinical trials performed failed to show efficacy?

Ms. WOODCOCK. As I said, I can't explain that particular statement by the companies. I am not familiar with that.

Mr. WALDEN. Has FDA ever told a company not to disclose the fact that clinical trials were performed and failed to show efficacy?

Ms. WOODCOCK. I don't know that.

Mr. WALDEN. Who is in charge that would know that?

Ms. WOODCOCK. We can also get back to you on that question.

Mr. WALDEN. Aren't you head of this division?

Ms. WOODCOCK. I am normally head of the Center for Drugs at the FDA, which regulates drugs.

Mr. WALDEN. And you do labeling.

Ms. WOODCOCK. That is correct.

Mr. WALDEN. And you can't tell me why the center that you head would prevent a company from putting on the label the fact that trials show no efficacy?

Ms. WOODCOCK. You asked me if it has ever happened, and I do not know. I don't have factual knowledge of that. Certainly, I wouldn't feel that companies should be prevented from disclosing

information, as I said at the beginning of my testimony, but I can't assure you that it never happened.

Mr. WALDEN. But does that include disclosing clinical trials that show no efficacy?

Ms. WOODCOCK. Correct.

Mr. WALDEN. They should not be precluded from disclosing that on a label. I mean shouldn't—I mean I don't know, I am not a doctor, but it seems to me that if you have got companies doing trials and 12 of the 15 trials show no efficacy in kids and you have got data that show that potential higher suicide rates and hostility, you would want that information out there.

Ms. WOODCOCK. Well, there is a distinction here. We cannot compel companies. That is the law and the regulations I was talking about. We can't compel companies to reveal this information.

Mr. WALDEN. But some of them have asked you for the ability to release that information and you have said no.

Ms. WOODCOCK. I don't have information on that.

Mr. WALDEN. Well, this is the hearing on disclosure and we had sort of hoped you would be prepared to address that. Who can answer this?

Ms. WOODCOCK. We have to go ask all the divisions, and we can do that and get back to you on that, that specific question.

Mr. WALDEN. Yes. We are going to have a hearing on the 23rd.

Ms. WOODCOCK. Right.

Mr. WALDEN. Fill the room with the people that can answer our questions.

Ms. WOODCOCK. Certainly.

Mr. WALDEN. My time has expired. I now turn to Mr. Waxman for his opportunity for questions.

Mr. WAXMAN. Thank you, Mr. Chairman. I find it hard to believe a company would like to put on the label some statement that they have a study that shows their drug may not be effective for children. Now, you are going to try to give us an answer to whether the company asked you to do that and was turned down. I suppose we could find out from the companies if they have made that request and turned down. We could find out from them what their thinking was.

Let me review the situation because it gets to be complicated. Manufacturer produces a drug, they do all the studies, they go into the FDA with their data and they have to show that they are safe and effective and they establish this through clinical trials. You review it, FDA, the data, and decide whether in fact the drug is safe and effective for a clinical purpose; is that right?

Ms. WOODCOCK. Correct, for an intended use or uses.

Mr. WAXMAN. For intended use. Now, once that drug is approved for that intended use, it can be prescribed for anything.

Ms. WOODCOCK. That is correct.

Mr. WAXMAN. That is what we refer to when we say off-label use. They don't have to go to FDA to prove that they are effective for that other use; they just have to have a doctor willing to prescribe the drug for that different use; is that correct?

Ms. WOODCOCK. Yes. And as you know, manufacturers are not permitted to promote any off-label use to physicians or others.

Mr. WAXMAN. But others can promote it on their behalf.

Ms. WOODCOCK. That is correct.

Mr. WAXMAN. And many drugs are prescribed by physicians without FDA having reviewed whether there is an effective for that other additional use; is that correct?

Ms. WOODCOCK. Yes. And that was one of the impetuses for the Best Pharmaceuticals for Children Act, as you know, because much therapy in children was off-label because drugs had not been studied in the pediatric populations.

Mr. WAXMAN. So we wanted—we meaning you and the medical world and the Congress—to give an incentive for the companies to do the studies for pediatric use of some of the drugs that are already being used for adults. If they came in and wanted to get an approval on the label for use with their drug for children, they would have to establish the validity of their statement, wouldn't they?

Ms. WOODCOCK. Yes.

Mr. WAXMAN. That would mean they would have to prove the effectiveness.

Ms. WOODCOCK. That is correct.

Mr. WAXMAN. But they still can sell it to kids even without getting your approval.

Ms. WOODCOCK. Right. As I said, they cannot promote it or cause others to promote it, but often these uses are taken up in the medical community because there are many diseases that lack adequate treatment. For example, pediatricians were not able to simply ignore children and not treat them when no good data were available on what drugs they should use.

Mr. WAXMAN. So the solution to this problem was, in effect, to bribe the pharmaceutical companies by saying, "Look, if at least you do the studies, we are going to give you 6 months more of a monopoly over your drug for everybody you sell it to." And for the most part, their drug could be sold to adults. It could be a very high-selling drug for adults; is that right?

Ms. WOODCOCK. Yes.

Mr. WAXMAN. Okay. But once we give them the additional monopoly time, we don't require them to come in and ask for a change in their label as it relates to the use of the drug for children.

Ms. WOODCOCK. What is required under the statute, the Best Pharmaceuticals for Children Act, is that the company submits studies that are responsive to the written request.

Mr. WAXMAN. Right. And the studies could show that the drug is positive and effective, it could show that it is not effective, the studies can show that they are inconclusive.

Ms. WOODCOCK. Correct.

Mr. WAXMAN. And unless it is a study that shows it is effective, they are not going to come in and ask for a label change, presumably.

Ms. WOODCOCK. Right.

Mr. WAXMAN. Now, I have been told that in some of these antidepressant trials that were not made public were inconclusive and that the FDA believed that those trials produced no useful information to be added to the label; is that correct?

Ms. WOODCOCK. That is correct. I can expand on that if you would like.

Mr. WAXMAN. Well, maybe we will come back to it, but I wanted to follow through on this. It is hard for me to see why a company would work hard to get conclusive results if they are rewarded for inconclusive results. They are going to get that 6-month monopoly. Why do all the extra tests to show some conclusive result when all they have to do is do a study even if it is inconclusive and they automatically get this 6-month monopoly?

Now, FDA may decide that one or two studies submitted in exchange for exclusivity are too inconclusive to put in the drug's label from the FDA's perspective. We just don't know if the drug works or not. Let me go back on this point. Under this law that gives them this reward for doing the studies, as it was revised, now called the Best Pharmaceuticals for Children's Act, you have the right to put out the studies that were inconclusive or even showed that it was not effective after 180 days; is that right?

Ms. WOODCOCK. That is correct, and we do that.

Mr. WAXMAN. And you do that. But that has only been recent.

Ms. WOODCOCK. Since 2002.

Mr. WAXMAN. And the antidepressant trials the information was not put out about the children's use of a lot of these antidepressants. I think that there were two studies that were made public, and then when there has been a lot of press attention, congressional concern, then you put out five more 3 weeks ago. Why weren't they all put out at the same time?

Ms. WOODCOCK. The original approval for an SSRI for pediatrics was of Prozac, and the data were made available at the time of approval. As I said earlier, that is our standard practice. One of the drugs, Effexor, I believe, was actually under the Best Pharmaceuticals for Children Act provisions, and therefore the 180-day posting kicked in and we were able to make those data available, the summaries available under the Best Pharmaceuticals for Children Act provisions.

Mr. WAXMAN. By the way, you only put out the summaries of the clinical trials; is that correct?

Ms. WOODCOCK. What we actually post is FDA's reviews, which are fairly detailed summary reviews of the safety and efficacy data. So that would go over the different studies that were done and discuss their results, but it wouldn't go into excruciating detail.

Mr. WAXMAN. Okay. Now, a doctor wants to find out more information about this drug, and they want to find out whether it is really a good idea to use it for the children but as the antidepressant cases illustrated all too well, physicians may be given a very different picture of the drug's effectiveness by the drug companies. In the case of both Paxil and Zoloft, the manufacturers had actually taken studies that FDA viewed as negative and published them as if they showed that these two drugs were effective in kids. Now, that raises a very serious problem. Do you think that the medical community is well served by allowing drug companies to cherry pick and even distort which data are made public and which are not?

Ms. WOODCOCK. As I said in my oral testimony, I believe that results of clinical trials should be made available to the medical community and to patients.

Mr. WAXMAN. When manufacturers choose to publish only the positive studies and to withhold the negative studies or, worse, to portray negative studies as if they were positive and FDA knows about the missing or distorted data, does FDA have any responsibility to the medical community?

Ms. WOODCOCK. We have long tried to deal with this issue. The differing interpretation of clinical trial results is by no means confined to the pediatric depression area, and this is a conundrum for the agency because it is often difficult for us to explain our actions to the public when we are constrained from revealing the data upon which our opinion is based.

Mr. WAXMAN. Well, that is really a very important point because when we talk about pediatric uses of drugs, you have the ability to release some of the data, at least a summary of it, but when we are talking about off-label uses for anybody other than a pediatric study, that information may never even get out to the public because you are restrained because of the proprietary nature of this. Shouldn't there be some mechanism for making the totality of the data on drugs available to the medical community, if only so that the expert groups making recommendations to physicians about how to use drugs have access to the full picture rather than only to the data the drug companies want them to have?

Ms. WOODCOCK. We recognize that there have been a number of good ideas circulating about this, and we look forward to participating in any thought process there would be about this issue.

Mr. WAXMAN. I know it is complicated and it is difficult, but don't you think there ought to be some way for the medical community to get this information? I know we have to work it out in detail, but the concept of withholding the information from them, having them set up to be in a position where the drug companies can misrepresent the situation to them and they have no other recourse to further information, that just seems to me absolutely wrong. So don't you think we need some mechanism to get the whole story out, all the tests out?

Ms. WOODCOCK. I think, as I said, the entire biomedical research community believes that information is needed, especially around effectiveness and safety trials so that physicians and patients can reach conclusions. I don't think there is a lot of disagreement about that.

Mr. WAXMAN. Well, we don't have the ability to do it yet, and so we have go to work together to establish that mechanism.

Mr. WALDEN. Thank you. The Chair now recognizes the gentleman from New Hampshire.

Mr. BASS. Thank you, Mr. Chairman. If I could continue the line of questioning of my friend from California. Could you repeat again for me, Dr. Woodcock, why isn't it a good idea for the FDA to compel or to have in place full disclosure of the entire clinical trials for these drugs before doctors have to make decisions with respect to whether they are going to prescribe them for children?

Ms. WOODCOCK. Under the Best Pharmaceuticals for Children Act, there is disclosure of this information.

Mr. BASS. But it is just a summary, right? How about the whole thing?

Ms. WOODCOCK. That isn't how the statute was set up.

Mr. BASS. But can't you ask the drug companies to do it?

Ms. WOODCOCK. My understanding is that under some of the announcements that have been made, a more expansive disclosure is going to be made voluntarily by some of the firms.

Mr. BASS. But can't you ask them to do it? They don't have to volunteer; you can ask them to do it, can you not?

Ms. WOODCOCK. Certainly.

Mr. BASS. Under law. Have you done that?

Ms. WOODCOCK. Oh, under law, no.

Mr. BASS. You haven't done it.

Ms. WOODCOCK. We can't compel——

Mr. BASS. Can you ask their permission to disclose the full clinical trial?

Ms. WOODCOCK. We ask their permission to disclose the summary information that would be the same as under BPCA.

Mr. BASS. But those are the results. What about the full trial?

Ms. WOODCOCK. No, we haven't disclosed that.

Mr. BASS. You haven't asked their permission to disclose it.

Ms. WOODCOCK. Right. That would be usually the obligation of the sponsor of the trial themselves.

Mr. BASS. Why is it the obligation of the sponsor of the trial and not—why can't you ask them?

Ms. WOODCOCK. We can ask them but we can't disclose their data.

Mr. BASS. No, but why haven't you asked them to disclose all that data? You don't think it matters?

Ms. WOODCOCK. I have personally talked to the members of the pharmaceutical industry and they are planning, as you know, to set up disclosure results of all clinical trials, but——

Mr. BASS. Just the results but not the clinical trials themselves. Just the seven-page results?

Ms. WOODCOCK. Yes. This would be extensive——

Mr. BASS. Do you think that the whole trial ought to be disclosed?

Ms. WOODCOCK. It is often very useful to see the protocol for somebody who is experienced in analysis of clinical trials to make sure that the analytic piece was done the same way it was prospectively laid out in the protocol; in other words, to make sure that there wasn't a post hoc modification of interpretation of the results. So I think a lot of experts in this area feel that looking at the clinical protocol is also are very important piece. However, you must recognize that what is submitted to the FDA in a new drug application is often 1,000 volumes long of raw data and there are very few individuals who are capable of going through all that at that level. So if you are talking about patients and physicians, we are talking about summary data.

Mr. BASS. Dr. Woodcock, in the third paragraph of your written testimony you state that public availability of the results, "is especially important for studies of marketed products, surgical inventions and other medical treatments where a bias toward publication or positive results may distort the community's overall understanding of an intervention's effectiveness or risk profile." In other words, are you saying that there may be a bias problem because medical journals tend to publish the positive results, the drug

works, but rarely the negative results that the drug doesn't work, and therefore the public may get a distorted understanding on the effectiveness of a medical product because the positive results are out there but very little of the negative?

Ms. WOODCOCK. You are absolutely right, and this has been well recognized in the medical community as a problem. It is not only pharmaceutical research, it is all sorts of research, and it is also that the journals are biased toward publishing good news.

Mr. BASS. So you get all the information for the positive trials and all you get is the summaries for the negative trials. Is that right or not?

Ms. WOODCOCK. No. What FDA publishes as summary data is an analysis of the trial. So you get FDA—who has reviewed all of the data—you get FDA's review opinion on what those trials showed in the summaries that FDA publishes. A report in a clinical journal may be subject to bias, all right, and that is what Mr. Waxman was alluding to earlier. And it is also a summary of the information. It doesn't include all——

Mr. BASS. All right. In your opinion, how do we get comparable disclosure then of negative and positive information? We are the policymakers here. We are trying to correct a problem——

Ms. WOODCOCK. Yes.

Mr. BASS. [continuing] and we are asking you to help us with this. Now, what would you do?

Ms. WOODCOCK. Well, I think you have already make great progress because there is a tremendous ground swell now of availability of information based on what the committee has accomplished already. But it is clear that the results of trials should be made available to the public in some form.

Mr. BASS. Just the results, though. We are back where we were before, but not the actual clinical trial.

Ms. WOODCOCK. Well, you have to decide what you are talking about. As I said, the raw data from a clinical trial, if you print it out, can run to hundreds or thousands of volumes.

Mr. BASS. Okay. Assuming that you agree with me that there may be on occasion a bias in publications information, what is the FDA's role in combating this bias?

Ms. WOODCOCK. The FDA's role has traditionally been the gatekeeper for approval, and so we get all the data and we are able to look at all the data. Although we cannot disclose this information, we look at it, and so we see all the negative trials and we see the positive trials. We don't approve drugs unless we think they are shown to be effective, that meets our effectiveness standards and that their benefit outweighs the risk because there is always going to be risk from drugs. That is the role we play.

Mr. BASS. Dr. Woodcock, do you believe such a problem existed in the area of antidepressant use in children? Is that the reason the FDA sought to publish the summaries of clinical trials even for studies not covered under the requirement that FDA publish the summaries of the results?

Ms. WOODCOCK. Clearly, yes. This is, as other members have said, is vital information in determining benefit and risk analysis.

Mr. BASS. So it is more than just evaluating the information in this case. You had reason to believe that you needed to get more information out.

Ms. WOODCOCK. As you know, these drugs are widely used in the pediatric population.

Mr. BASS. I am going to talk for a minute about the Columbia study. FDA asked Columbia University to conduct a blinded interview of reported behaviors associated with the pediatric use of antidepressants using a rigorous classification system. Was Columbia University given a sole source contract, and if so, why?

Ms. WOODCOCK. I read over that material. I believe they were, and, if so, it would be—I can't tell why that would be. Probably because they had experts in suicidality, specific expertise.

Mr. BASS. Has the FDA ever before used a sole source contract for an outside use of drug data?

Ms. WOODCOCK. I believe so.

Mr. BASS. Can you give us some citations for that?

Ms. WOODCOCK. I could get back to you with that. That is kind of specific information going back many years. I know we have previously contracted for reviews by outside parties. We have done that.

Mr. BASS. Sole source?

Ms. WOODCOCK. I don't know how we did it.

Mr. BASS. Okay. Well, if you could answer that question, that would be helpful.

Ms. WOODCOCK. I certainly will.

Mr. BASS. Was this contract reviewed by any government oversight board to assure that this contract was a good deal for the government? You wouldn't know because—I guess the answer is you wouldn't know, right?

Ms. WOODCOCK. Well, I know that it went through standard procedures if it was an FDA contract.

Mr. BASS. What are the procedures?

Ms. WOODCOCK. There is a separate contracts office that makes sure the applicable regulations——

Mr. BASS. Do they check for conflicts of interest?

Ms. WOODCOCK. I can get back to you on exactly what was done.

Mr. BASS. Does the FDA concede that some members of the Columbia University have financial relationships with some of the drug companies that manufacture antidepressants?

Ms. WOODCOCK. I can't specifically answer that. We can certainly look at that.

Mr. BASS. Okay. If there were, it would be a pretty serious issue, wouldn't it?

Ms. WOODCOCK. I think it depends on the magnitude of that relationship. Most experts in the field, in every field, be it HIV, cancer, depression, suicidality, have been consulted by members of the pharmaceutical industry or other medical product industries.

Mr. BASS. Is there, in your opinion, any process for evaluating whether or not a conflict of interest is serious or not?

Ms. WOODCOCK. We have an extensive process for our Advisory Committee members. They must undergo this vetting at every Advisory Committee meeting on the specific topics that are being aired at that meeting, and we also have disclosure procedures.

Mr. WALDEN. I want to thank the gentleman from New Hampshire, his time has expired, and the Chair would recognize the gentlewoman from Colorado.

Ms. DEGETTE. Thank you, Mr. Chairman. Dr. Woodcock, as I understand it, there is one drug that is specifically approved by the FDA for use in pediatric depression and that is Prozac, correct?

Ms. WOODCOCK. That is correct.

Ms. DEGETTE. And I understand that there are some—I am a little confused about the number but somewhere up to 10 million people who are being prescribed some kind of antidepressant off-label. Do you have any idea how many of the 10 million are being prescribed off-label?

Ms. WOODCOCK. No.

Ms. DEGETTE. It is a substantial number, would you agree with that?

Ms. WOODCOCK. I would agree that much of the pediatric use of antidepressants is currently off-label.

Ms. DEGETTE. Right. That is millions of people, right?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. Does that concern the FDA that there is all this off-label use?

Ms. WOODCOCK. It has always concerned the FDA, and that is why FDA passed the pediatric regulation back in the nineties that led to the provision in the Modernization Act, which led to the Best Pharmaceuticals Act.

Ms. DEGETTE. I was just going to say that is one of the reasons why Congress passed the Best Pharmaceuticals for Children Act, right?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. But that was 2 years ago, and it seems like the practices we are all concerned about have not changed, at least with respect to prescriptions for depressions for pediatric patients, right?

Ms. WOODCOCK. What happened is those trials were done under either the pediatric regulations or the FDAMA that didn't have disclosure requirements. That has been remedied to some extent under the Best Pharmaceuticals for Children Act.

Ms. DEGETTE. Well, is there a provision of BPCA that says that you can't disclose the results of trials that were done before the bill was passed?

Ms. WOODCOCK. We were following the law to——

Ms. DEGETTE. Well, what law was it that said that?

Ms. WOODCOCK. The Best Pharmaceuticals for Children Act had provisions for disclosure for studies, written requests done under the Best Pharmaceuticals for Children Act.

Ms. DEGETTE. So your interpretation is then that you had no authority to even request disclosure of studies done before that?

Ms. WOODCOCK. I am not an FDA lawyer; however, we evaluated this issue and we attempted to follow the provisions of the law.

Ms. DEGETTE. Well, so what is that answer?

Ms. WOODCOCK. We think that is what the law said.

Ms. DEGETTE. So you think the law says you cannot require the results of these clinical trials that occurred before 2002?

Ms. WOODCOCK. That is right.

Ms. DEGETTE. Did you ever talk to the pharmaceutical companies about whether they would voluntarily disclose this?

Ms. WOODCOCK. Recently, we certainly did when they disclosed——

Ms. DEGETTE. After we started these investigations——

Ms. WOODCOCK. Correct.

Ms. DEGETTE. [continuing] of this committee. Did it occur to anybody to do that before?

Ms. WOODCOCK. I do not know.

Ms. DEGETTE. Because most of these drugs have been approved for a long time for adult usage, right?

Ms. WOODCOCK. Correct.

Ms. DEGETTE. So the clinical trials wouldn't have happened before 2002 because they are not new drugs, right?

Ms. WOODCOCK. The clinical trials were maybe started under the pediatric rule that FDA passed or under the Food and Drug Modernization Act.

Ms. DEGETTE. Well, I understand that, but given the fact that there is so much off-label prescribing going on, there is absolutely no incentive for the pharmaceutical companies to now start conducting new studies, right? I mean there is absolutely no reason why someone would do a clinical trial right now on an established drug that is being prescribed with abandon off-label.

Ms. WOODCOCK. Well, there are the exclusivity provisions.

Ms. DEGETTE. Good point. Now, I would like to know why the FDA waited 6 months to send the letter to the drug sponsors, the written requests that were sent in July 2002? Why did it take so long to send that letter out after the BPCA was passed?

Ms. WOODCOCK. There were many technical issues on implementation of the BPCA that the FDA addressed, and we got that out as soon as we could.

Ms. DEGETTE. Now, I wonder if you can tell me how the FDA considered the studies for Paxil, Celexa and Serzone to have been submitted under FDAMA and did not consider their written requests to be reissued and did not apply the public disclosure provisions of the Best Pharmaceuticals for Children Act to those studies, but the only reason the FDA made such a determination is because of the 6 months that the agency let pass before issuing their letter to the drug sponsors; is that right?

Ms. WOODCOCK. That is the legal interpretation that was made, correct.

Ms. DEGETTE. Okay. Now, you said that after having examined the initial reports of suicidality, the FDA found it unclear whether some of the identified suicidal behaviors reported in those studies represented actual suicide attempts or self-injurious behavior that was not suicide behavior, right?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. Now, was not Dr. Andrew Mosholder the person chosen by both the Office of Drug Safety and Neuropharm to do the FDA analysis?

Ms. WOODCOCK. Correct.

Ms. DEGETTE. Now, was it unclear to Dr. Mosholder what a suicide attempt or self-injurious behavior was, do you know?

Ms. WOODCOCK. Well, I think you need talk to Dr. Mosholder about that specifically.

Ms. DEGETTE. Okay. Now, was it unclear, do you know—did you look at the conclusion of the British reviewers who came to the conclusion that antidepressants should not be prescribed to pediatric patients?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. And what was the view of the agency on that?

Ms. WOODCOCK. The agency's view is that the jury is still out on these drugs. Depression, as you know, is—suicide is a very serious problem for adolescents in the United States. It is third leading cause of death and only ranked above by accidents and homicides in this country. Much of the underlying cause of suicide in adolescents is depression, and, as you said, there is only one current drug approved for the treatment of depression in this age group in this country.

Ms. DEGETTE. Right. But this is why—I completely agree with you, so I would think that rather than waiting till the attorney general of New York undertook an investigation and Congress undertook an investigation to act on this, there are millions of parents out there, as I said in my opening statement, these parents are frantic. Their children are depressed, and they are under the illusion that these drugs will work.

Ms. WOODCOCK. Right.

Ms. DEGETTE. And not only do the drugs have no known efficacy under the clinical trials that have been undertaken, but what is worse there is some evidence that they may increase suicidal tendencies, right?

Ms. WOODCOCK. Correct.

Ms. DEGETTE. I mean this may be the biggest problem we have right now with respect to adolescent health vis-a-vis pharmaceuticals, right?

Ms. WOODCOCK. Possibly.

Ms. DEGETTE. What do you think we can do to clarify what you believe to be the deficiencies in the law that would allow you to require full disclosure of all of these trials?

Ms. WOODCOCK. We would be glad, as I said, to work with the Congress on this issue.

Ms. DEGETTE. Do you have any specific ideas?

Ms. WOODCOCK. Well, I think we need to balance a number of things, and I do believe it is a complex issue, but I think we would be very willing to work with you on it.

Ms. DEGETTE. So you don't have any—do you have any specific—I mean would you like to supplement your testimony with any specific ideas?

Ms. WOODCOCK. We would be happy to work with you on our thoughts.

Ms. DEGETTE. Well, we may have some thoughts of our own based on these hearings. I just have one more question. I am sure you are aware of the settlement between the New York Attorney General Spitzer and GlaxoSmithKline as it relates to Paxil, correct?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. And that was August 30, right, of this year. Now, as a part of that settlement, GlaxoSmithKline agreed to put all of the clinical trial results online, right?

Ms. WOODCOCK. That is my understanding.

Ms. DEGETTE. And in fact they did it. Now, have you looked at both the summary and the—have you looked at the posting online?

Ms. WOODCOCK. I have not, personally.

Ms. DEGETTE. Okay. Well, I mean the good news, from my perspective, and I might disagree with some of my colleagues, I actually thought the summary was pretty clear. For example, it says, "GlaxoSmithKline has conducted several trials in pediatric patients," and then it says, "In the GS case studies for treatment of major depressive disorder in pediatric patients, treatment with Paxil was not statistically superior to placebo with respect to efficacy." That is pretty clear, right?

Ms. WOODCOCK. Yes.

Ms. DEGETTE. Certainly, it would be clear to a physician.

Ms. WOODCOCK. Right.

Ms. DEGETTE. Why is it that the FDA can't either require or work with voluntarily the pharmaceutical companies to make sure things like this are posted online?

Ms. WOODCOCK. Well, as I said, we have talked to the pharmaceutical companies. They have announced a plan that, had it been in effect at this time, these studies would have been posted according to their plan and made available.

Ms. DEGETTE. But what? I don't understand, they would have.

Ms. WOODCOCK. Had the proposal that the pharmaceutical industry has now made for revealing trial results such studies as these pediatric depression trials would be made public.

Ms. DEGETTE. And would that all be made public?

Ms. WOODCOCK. Pardon me?

Ms. DEGETTE. Under the proposal by PhRMA, would all of those be made public? I know they will be testifying in a minute.

Ms. WOODCOCK. Yes, because those are drugs that are marketed drugs, and the trials were testing outcomes.

Ms. DEGETTE. And do you think that is sufficient to ensure that Congress and most importantly the parents and physicians of this country know the results of these trials? Is this a voluntary program?

Ms. WOODCOCK. If it is followed through on, those trials would be available.

Ms. DEGETTE. Okay. Thank you.

Mr. WALDEN. Before I go to Mr. Ferguson who has stepped out of the room for a moment, I am going to go Mr. Stupak. Before I do that, I just have to reiterate what the full committee said about cooperation from the FDA and again say I appreciate your statements about your willingness to cooperate, but it is pretty hard to swallow when we have these emails from Mr. McGarey basically outlining to other employees in your agency how not to cooperate with this committee and so things are going to change. Mr. Stupak.

Mr. STUPAK. Thank you. Dr. Woodcock, did the FDA receive notice from the manufacturers that the British had said they should not be using these antidepressants in adolescents?

Ms. WOODCOCK. I believe so, yes. Our reviewers had originally detected the signal in our own review of the clinical trials and had requested additional information, and that was then submitted to the British authorities, and that led to their decision.

Mr. STUPAK. You submitted your information to the British authorities, but you didn't submit it to the American people?

Ms. WOODCOCK. It was submitted then to FDA as well.

Mr. STUPAK. Okay. But my question was did the manufacturers, as required under the Food and Drug and Cosmetic Act, notify you of the action of the British government in pulling these drugs for adolescent use in December of last year?

Ms. WOODCOCK. I can't answer specifically for each manufacturer. We can get back to you on that question.

Mr. STUPAK. Okay.

We have talked a lot about summaries and publishing summaries, not the trials, the clinical trials. Who prepares the summaries?

Ms. WOODCOCK. The FDA medical officers and clinical pharmacologists.

Mr. STUPAK. Okay. So it is something internal then.

Ms. WOODCOCK. That is correct.

Mr. STUPAK. Where does the information gleaned from?

Ms. WOODCOCK. As you know quite well, we receive reports. We are required by law to receive reports of all clinical investigations and all literature at the time a submission is made to FDA for an application, and so we receive that all from the company. We have extensive audit system where we try to verify the validity of all the information that is submitted to the FDA.

Mr. STUPAK. If you go through this audit and try to verify the validity of this information, studies and trials submitted by a manufacturer, then in hindsight now wouldn't it be best to grant a pediatric exclusivity extension after you had a chance to do that, after there are—shouldn't a pediatric exclusivity patent extension only be granted if the drug is proven to be safe, effective and all necessary changes are made on the packaging label? Isn't that what it should be?

Ms. WOODCOCK. Well, I am not one to presume to tell Congress where it should be. There are obviously considerations on either side.

Mr. STUPAK. I am not asking you to tell Congress; I am asking for your opinion.

Ms. WOODCOCK. My opinion is that it is desirable to have information available to the physicians and the public about the results of clinical trials so they can make considered treatment decisions.

Mr. STUPAK. And before you grant the patent extension like we did here and we find these drugs are not effective and in some cases not safe, what the heck are we doing granting extensions to a drug?

Ms. WOODCOCK. That is how these statutory provisions are set up.

Mr. STUPAK. But in hindsight, is that not incorrect? Shouldn't we really change that statute? Isn't that one of the examples you could give to Ms. DeGette of some of the things we should do here in Congress when she asked you?

Ms. WOODCOCK. Again, we would be happy to work with you on this.

Mr. STUPAK. All right. Well, you said that this information should be available for physicians and families and patients. We talked about labeling here today. The labeling we are discussing really goes just to the physicians, does it not?

Ms. WOODCOCK. Yes.

Mr. STUPAK. So all this labeling we have heard for the last couple of hours really never gets to the American people, to the patients and to the families unless it is on package labeling, and package labeling is much different than just what you call labeling; isn't that correct?

Ms. WOODCOCK. Yes, and in fact for many drugs, as you know, if you go to the drug store, you get a bottle prepared by the local pharmacy.

Mr. STUPAK. Sure.

Ms. WOODCOCK. And it has information sheet that the local pharmacy gives you, information for a patient.

Mr. STUPAK. That is really a summary. What the labeling that we have been talking about here for the last few hours really deals with between manufactured notice, as required by the FDA, to the physicians, not to the American people.

Ms. WOODCOCK. That is correct.

Mr. STUPAK. And the only place the American people are really going to find it is on the package because when you go there you may get a little slip that has the price of your drug and gives a quick overview of things on it. You don't get the whole label that the physician has; isn't that correct?

Ms. WOODCOCK. Well, patients may get the label. We certainly get the label at my pharmacy. It is folded up inside the pill bottle. It depends on how the drug is dispensed. But your point is, I think, that that label is written for a professional audience; it is not really accessible to patients and consumers.

Mr. STUPAK. And you would agree with me when the American people take their pills they don't go and unwrap these little things and read it all the way through. They look at the box, they look at the bottle and they say, "Okay. I take this three times a day. I have to take it with food, I don't have to take it with food." That is the labeling the American public relies upon, is it not?

Ms. WOODCOCK. Yes.

Mr. STUPAK. Okay. On these antidepressant behaviors, you have got the British who reached a conclusion that said it was not good for young people, you have the Columbia report which shows it is 1.8 times greater chance of suicidal behavior with these antidepressants, and you have Dr. Mosholder that reached the conclusion that these should not be used for young people because there may be—they are not effective and they are not safe. So you said in your testimony to the other members here that the SRI these studies are inconclusive. How can the British be conclusive, how can Columbia University be conclusive, how can Dr. Mosholder be conclusive but yet the FDA isn't conclusive? So what does it take to get the FDA to be conclusive on this issue?

Ms. WOODCOCK. As I said, the jury is still out on the effectiveness of these drugs. Some of the studies were not conclusive. It is

very common for effective drugs when they are tested in adult depression to show no effect.

Mr. STUPAK. We are not talking about adult depression; we are talking about young people here.

Ms. WOODCOCK. I understand.

Mr. STUPAK. We are talking about adolescents.

Ms. WOODCOCK. I agree.

Mr. STUPAK. Who is the jury? Who is the member of this jury that makes this decision on whether or not this is conclusive and these drugs should be—actions should be taken, either pulled or removed or further warnings? Who is this jury?

Ms. WOODCOCK. The members of the Center for Drugs who are the regulators of this class of drugs are evaluating that issue.

Mr. STUPAK. And when will that jury reach its deliberations?

Ms. WOODCOCK. The FDA is seeking advice from its Advisory Committee, as I said, next week on the question of the interpretation of the adverse events, the psychiatric adverse events and the trials. And questions are posted on the Internet as far as what we are going to be asking the committee about.

Mr. STUPAK. Well, is the Advisory Committee because of the pressure put forth from the Members of Congress and the press? Is that why you are having an Advisory Committee?

Ms. WOODCOCK. No. We are trying to wrestle with this scientific question about the potential benefits and the potential risks of this type of intervention.

Mr. STUPAK. Let me go to the Best Pharmaceuticals Act, okay? Section 17. Since I couldn't get the pediatric exclusivity amendment I wanted, I did a couple other amendments to this bill. No. 1, it says that all adverse events should be reported, and to help people understand how to report it, we have to put in a 1-800 number so people could report adverse events. And it says that is where pediatric drugs or use in pediatric population, regardless of the date of approved, it would include a toll free number maintained by the Secretary. And this was supposed to be done here within, I believe, 1 year of enactment of this law. Has that been done?

Ms. WOODCOCK. I am sorry, I don't know the answer to that question.

Mr. STUPAK. The answer is no. It was December 2001. It is now 2004; still not done. Not only that, we gave you something else. Drugs dealing with pediatric market exclusivity. During 1 year, beginning the date on which the drug receives a period of market exclusivity, you have a right to put together a Pediatric Advisory Subcommittee to review the adverse effects and to look at these drugs for their safety. Has that Pediatric Advisory Subcommittee for any of these antidepressant drugs we have been talking about here today been convened?

Ms. WOODCOCK. Yes. In June 2003, Sertraline adverse events were reported to the Pediatric Advisory Subcommittee as part of this mandate under Best Pharmaceuticals.

Mr. STUPAK. For what drug was that for?

Ms. WOODCOCK. Sertraline.

Mr. STUPAK. What is Sertraline?

Ms. WOODCOCK. It is one of the antidepressants.

Mr. STUPAK. Not Paxil? Not Effexor? Not Prozac? Not any of these, just one of them?

Ms. WOODCOCK. Correct.

Mr. STUPAK. What about the rest of them? How come the Advisory Committee was not put forth for them?

Ms. WOODCOCK. We will be having, I believe, Advisory Committee meetings on these additional products.

Mr. STUPAK. Well, geez, it says here you have to do it within 1 year, so you missed that date too.

Ms. WOODCOCK. Well, we did—the Sertraline one was completed.

Mr. STUPAK. We missed it on the other ones. The point being you are telling Mr. Waxman that you do not have any mechanisms. The mechanisms are built there if they were utilize and if they were used by the FDA. You responded to Mr. Bass that we have made progress with this hearing and all that, but the progress, if you will say because we had this hearing, is not because of anything the FDA did, it is because of pressure from the media and pressure from Congress to do something on this issue. So I go back to my question, where is the FDA in all this? You said you saw these signals, you informed the British and that had to be in 2002, 2003. And the jury is still out. How many years is this jury going to be out? When are we going to have some decisions?

Ms. WOODCOCK. We saw the signals and informed the company and requested additional analyses. We have been trying to look at these data ever since and make some sense out of the data. The information has been made public on the adverse events in suicidality. What wasn't made public was the information on effectiveness of the products.

Mr. STUPAK. Okay. So if the information was made public on suicidality and it shows that these antidepressants increase the likelihood of suicide behavior, then why are these drugs being still used and prescribed for young people?

Ms. WOODCOCK. Because when faced with a depressed young person who has perhaps a life-threatening illness, there are not that many choices available to clinicians.

Mr. WALDEN. The gentleman's time has expired. I appreciate the gentleman's line of questioning. The Chair now recognizes the gentleman from New Jersey, Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman. I appreciate the opportunity, and I appreciate Dr. Woodcock answering many, many questions. I have just a few more.

Would you turn to tab 69, please? I want to refer to this Powerpoint presentation which was given at the Advisory Committee meeting on February 2. It is about the use of antidepressants in the pediatric population. Just so we are perfectly clear, I think this has been referred to earlier, but Prozac is the only antidepressant that is approved for pediatric depression; is that correct?

Ms. WOODCOCK. That is correct.

Mr. FERGUSON. The only drug that the FDA has approved for pediatric depression. On page 13, there is a chart showing that the highest prescribed antidepressants for kids from 1 to 17 years old.

Ms. WOODCOCK. Yes.

Mr. FERGUSON. And it goes through and names several of the drugs. Is FDA concerned at all about your own analysis? These are your numbers. These are numbers that were given to us, compiled by someone else but provided to us by FDA. Are you at all concerned about your analysis that shows that kids are being prescribed these drugs, Zoloft and Paxil and Celexa, all antidepressants that unapproved for kids because they haven't—I mean why haven't these drugs been approved by the FDA for use in children?

Ms. WOODCOCK. Because they haven't met the FDA standards for effectiveness.

Mr. FERGUSON. Okay. So FDA says these drugs are not approved for use with children because they haven't been shown to be effective, yes FDA knows by the data that have been submitted to us that they are being prescribed a lot for children. Is there any concern at FDA about the increasing prescriptions for these drugs that are not approved for kids to children?

Ms. WOODCOCK. Of course, and this has been the whole impetus for the Best Pharmaceuticals Act and everything that went before it. In fact, until very recently most of the prescribing of any drugs for children was off-label and the drugs had not been studied in that age group. So this is something that the clinical community is very used to doing because studies were simply not done in kids. This is a problem. We still don't know. As I said, the jury is still out on these drugs whether or not they work for depression in children, and of course this is a great concern.

Mr. FERGUSON. What about labeling? What about letting people know, perhaps pointing out to doctors and the kids' parents and families? Wouldn't FDA want some stronger labeling? Wouldn't drawing attention to the fact that even though this drug may be being prescribed for your child, it has not been approved by the FDA for use with children or adolescents because they have not shown to be effective? What about no efficacy labeling, some stronger labeling? Has that been considered, and, if not, why not?

Ms. WOODCOCK. Well, we certainly in our warning that we put out in March had some language about the side effects and the need for caution and everything, but because the jury is still out on this class of drugs, I think disclosure of the information is very important, but I think the way the message is given is also very important, if that answers your question.

Mr. FERGUSON. Important, why? I agree with you. Why do you think it is important?

Ms. WOODCOCK. I think it is important because pediatric depression is a life-threatening illness. I believe that clinicians and patients deserve to have information, reliable information on which to base prescribing decisions. I believe this is what we have got now, this is what we know. We have several positive trials for Prozac, we know these drugs are effective in adults, we know they have not been effective in some of the trials, a number of the trials that have been done. That is the state of the science, and we know the information about the suicidality and other psychiatric side effects from these analyses that have been done. This will all be discussed next week at our Advisory Committee meeting.

Mr. FERGUSON. Yes. Well, I agree with you on the need and the importance of making this information available. It seems to me that enough of this information hasn't been made available enough or clear enough or translated into something that kind of regular people, non-clinicians, non-doctors, non-scientists can understand, particularly parents who are concerned about perhaps their child's affliction or illness and need the information to know that the drug they are giving their child hasn't been shown to be effective in children. It just seems to me if the FDA acknowledges and knows that there is skyrocketing off-label prescriptions being done with drugs on kids and some cases that have been shown not only to be not effective but in some cases were known to—or at least anecdotally are known to be dangerous, it seems to me there is a huge responsibility that the FDA needs to make that information more available to parents and families. Let me move to another question.

Let me talk about who is prescribing these drugs, and I want to ask you to turn to page 15 in the tab. My question is if FDA sees a problem with pediatricians and family practitioners, folks who are not specialists, writing prescriptions for antidepressants in kids? So it is not just—we are not talking about—in referring to my previous line of questioning, we are not just talking about specialists who are prescribing drugs off-label for kids when they haven't been shown to be effective in kids. We have family practitioners and pediatricians, and if you look at the numbers, we see a trend where pediatricians are prescribing more and more over the last few years of antidepressants for kids. Is there a concern at FDA that you have folks who are not experts in childhood depression, they are not experts in psychiatry or psychology, they are not specialists in this field, yet they are responsible for more and more of the off-label prescriptions for kids to receive antidepressants? Is that a concern at FDA?

Ms. WOODCOCK. Yes, it is a concern, and it isn't a concern only in the area of pediatric antidepressants. Some of the problems that our health care system has around mental health care and other care are reflected in problems with drug utilization. And the current system of prescription medication in this country is predicated on the "learned intermediary," that that prescriber has all the information needed to make that benefit/risk choice of therapies. And if that prescriber does not have all the information, then the system is not working effectively.

Mr. FERGUSON. Yes. Well, clearly, I agree with you that the learned intermediary is key to the kind of functioning of our system properly, but the learned intermediary, if they are not really learned, they are not a very effective intermediary.

Ms. WOODCOCK. I agree.

Mr. FERGUSON. It just seems to me if you have got a quarter of the prescriptions for antidepressants to adolescents are being written by pediatricians and family practitioners, nothing against those good folks, I mean they are doing the very best they can to care for their patients, but they are not specialists.

Ms. WOODCOCK. That is correct.

Mr. FERGUSON. They are not experts in this field, and, gosh, if they are—this is an alarming trend when you see the increases in the rates of folks who are not specialists, who are not experts in

this particular field prescribing drugs that are not approved by the FDA for this particular use and then are being given to kids and are having incredibly adverse reactions and sometimes unpredictable reactions which are, as you stated, quite literally life-threatening. That is very, very alarming, I know, to many on the panel and I am sure to you as well.

I would just, I guess, ask and urge that you and your colleagues at FDA continue to be imaginative and continue to redouble and retriple your efforts in terms of labeling, in terms of efficacy, making that is understandable to normal folks, folks who don't have a degree in this stuff and, frankly, depending on where we go after this hearing in terms of our discussions on the committee, there may be additional steps that we need to take and work that we need to do with you all and the companies and the health care professionals to make sure that folks are getting the information that they need, because, clearly, right now they are not. And part of that responsibility, as I said in my opening statement, there is plenty of responsibility to go around, but, clearly, some of that responsibility falls with FDA, and we would certainly appreciate your cooperation and your help and your partnership as we continue to address that. Thank you, Mr. Chairman.

Mr. WALDEN. Thank you, Mr. Ferguson. We appreciate your participation in this hearing. Dr. Woodcock, as we wrap up this panel, please know, I think it has been obvious, we are very concerned about what has happened at the FDA or what has not happened. We are very concerned about the lack of candor and cooperation, as evidenced by certainly this May 3 email from Mr. McGarey to others. We expect on September 23, when this subcommittee reconvenes, that the FDA's witnesses will be fully prepared to answer our questions, and we intend then to be probably just as tough as we have been today.

Ms. DEGETTE. Mr. Chairman, would you yield for one moment?

Mr. WALDEN. Yes.

Ms. DEGETTE. I would also supplement that request with the request that all of the information that the panel has asked for today in writing be submitted before that hearing so that we may be able to actually use the information at the hearing.

Mr. WALDEN. Absolutely. And, in fact, as I think our standard procedure, the record will be open for additional questions of the agency, and we would appreciate those being responded to before September 23. I think you have heard, Doctor, the seriousness of what we are hearing from our constituents and our views on this committee, and we want to get to the bottom of this, we want to know answers to our questions. This is too big of a health care issue not to be addressed appropriately. And if the law is preventing you from acting, then we need to know that and you need to tell us where you are handcuffed and shouldn't be. If it is your own rules, then you need to fix them. And we are going to be one this one. So I appreciate your coming today, and you are now excused.

Ms. WOODCOCK. Thank you.

Mr. WALDEN. We will call up the second panel to testify. Dr. David Wheadon, senior vice president, Regulatory Affairs for GlaxoSmithKline; Dr. John R. Hayes, product team leader for Eli

Lilly Company; Dr. Cathryn Clary, U.S. Medical for Psychiatry and Neurology for Pfizer, Incorporated; Dr. Joseph S. Camardo, senior vice president, Wyeth Pharmaceuticals; Dr. Lawrence Olanoff, executive vice president, Scientific Affairs, Forest Laboratories, Incorporated; Patrick Osinsky, esquire, general counsel, Organon USA; and Dr. Ronald N. Marcus, Neuroscience Global Clinical Development, Bristol-Myers Squibb Company.

Ladies and gentlemen, we appreciate your attending our hearing and your willingness to testify before the Subcommittee on Oversight and Investigations. You might wait to take your seats. As you are aware, the committee is holding an investigative hearing, and when doing so has had the practice of taking testimony under oath. Do you have any objection to testifying under oath? Anyone have objection to that? Let the record show no one objects to that. The Chair then advises you that under the rules of the House and the rules of the committee, you are entitled to be advised by counsel. Do you desire to be advised by counsel during your testimony today? Does anyone—okay. Let us go first, Dr. Wheadon? No. Dr. Camardo?

Mr. CAMARDO. Yes.

Mr. WALDEN. And who is your counsel? Could you speak—somebody turn on one of the microphones, if you would there, sir.

Mr. CAMARDO. My counsel is Ms. Feliciano who is in the second row in the back here.

Mr. WALDEN. All right. Thank you very much. Dr. Olanoff?

Mr. OLANOFF. Yes. And my counsel—I wish to be advised, and my counsel is Mr. Jim Johnson, James Johnson, behind me.

Mr. WALDEN. Okay. Thank you, sir. Dr. Hayes, are you represented by counsel? Oh, I am sorry, we have our names flopped around here. It is the name tags we need to get straightened out there. All right. Dr. Marcus?

Mr. MARCUS. Yes, please.

Mr. WALDEN. And you are represented by counsel today?

Mr. MARCUS. Yes, I am.

Mr. WALDEN. And could you identify your counsel, sir?

Mr. MARCUS. Mary Alice Barrett.

Mr. WALDEN. Thank you. Dr. Osinsky?

Mr. OSINSKY. No.

Mr. WALDEN. Okay. Dr. Clary?

Ms. CLARY. Yes. And it is Justin McCarthy who is in the room.

Mr. WALDEN. Okay. Thank you very much. In that case, if then you would please rise and raise your right hand and I will swear you in.

[Witnesses sworn.]

Mr. WALDEN. Okay. Let the record show the witnesses all answered in the affirmative. You are now under oath, and you may give a 5-minute summary of your written statement. And we will start with Dr. Wheadon.

Try it now. Third time.

TESTIMONY OF DAVID E. WHEADON, SENIOR VICE PRESIDENT, REGULATORY AFFAIRS, GLAXOSMITHKLINE; JOHN R. HAYES, PRODUCT TEAM LEADER, ELI LILLY COMPANY; JOSEPH S. CAMARDO, SENIOR VICE PRESIDENT, WYETH PHARMACEUTICALS; LAWRENCE S. OLANOFF, EXECUTIVE VICE PRESIDENT, SCIENTIFIC AFFAIRS, FOREST LABORATORIES, INCORPORATED; RONALD N. MARCUS, NEUROSCIENCE GLOBAL CLINICAL DEVELOPMENT, BRISTOL-MYERS SQUIBB COMPANY; PATRICK J. OSINSKY, GENERAL COUNSEL, ORGANON USA; AND CATHRYN M. CLARY, U.S. MEDICAL, PSYCHIATRY AND NEUROLOGY, PFIZER, INCORPORATED

Mr. WHEADON. Should be a charm.

Mr. WALDEN. There you go.

Mr. WHEADON. Mr. Chairman, ranking member and members of the committee, good afternoon. I am David Wheadon, senior vice president for U.S. Regulatory Affairs at GlaxoSmithKline. I am a psychiatrist by training and have held various positions in clinical development at both Eli Lilly Company and GlaxoSmithKline. At Lilly, I was involved in the development of Prozac and have worked extensively on Paxil during my tenure at GlaxoSmithKline.

It is appropriate for GlaxoSmithKline to testify on the subject of this hearing; namely, publication and disclosure issues in antidepressant pediatric trials. A fact that has been obscured in all the recent publicity is that in 2003 it was GlaxoSmithKline that voluntarily brought the potential issue of suicidality in pediatric patients being treated with antidepressants to the attention of the FDA and to the attention of other regulatory agencies.

Another important point that gets lost in the discussion is the fact that there were no suicides in our nine trials studying pediatric patients who suffer from depression, excessive-compulsive disorder or social anxiety disorder. Furthermore, we did not see a statistically significant signal of increased suicidality in any of these individual trials. It was only when we combined the performed analyses on all nine studies together, a procedure known as a metaanalysis, that we saw a possible signal primarily in adolescent patients with depression.

After completing these analyses in 2003, we proactively sought the advice of external experts and regulatory agencies, including the FDA. The FDA issued a talk paper in June 2003 which addressed this issue. More broadly, it has been the practice of GlaxoSmithKline to communicate to the medical community safety and efficacy data from our clinical trials through posters, abstracts presented at medical conferences, peer review journal articles and through medical information letters provided to physicians upon request. We have not stopped there, however. In the interest of full transparency and because we felt it was important to clarify the data related to GlaxoSmithKline's clinical trial results regarding Paxil and children and adolescents, on June 14 of this year, we took the unprecedented and extraordinary step of providing access via our web site to clinical trial reports and other information concerning Paxil studies in children and adolescents.

GSK has since gone even further. We have created the GlaxoSmithKline clinical trial register which provides online access to summaries of trial protocols and corresponding results for

GlaxoSmithKline-sponsored trials for all products marketed since the date of our merger in 2000.

Just as the FDA and the public are struggling with this issue with pediatric suicidality, GlaxoSmithKline has struggled with understanding the data and its implications. The FDA has recently required a new warning for products in the newer antidepressant classes, including Paxil, that expands upon the disease-related risk of suicidality that has been an antidepressant labeling factor for many years. Both the new and old language reflect the phenomenon that during early treatment and recovery symptoms such as lack of energy and motivation may improve ahead of depressive and suicidal thinking with the result that still depressed patients may now have the energy and the motivation to act on their suicidal thoughts. This new language underscores the complexity of treating depression and the need for physicians and family members to observe patients for worsening depression or signs of suicidality, whether or not they are taking antidepressants.

It is critical to recognize that studying, diagnosing and treating depression is extraordinarily complex. As a psychiatrist, one of my greatest fears is that all of the publicity about suicidality associated with antidepressant treatment will discourage families from seeking treatment of depression for their affected children. This would truly be an unacceptable and devastating outcome for these children. The end result of this and many other deliberations on this matter must be a greater appreciation of safely and effectively tackling this significant and potentially devastating disease in children. Thank you.

[The prepared statement of David E. Wheadon follows:]

PREPARED STATEMENT OF DAVID E. WHEADON, M.D., SENIOR VICE PRESIDENT, U.S. REGULATORY AFFAIRS, GLAXOSMITHKLINE

Mister Chairman, Ranking Member and Members of the Committee, good morning.

My name is Dr. David Wheadon, and I am Senior Vice President for U.S. Regulatory Affairs at GlaxoSmithKline. I appreciate the opportunity to appear before the Subcommittee today and look forward to answering your questions.

As a bit of background, I am a psychiatrist by training, and have held various positions in Clinical Development at both Eli Lilly and Company and GlaxoSmithKline, primarily focusing on central nervous system products. While at Lilly, I was involved in the development of Prozac for the treatment of depression as well as other psychiatric disorders, and have worked extensively on Paxil during my tenure at GlaxoSmithKline. In my current position, I am responsible for GlaxoSmithKline's interactions with the FDA on all of our prescription drug and vaccine products.

I appreciate this opportunity to describe to you GlaxoSmithKline's continuing efforts to share information to ensure that our antidepressant paroxetine hydrochloride, known under the brand name Paxil®, is used appropriately by all patients.

BACKGROUND ON PAXIL

Paxil is a member of a class of antidepressants called selective serotonin reuptake inhibitors, or SSRIs. Paxil was launched in the U.S. market in 1993 for the treatment of depression in adults, also known as major depressive disorder. Since its launch, as is the case with all new drugs, we have continued to study Paxil's safety and efficacy and have sought, and received approval for, additional indications for its use. Currently, the FDA has approved Paxil and/or Paxil CR as safe and effective to treat depression, generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive compulsive disorder, pre-menstrual dysphoric disorder and posttraumatic stress disorder in adult patients. Paxil has never been licensed in North America or Europe for use in pediatric patients, and GlaxoSmithKline does not promote Paxil for use in this age group.

GlaxoSmithKline is committed to the research and discovery of medicines to improve human health and fill unmet medical needs. The unmet need in child and adolescent depressive and anxiety disorders is substantial; the consequences of not adequately recognizing and treating such disorders include significant morbidity, disability and indeed death. Suicidal behavior, suicide attempts and completed suicide can all be extremely unfortunate complications of childhood and adolescent depression. We have studied Paxil in pediatric patients who suffer from depression, obsessive compulsive disorder and social anxiety disorder. We conducted eight major safety and efficacy trials, and one pharmacokinetics study. Seven of these studies were conducted under an Investigational New Drug application with the FDA, and the other two were conducted under similar applications in Canada or France.

COMPLEXITY OF DEPRESSION

As a psychiatrist, I would like to take a moment to talk about some unique characteristics of depression and similar psychiatric disorders. Depression is a complex and devastating disease, and one of its cardinal symptoms is suicidality—defined as suicidal thinking, suicide attempts, or completed suicides. It is well recognized that suicide can be a tragic outcome of depression, and it is one of the leading causes of death among young people. According to researchers supported by the National Institute of Mental Health, among adolescents who develop major depressive disorder, as many as 7% may commit suicide in their young adult years. Tragically, suicide is the third leading cause of death among young people.

Although most antidepressants are not approved for use in the pediatric population, physicians sometimes will prescribe these drugs to depressed children "off-label." We are aware that prescriptions have been written for children for the various products represented by the companies here today, that may or may not be indicated for their use. It is important to recognize that the increased use of antidepressants among children 10-19 years of age has been accompanied by a decrease in the suicide rate in this age group. According to a study published in the Archives of General Psychiatry in October 2003, for each 1 percent increase in the use of SSRIs among adolescents, there was a decrease of 0.23 suicides per 100,000 adolescents per year. Although this is an epidemiologic association that does not necessarily prove cause-and-effect, it does suggest that we as a society are beginning to recognize and appropriately treat depression in children and adolescents.

While physicians have found antidepressants to be useful in treating pediatric patients with depression, these drugs have historically been very challenging to study in clinical trials. Not only is demonstration of efficacy a challenge due to the particularly high placebo-response rates in pediatric depression, but evaluation of safety and tolerability is confounded by the fact that cardinal symptoms of the disease such as anxiety, sleep disturbance and suicidality may masquerade as side-effects of treatment. It is precisely for this reason that the symptom complex of suicidal thinking, suicide attempts, and completed suicides—which we refer to as suicidality—is particularly difficult to assess in antidepressant clinical trials. Not all acts of self-destructive behavior often seen in adolescents are associated with real suicidal intent. GSK's meta-analysis of the pediatric clinical trial data described below utilized an algorithm approach, evaluating adverse event reports and classifying them as "possibly suicide-related" and/or as a "suicide attempt". This could be imprecise; for example, one classification of "suicidality" in one of our trials consisted of a subject slapping her face.

Paxil is an effective and generally well-tolerated drug for adults with depression and other psychiatric disorders. Given the unmet medical need in children and adolescents with depression, GlaxoSmithKline undertook to study Paxil in pediatric populations in the hope that it might help some of these young patients. Our three trials in pediatric depression as a group did not, however, provide sufficient evidence that Paxil is more effective than placebo, although we did see some signs of efficacy in our first pediatric depression trial. It is important to note that even for known effective, approved antidepressants, 4 out of 10 studies failed to demonstrate efficacy because of the high placebo response rates seen in these studies. Given those statistics, we were encouraged by the results of our first trial.

One possible explanation for the outcome of our pediatric depression trials was the high placebo response rate, which made it difficult for the drug to show statistically significant efficacy. Our trials showed a high response rate to Paxil but also a high response rate to placebo—as is common in clinical trials for depression—so it was difficult to demonstrate a statistically significant difference between the two. Another impediment to measuring efficacy in the pediatric population is the need for more refined scales for measuring antidepressant efficacy in this population.

Of note, in our studies of pediatric patients with obsessive-compulsive disorder and social anxiety disorder, Paxil did demonstrate statistically significant evidence of efficacy.

COMMUNICATION OF RESULTS

GlaxoSmithKline's policy is to ensure transparency of the clinical data the company collects on its marketed medicines. Specifically, we endorse the principles of our trade association, the Pharmaceutical Research and Manufacturers of America, also known as PhRMA, that call for timely publication of meaningful trial results. In fact, we helped to draft the PhRMA principles.

Although we were not able to demonstrate efficacy in pediatric depression, data from clinical trials was shared with the healthcare community. Over the past six years or so, data from the pediatric depression studies has been communicated through peer-reviewed journals, poster presentations at scientific meetings, and medical letters to health care professionals—all of which are accepted standard practices for making data available to prescribers. A bibliography of publications and posters derived from these studies was posted to the GlaxoSmithKline corporate website on June 14, 2004.

As for our safety data concerning suicidality in pediatric patients treated with Paxil, I should first point out a few issues that seem to get lost in the discussion surrounding the pediatric use of antidepressants. Firstly, not a single person committed suicide in any of our pediatric trials, which included over 1,000 patients treated with Paxil. Secondly, we did not see a statistically significant signal of increased suicidality in any of the trials individually. However, when, as part of our standard internal process of continuing ongoing safety reviews, we combined and performed analyses on all nine completed studies together—the meta-analysis—we did see a possible signal, primarily in adolescent patients with depression. On completion of those analyses in 2003, GlaxoSmithKline proactively sought the advice of external experts and regulatory agencies including the FDA. The FDA promptly issued a Talk Paper and brought this issue to the attention of the medical community and the public in June 2003. Thirdly, it is important to note that the possible signal of suicidality seen in the adverse event data was not confirmed by analysis of the data from the depression rating scales. In all of our depression studies, the depression rating scales used contained a "suicidality" question, a physician rated score of suicidality. Analysis of this data showed no signal of suicidality associated with Paxil in pediatric patients.

The FDA is in the midst of further considering this issue, recognizing that any such review must be done thoroughly and be guided by the best scientific and clinical research that exists. Thus, we welcome the FDA's approach of asking researchers at Columbia University to undertake an independent evaluation of the data on all antidepressants, including SSRIs. As I am sure you are all aware, the agency will convene a meeting of experts next week to review the outcome of this evaluation. Given the complexity of this matter, we believe the FDA's approach has been appropriate.

Concurrent with this review and with our support, the FDA has required a new warning on all products in the newer antidepressant class, including Paxil. This new labeling expands upon—and gives more prominence to—language regarding the disease-related risk of suicidality that has been in antidepressant labeling for many years. Both the new and old language reflect the phenomenon that, during early treatment and recovery, symptoms such as lack of energy and motivation may improve ahead of depressive and suicidal thinking. The possible consequence of this is that these still-depressed patients may now have the energy and motivation to act on their suicidal thoughts. The new language underscores the need for physicians and family members to observe the patients for worsening depression or signs of suicidality—whether or not they are taking antidepressants. We support this new warning, and we have included it in our labeling.

Finally, as noted above, in the interest of full transparency, and because we feel it is important to clarify the data related to GlaxoSmithKline's clinical trial results regarding Paxil in children and adolescents, on June 14, 2004, we took the unprecedented and extraordinary step of providing access via our website to the clinical trial reports and other information about Paxil data in children and adolescents. We hope this information will be useful and informative to all those who access it.

CLINICAL TRIAL REGISTER

It has been the practice of GlaxoSmithKline to communicate to the medical community safety and efficacy data from our clinical trials through posters and ab-

stracts presented at medical conferences, through peer-reviewed journal articles, and through medical information letters provided to physicians upon request.

GlaxoSmithKline has also recently taken the additional step in on-line access to clinical trial information by beginning to put study summaries of our marketed pharmaceutical products on a single Internet site accessible to physicians and the public. The database, called the GlaxoSmithKline Clinical Trial Register, provides summaries of trial protocols and corresponding results for GlaxoSmithKline-sponsored trials of marketed medicines. In addition, the register provides citations to publications that have appeared in the medical literature. Just last week we began posting data for our antidiabetic Avandia—one of the company's most important products—and we will begin posting summaries for other products in the near future.

This Clinical Trial Register had been under consideration and development for several months. Our company acts in the interests of physicians and patients, and we will take whatever measures are necessary to maintain their trust.

Of course, we will also continue to communicate clinical data in journals, at scientific meetings, and in letters to healthcare professionals. It is also important to emphasize that while we are pleased that we will be able to provide this clinical data online, it is the prescribing information approved by regulatory agencies that must continue to guide the appropriate use of our medicines.

CONCLUSION

We strongly believe that GSK acted appropriately in analyzing, interpreting and communicating data from Paxil trials in children and adults given the information available at any given time over the last 11 years.

Thank you for your time. I look forward to answering any questions you may have.

Mr. WALDEN. Thank you, Dr. Wheadon.

Dr. Hayes.

TESTIMONY OF JOHN R. HAYES

Mr. HAYES. Thank you. I am John Hayes. I am a licensed physician and board certified psychiatrist. I work for Lilly and have since 1998. Before that I was a health system administrator, president of St. Vincent Hospital and Health Services and the CEO of Seton Health of Indiana, and I had a long career before that as an academic psychiatrist with appointments at Indiana University School of Medicine in Internal Medicine and Psychiatry, and I still hold those appointments.

I am happy to be here because we think that this is a very important set of issues to discuss. That seems obvious. Depression is a very serious illness. It is a very serious burden for the individuals who have it and for our society. The lost opportunities for children and adolescents with depression are a tragedy, and the major lost opportunity, which would be the death of such a person, is, as Dr. Woodcock said, one of the top three reasons for the death of children and adolescents in our country.

Lilly has been for a long time really committed to discovering and developing medications to help people with serious mental illnesses, certainly including depression and of course Prozac, which is arguably the world's most widely recognized antidepressants. It has been marketed since 1987 and is the drug which, as several people have noted this morning, is the first and the only antidepressant which actually has a labeled indication for the treatment of children who are depressed.

That labeled indication is based on a body of data that includes five studies. One of those was a pharmacokinetics study, and of the other four, three of them had positive outcomes, and one of them

was a failed study or did not show effectiveness. All five of those have been published, including the negative study.

The other thing that is important to say is that this indication to treat children is in the context of a massive amount of data about Prozac, its efficacy and its safety. Fifty million people have taken Prozac to this date. There have been 400 or so clinical trials and over 30,000 people have participated in some kind of research as subjects with Prozac. If you punch fluoxetine into a search engine on the net, you will get 15,000 or so articles, citations, and 7,500 of those are articles that have fluoxetine as the major object of the study. It is one of the most analyzed and scrutinized drugs in history.

The issue of Prozac and suicidality is perhaps the most analyzed and scrutinized issue about Prozac and has been examined continuously and repeatedly for years. The recent FDA analysis and the reanalysis with the Columbia criteria, as people have discussed this morning, has again shown no signal for suicidality induced by Prozac in children and adolescents, and that collaborates our belief that there are no credible data that show such a signal in adults either.

I noted that all the Prozac studies have been published, but, obviously, this hearing is not just about the content of those things but whether or not information is disclosed appropriately. Lilly has a long-standing history of such disclosure, has, I think, been very diligent in populating the current clinicaltrials.gov site with our serious or life-threatening illness trials. Since its inception—and we have recently enhanced our policy to create, as we announced several weeks ago, a new web site of Lilly's for complete disclosure of all of our clinical trial results.

On that web site, which we hope to bring online in the fourth quarter of this year at www.lillytrials.com, we will post, first of all, the initiation of all of our trials and all phases in all countries, phase one, two, three or four, with an identifier so that people can see what trials are going on. As those trials are completed and as new indications are approved, we will populate those identified study trial titles with the results, with methodology, with primary and secondary outcomes. We intend to do that at the time of the approval of any new indication for all phase one, two and three trials, and for phase four trials, we will do it as soon as possible after the completion of the trial but not more than 1 year afterwards. We are going to do that prospectively starting with trials ending July 1, 2004 and retrospectively will populate the data base to 1994, and we will have third party objective and independent auditing of this trial to assure our own compliance with our intentions.

I think our logo says, "Answers that Matter." We believe in that strongly and applaud the committee's wish to supply answers that matter to everyone who cares, and I am happy to be here to help.

[The prepared statement of John R. Hayes follows:]

PREPARED STATEMENT OF JOHN R. HAYES, PRODUCT TEAM LEADER, ELI LILLY & COMPANY

My name is John R. Hayes. I am a licensed physician, Board-Certified in Psychiatry, and a product team leader for Eli Lilly and Company. I joined Eli Lilly and Company in 1998. Prior to joining Lilly, I was president of St. Vincent Hospital and

Health Services in Indiana and CEO of Seton Health Corporation of Indiana for several years, after having a long career in clinical and academic psychiatry as a consultation-liaison psychiatrist. I was a tenured member of the faculty at the Indiana University School of Medicine in both the departments of Psychiatry and Medicine. I continue to hold appointments in those departments.

It is a privilege to appear before you on behalf of Eli Lilly and Company. My testimony before your Subcommittee is focused on the issue of publication and disclosure of data from clinical trials with antidepressant medications in children and adolescents, and in particular, our experience with, and data concerning, Prozac.

Everything I have to say is based in Lilly's belief that all pharmaceutical companies have a public health responsibility to:

1. Provide safe and efficacious medications with supporting usage information to adults and children.
2. Monitor the safety and efficacy of these medications and their effects throughout the life cycle of the product, from the time it is initially tested in humans, until it is no longer marketed.
3. Disclose the results of clinical trials and safety monitoring efforts to clinicians and patients in a timely and accurate manner.

In that context, then, there are four main themes that I will cover in today's oral testimony:

1. Depression is a devastating illness for not only adults, but also for children and adolescents. This is a serious public health issue.
2. Fortunately for those suffering with depression, there are treatments available, both pharmacological therapies and "talk therapies," that have proven beneficial in research studies. Among the pharmaceutical therapies, Prozac was the first antidepressant to be approved by the FDA for use in children and adolescents. That approval was based on extensive studies submitted to the FDA for their review. Prozac is also approved for use in adult and geriatric patients. It is reasonable and ethical to make available appropriate treatments for patients with depression, which can be a life-threatening illness, regardless of the patient's age.
3. There is an abundance of clinical data supporting the safety and efficacy of Prozac. Prozac is available to patients in over 100 countries. It is estimated that there have been over 50 million patients who have taken Prozac; including over 400 clinical trials in which more than 30,000 patients have participated. These clinical trial data have been supplemented by safety data reported to Lilly's pharmacovigilance databases and regulatory authorities around the world since 1983, updated at least annually in a comprehensive manner.
4. Finally, I will share with you Lilly's policy regarding the disclosure of clinical trial results across all areas of study. Lilly is committed to publicly disclose all medical research results that are significant to patients, healthcare providers or payers—whether favorable or unfavorable to a Lilly product—in an accurate, objective and balanced manner in order for patients and health practitioners to make more informed decisions about our products.

A. DEPRESSION IS A DEVASTATING ILLNESS FOR ADULTS AND FOR CHILDREN AND ADOLSECENTS

Prevalence estimates for Major Depression in all children range from 16% to 22 % (Costello et al, 1996; Roberts et al, 1998). According to a report from the United States Surgeon General (Report of the Surgeon General's Conference on Children's Mental Health, 2000, p. 11), at least "one in ten children and adolescents suffer from mental illness severe enough to cause some level of impairment." Additionally, it states "recent evidence compiled by the World Health Organization indicates that by the year 2020, childhood neuropsychiatric disorders will rise proportionately by over 50 percent, internationally, to become one of the five most common causes of morbidity, mortality, and disability among children." In this same report, it was noted that, in the United States, for children between the ages of 1 and 19 years, the group of conditions that lowers the quality of life and reduces life chances (opportunities) the most are emotional and behavioral problems and associated impairments. Children with these disorders are at an increased risk for dropping out of school, and of not being fully functional members of society in adulthood. The cost to society is high in both human and fiscal terms (Id. p. 17). There is also the significant role that stigma plays in inhibiting parents from seeking, and children from receiving, appropriate mental health care. Untreated depression can result in poor social and school performance, family problems, interpersonal difficulties, alienation, isolation, and sometimes, suicide. It is not well appreciated that more teenagers and young adults die from suicide than from cancer, heart disease, AIDS, birth defects,

stroke, pneumonia and influenza, and chronic lung disease combined. Suicide is also the fourth leading cause of death among children between the ages of 10 and 14 years. (CDC. National mortality statistics. http://www/cdc/gov/ncipc/osp/usmort.htm.)

Lilly is dedicated to discovering and developing medications to help all patients, including children and adolescents, who suffer from mental health disorders, including Major Depression.

B. THERE ARE TREATMENTS AVAILABLE THAT HAVE BENEFIT; OF THESE, PROZAC WAS THE FIRST ANTIDEPRESSANT APPROVED BY FDA FOR USE IN CHILDREN AND ADOLESCENTS

Fortunately, there are several treatments currently available for children and adolescents with depression, including pharmacological and "talk therapies," that appear to have benefit. One of these is the medication, fluoxetine, or Prozac.

After reviewing the clinical trial data submitted by Lilly in September 2000, the FDA approved Prozac for the treatment of Major Depressive Disorder in children and adolescents on January 3, 2003. Prozac was the first and continues to be the only antidepressant approved by the FDA for the safe and effective treatment of depression in children and adolescents. Prozac has also been approved by FDA for use in children and adolescents to treat Obsessive-Compulsive Disorder, a potentially disabling and life-threatening condition.

Lilly is committed to providing patients, prescribers and payers with all medical data that may influence the health care decision process. All five Lilly-sponsored clinical trials using Prozac in children and adolescents were not only submitted to, and thoroughly reviewed by, the FDA but also published in peer-reviewed medical journals upon the completion of the trials. This information is readily accessible to patients, health care providers and payers. [See Table of Fluoxetine Pediatric Studies and Related Publications. Attachment 1.] Four of the five trials demonstrated the efficacy and safety of Prozac in children and adolescents. One of the trials, a pilot study, did not demonstrate a significant effect. It is important to note that on August 3, 2004 the Wall Street Journal erroneously reported that Lilly had failed to disclose some of the results from its Prozac pediatric studies. Lilly contacted the author who acknowledged she had misinterpreted information she obtained from the Lancet. The article was subsequently corrected. Results from all five of the Lilly-sponsored pediatric Prozac trials have in fact been published.

Beyond these five trials, Lilly continues to monitor the safety of children and adolescents being treated with Prozac. Data are collected from patients and healthcare providers, reviewed by Lilly and submitted to the FDA. Any significant findings result in a label change, which may be initiated by Lilly or the FDA. Lilly also continues to conduct studies in adolescents and children using Prozac in order to understand the long-term effects of its use. We are doing this to honor commitments we have to children and their physicians as well as the FDA, despite the fact that Prozac's patent has expired and generic fluoxetine has been available for some time. For instance, Lilly is in discussion with the FDA for an additional study of the long-term effects of Prozac on growth in adolescents. It should be noted that Prozac has not been and will not be actively promoted by Lilly sales force or advertised for use in children.

C. THERE IS ABUNDANT DATA, BOTH FROM CONTROLLED CLINICAL TRIALS AND FROM SPONTANEOUS REPORTS IN OUR PHARMACOVIGILANCE DATABASE, WITH WHICH TO EVALUATE THE SAFETY AND EFFICACY OF PROZAC.

Prozac was first marketed in 1987, and is now available to patients in over 100 countries. It is estimated that Prozac has been used to treat over 50 million people worldwide, improving the lives of millions of people suffering from depression and other disorders. Prozac has been the subject of more than 400 clinical trials, and has been studied in more than 30,000 patients worldwide. There are more than 15,000 articles in medical and scientific literature with fluoxetine (Prozac) in the title, and over 7,500 in which Prozac is the primary topic of the article. Lilly has maintained pharmacovigilance databases on Prozac since 1983, in which all manner of events reported while patients have taken Prozac are recorded. This database, together with controlled data from clinical trials and pre-clinical studies, form the basis for our assessment of safety and efficacy of this product.

D. LILLY DATA DISCLOSURE POLICY INFORMATION

Lilly has had a long-standing commitment to provide our customers with "answers that matter." We strive to provide information about all of our products, and clear responses to questions that add value to the healthcare decision process, just as I have outlined in the Prozac example.

Lilly has internal standards for conducting, funding and communicating the results of our medical research. In these standards, Lilly commits to publicly disclose all medical research results that are significant to patients, health care providers or payers—whether favorable or unfavorable to a Lilly product—in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products. Lilly understands that patients and health care providers are looking for transparent answers, therefore, Lilly has enhanced recently its internal standards by committing to disclose publicly the results of all Lilly-sponsored clinical trials of its marketed products. [See Principles of Medical Research—Clinical Trial Registry. Attachment 2] This includes the results of all Phase I (early exploratory), Phase II (proof of concept), Phase III (registration), and Phase IV (post marketing) trials conducted anywhere in the world.

Lilly commits to disclose the clinical trial results of the primary and secondary outcome measures that are specified in the study protocol, as well as additional safety and efficacy results that impact patient care and the use of our products. Also, Lilly commits to disclose a comprehensive description of the trial design and methodology for each study. Results which do not support the hypothesis being tested, or which are contrary to the intended outcome, will be disclosed.

Lilly further understands that patients and health care providers are not only looking for the results of our clinical trials, but they also want to be assured that they are not just receiving select results. Therefore, Lilly also commits to publicly report the initiation of all Phase III and Phase IV clinical trials, with an identifier assigned to each trial. When the trial is completed and the drug is commercially available, the results of the trial will be appended to its identifier in order to assure patients and providers they are receiving full transparency. Beyond that, Lilly will assign an independent third party to audit and verify adherence by Lilly to these standards for results disclosure.

Lilly is committed to providing answers in a timely manner. For Phase I, II and III studies, Lilly will disclose clinical trial results when a drug's indication is approved and it is commercially available. For Phase IV studies, Lilly will disclose clinical trial results as soon as possible after the data analysis is completed but no later than one year after the trial has completed.

In all cases, Lilly will disclose clinical trial results on a publicly available, on-line registry. Lilly also will seek to disclose results through a peer-reviewed medical journal, subject to the discretion of the journal editors. For studies that are under review by a peer-reviewed journal that prohibits pre-publication disclosure of results, the results will be posted on the registry at the time of the publication. Lilly commits to providing a reference in the clinical trial registry for study results that are disclosed in a peer-reviewed journal. In addition, Lilly's clinical trial results may be disclosed through presentations or abstract submissions at professional scientific meetings.

Implementation of these standards will begin with all clinical trials of marketed products that are completed after July 1, 2004. In addition, the registry will be populated retrospectively with results of core efficacy and safety registration trials of marketed compounds approved since July 1, 1994.

Lilly is interested in disclosing clinical trial results and the initiation of trials through an industry-wide registry. However, because of the importance of this issue, we have chosen a Lilly-sponsored registry at this time to disclose our clinical trial information. Beginning in the forth quarter of this year, our information will be publicly available at www.lillytrials.com.

Lilly has been actively engaged in PhRMA's efforts to create a results disclosure database and fully supports this initiative. In fact, Lilly was a leader in developing the PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results originally adopted by member companies in 2002. Lilly also led the recent development of clarifying Questions and Answers that were adopted by member companies in June 2004 and now append the PhRMA Principles text. These principles reinforce each PhRMA member's commitment to the safety of research participants, integrity and objectivity of clinical research and public disclosure of clinical trial results. Among other things, these Q&A clarify that member companies commit to disclose the results of all hypothesis-testing clinical trials of marketed product. Lilly's active involvement in shaping the content and rigor of such efforts has contributed to making these Principles more specific and affirmative on the publication of clinically meaningful study results than anything the trade association has set forth before.

Additionally, we continue to be actively engaged in the posting of information on the initiation of clinical trials for serious and life-threatening diseases via the U.S. government web site, www.clinicaltrials.gov. This website gives the patients and the general public a central place—to learn about what potential life-saving clinical

trials are underway involving those disease states. Lilly met the U.S. Food and Drug Administration timeline in 2002—to post the required trials and continues to regularly update its list. Lilly has been so proficient at site participation, with—dozens of Lilly clinical trials listed on clinicaltrials.gov,—that we recently provided a speaker—on the topic for the—Drug Information Association conference at—the FDA moderator's invitation.

In closing, Eli Lilly and Company thanks the Subcommittee for the opportunity to participate in this important dialog. The issue of data disclosure of child and adolescent antidepressant clinical trials is ultimately an issue of public health responsibility in which we all, as regulators, legislators, antidepressant manufacturers and the medical community have a role to play. For Lilly, that role is to provide safe and effective medications for the people who need them; to continue to monitor the safety of those medications and to share information promptly about the safe use of its products with the community. Thank you.

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Mr. WALDEN. Thank you for your testimony.

Dr. Camardo.

TESTIMONY OF JOSEPH S. CAMARDO

Mr. CAMARDO. Good afternoon, Mr. Chairman and members of the subcommittee. I am Dr. Joseph Camardo, head of Medical Affairs for Wyeth Pharmaceuticals. venlafaxine, an antidepressant drug, also called Effexor, is our product. It is a dual reuptake inhibitor that has been used successfully in adults for over 10 years.

Our policy at Wyeth is to communicate the meaningful results of our clinical studies regardless of the outcomes. So we appreciate the opportunity to testify at this hearing about this topic.

I want to first highlight three facts about depression and venlafaxine. First, depression in children is a tragic medical condition, and some children with depression may commit suicide. Second, venlafaxine has never been indicated for children, and Wyeth did not recommend or promote venlafaxine for pediatric patients. Nevertheless, physicians have used the newer antidepressants, including venlafaxine, cautiously to help relieve depression in individual children because depression is a serious problem. And, third, the label for venlafaxine advises that there is a risk of suicide in depressed patients and recommends supervision of high-risk patients when drug treatment is initiated.

Now, I want to tell you about our pediatric studies. We performed five studies of safety and efficacy of venlafaxine for depression and anxiety disorder in children. The data were collected, analyzed and compiled into reports within about a year after completing the last study. Our internal Executive Safety Committee reviewed all the study results in June 2002. This is a committee of senior physicians at Wyeth and at this meeting were two psychiatrists, one of whom is a specialist in child psychiatry. This committee concluded that while the children in the depression studies improved during the study period, the main analyses did not show a statistically significant difference between the active and placebo-treated children. For anxiety, one study showed a clear benefit of

venlafaxine over placebo, and a second study showed a difference favoring venlafaxine that did not reach statistical significance.

This committee also reviewed the safety data and discussed the reports of suicidal ideation, hostility and self-harm. No child committed suicide. The small number of reports and the facts of each report did not demonstrate to us a clear and unambiguous relationship between venlafaxine use and suicide-related events. Nevertheless, despite the lack of a clear relation, we decided that this information should be posted to our product label to advise of the reports of suicide ideation and to advise that venlafaxine had not been demonstrated to be effective for depression in children in these two studies. We disclosed all the data along with our recommendations for the label change to FDA in September 2002. Also in September 2002, our Medical Department prepared letters to provide information to physicians who called to inquire about pediatric use of venlafaxine. These letters explained the results of the studies and the safety information.

In March 2003, the FDA review of our pediatric data was posted on the FDA web site. Reflecting a lack of certainty about the reports of suicide ideation, FDA at this time did not approve our proposal to amend the product label. In April 2003, we presented the pediatric data to outside expert psychiatrists, and these experts suggested that the information about suicidal ideation should be communicated. We also learned about similar reports with paroxetine, another manufacturer's antidepressant.

Our Safety Committee met again and recommended that we do the following, which we did: First, in August 2003, we published an amended label to include the reports of suicidal ideation, hostility and self-harm; second, we sent a letter to more than 450,000 physicians and other health care professionals in the United States. The letter disclosed the reports of suicidal ideation and hostility and reminded practitioners that venlafaxine was not demonstrated to be effective in clinical studies in children with depression. I want to emphasize that changing the label and notifying physicians directly is a most effective and timely way to provide new information. Third, we posted the information on the physician and consumer web sites for venlafaxine, so it was widely available. And, fourth, the Medical Department updated the letters to respond to any direct physician inquiries.

Most recently, in April 2004, Wyeth adopted the antidepressant class label concerning suicide risk, as recommended by FDA, and we again notified physicians by letter. The pediatric study results were presented in May at the American Psychiatric Association meeting.

We continue to operate our safety oversight process to assure that new information is reviewed and that medically important information is communicated. Thank you.

[The prepared statement of Joseph S. Camardo follows:]

PREPARED STATEMENT OF JOSEPH CAMARDO, SENIOR VICE PRESIDENT OF MEDICAL AFFAIRS, WYETH PHARMACEUTICALS

Good morning, Mr. Chairman. I am Dr. Joseph Camardo, Senior Vice President of Medical Affairs for Wyeth Pharmaceuticals based in Collegeville, Pennsylvania. Wyeth developed and has marketed venlafaxine, an antidepressant that is a dual

reuptake inhibitor, under the brand name Effexor, since 1994. We appreciate this opportunity to testify before the Subcommittee.

It is Wyeth's policy to communicate meaningful clinical results of studies of our products regardless of the trial outcome, consistent with the Principles on the Conduct of Clinical Trials put forth by the Pharmaceutical Research and Manufacturers Association.

I want to highlight three facts about depression and venlafaxine.

- First, depression in children is a tragic medical condition associated with a significant incidence of suicide. Physicians need to find ways to treat individual children and they have cautiously used the newer antidepressants.
- Second, venlafaxine has never been indicated for children and Wyeth did not recommend or promote its use in children.
- Third, the product's label has always included a precaution that the possibility of a suicide attempt is inherent in depression, and that close supervision of high-risk patients should accompany initial drug therapy.

Wyeth performed five safety and efficacy studies of venlafaxine for depression and generalized anxiety disorder in children according to a written request by the Food and Drug Administration (FDA). At the conclusion of each study, in accordance with standards of Good Clinical Practice,[1] the data were collected from the various clinical sites, entered into our database, and verified for accuracy. The data were analyzed for efficacy and safety and compiled into a study report. For the five studies in this program, these activities took one year after completion of the last study which is about average for a program of this size.

In preparation for submitting an application to the FDA, our internal Executive Safety Committee reviewed the study results in June 2002. Our reviewers included senior, experienced physicians from our medical, clinical research, safety surveillance, and regulatory affairs departments and two experienced psychiatrists, one of whom is a specialist in child psychiatry. This committee concluded that while the children in the studies of depression showed improvement during the study period, the main analyses did not find a statistically significant difference between children with depression treated with venlafaxine or placebo. One study of anxiety in children showed a clear benefit of venlafaxine over placebo in the main analyses, and the second study showed a non-significant difference favoring venlafaxine.

In reviewing the collective data from these studies, the committee discussed the reports of suicidal ideation, hostility, and suicide attempts. None of the children in these studies committed suicide. The numbers of reports and the facts surrounding each report did not demonstrate a clear relation between venlafaxine use and suicide-related events.

Nevertheless, despite the lack of a clear relation we decided that our label should be amended to add a precaution to advise of the reports of suicidal ideation and hostility and to state that studies had not demonstrated venlafaxine to be effective in children with depression. In September 2002 Wyeth disclosed all data to FDA in a pediatric NDA supplement that included recommended label changes.

At the same time, our medical department prepared letters to respond to physicians who called us to inquire about pediatric use. These letters included detailed information about the efficacy results and the safety information from these pediatric studies.[2] In March 2003, the FDA informed Wyeth that our supplemental application was not approved. Subsequently, the FDA posted its clinical review of this supplement on the FDA website.[3] Reflecting the lack of certainty about the reports of suicidal ideation, FDA did not approve our proposed label additions concerning suicidal ideation in children.

In April 2003 we reviewed our pediatric data with outside expert psychiatrists who had not been involved with the studies. These experts concurred that the information about suicidal ideation should be disseminated. We learned of similar observations with paroxetine and we judged that these findings raised the level of importance of our own findings. At this time, our Executive Safety Committee recommended and we took the following actions:

- First, in August 2003 Wyeth published an amended label to notify health professionals about the reports of suicidal ideation, hostility, and self-harm.
- Second, also in August 2003, we sent a letter to more than 450,000 physicians and other health care practitioners in the United States. This letter disclosed the reports of suicidal ideation and hostility and reminded practitioners that venlafaxine was not demonstrated to be effective in children and was not ap-

[1] ICH Harmonised Tripartite Guideline for Good Clinical Practice.
[2] A copy of Wyeth's response letter from October 2002 is Attachment A.
[3] A copy of FDA's clinical review is Attachment B.

proved for use in children.[4] Changing the label and notifying physicians directly is the most effective and timely way to get the information to physicians.
- Wyeth posted the information on the physician and consumer sections of the Effexor website.
- Our medical department's inquiry responses were updated to include this information.[5]

In April 2004 on the basis of FDA's recommendation, Wyeth incorporated class label changes to the warnings section concerning suicide risk. In addition, the pediatric data, including the results of the depression studies showing no difference from placebo, have been presented at the American Psychiatric Association.

We continue to operate under our safety review process in which new information from any source is reviewed by our Executive Safety Committee and, if warranted, by outside experts. Medically important new drug information is disseminated.

Again, Mr. Chairman, we thank you for this opportunity to appear before the Subcommittee.

ATTACHMENT A

October 2002 Response Letter

THE USE OF VENLAFAXINE IN CHILDREN OR ADOLESCENTS

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI).[1,2] Its active metabolite, O-desmethylvenlafaxine (ODV), also inhibits serotonin and norepinephrine reuptake, with similar potency to venlafaxine. Venlafaxine and ODV are weak inhibitors of dopamine reuptake and have no significant affinity for muscarinic cholinergic, H_1-histaminergic, or $a_1$adrenergic receptors in vitro. Effexor XR Capsules are indicated for the treatment of depression and Generalized Anxiety Disorder (GAD). Effexor Tablets are indicated for the treatment of depression. Please see the enclosed prescribing information for the recommended dosage and administration.

Summary Points

- The safety and efficacy of venlafaxine in children and adolescents less than 18 years of age have not been established; therefore, we cannot recommend the use of these products in this patient population.[3,4]
- The safety and efficacy of venlafaxine extended-release (XR) for the treatment of GAD in children and adolescents was assessed in 2 double-blind, 8-week, placebo-controlled trials.[5,6,7] In the first randomized controlled trial, patients in the venlafaxine XR group had a mean decrease of 18.6 points on the Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia (C-KIDDIE-SADS) GAD (9 delineated items) compared to a 12.4 point decrease in the placebo group ($P < .001$).[5,6] In the second randomized controlled trial, the decrease from baseline in the C-KIDDIE-SADS GAD was greater in venlafaxine XR- compared with placebo-treated patients (15.8 versus 13); however, this difference did not reach statistical significance ($P = .060$).[7]
- Several randomized placebo controlled trials assessed the safety and efficacy of venlafaxine for the treatment of depression in children and adolescents.[8-11] Data from these clinical trials indicated that venlafaxine was well-tolerated but not efficacious for the treatment of depression in children and adolescents.
- In a 5-week, open trial of 16 children (aged 8-16) with ADHD, 44% (7/16) of the subjects responded favorably to venlafaxine therapy based on the Conners Parent Rating Scale (CPRS), while no significant effects were found on the Continuous Performance Test (CPT).[12] Treatment was initiated at a dose of 12.5 mg/day and gradually increased to a target dose of 75 mg/day.
- In an open-label, retrospective evaluation of 10 patients (aged 3-21) with autism, 60% (6/10) of the patients were rated as sustained responders with a Clinical Global Impression (CGI) improvement score of 1 or 2 and showed improvement of symptoms in autism.[13] Treatment was initiated at a dose of 12.5 mg/day and gradually increased based on clinical response and adverse events.
- Pharmacokinetic studies demonstrated that the mean clearance (normalized-body weight) of venlafaxine and ODV was 2.5-fold to 3.0-fold higher, and plasma concentrations lower, in children and adolescents compared to adults who received the same mg/kg dose.[14,15]

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[4] A copy of Wyeth's August 2003 Dear Healthcare Provider Letter is Attachment C.
[5] A copy of Wyeth's response letter from August 2003 is Attachment D.

GAD

The safety and efficacy of venlafaxine XR for the treatment of GAD in children and adolescents was assessed in 2 double-blind, 8-week, placebo-controlled trials that evaluated 158 and 164 patients, respectively.[5,6,7] For both trials, patients had symptoms of anxiety for ≥6 months and met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and C-KIDDIE-SADS criteria for GAD. All patients in the active-treatment groups started venlafaxine at 37.5 mg/day for the first week. Primary efficacy assessments were obtained on days 7, 14, 21, 42 and 49, and safety assessments were obtained at each visit. The primary efficacy variable was the C-KIDDIE-SADS GAD (9 delineated items). The dose was then titrated according to weight and response, according to a flexible-dosing regimen.

In the first randomized controlled trial, patients in the extended-release venlafaxine group had a mean decrease of 18.6 points on the primary efficacy variable compared to the 12.4 point decrease in the placebo group ($P < .001$).[5,6] The discontinuation rate for adverse events between extended-release venlafaxine (3%) and placebo (9%) was not significant. The most common treatment-emergent adverse events were asthenia, anorexia, weight loss, thinking abnormal, hyperkinesia and epistaxis.

In the second randomized controlled trial, the decrease from baseline in the C-KIDDIE-SADS GAD was greater in venlafaxine XR- compared with placebo-treated patients (15.8 versus 13); however, this difference did not reach statistical significance ($P = .060$).[7] The adverse events observed in venlafaxine XR-treated patients were similar to that observed in adult patients with GAD. Adverse events were the primary or secondary cause of discontinuation in 4% of venlafaxine-treated patients compared with 2% of placebo-treated patients.

These trials suggested that venlafaxine-XR is an efficacious and well-tolerated treatment for children and adolescents with GAD.[5-7]

Depression

The safety and efficacy of venlafaxine XR for the treatment of depression in children and adolescents was assessed in 2 double-blind, 8-week, placebo-controlled trials,[8,9] and one open-label 6-month trial.[10] The double-blind trials included 161 and 193 patients,[8,9] respectively, that were evaluated for efficacy; the open-label trial evaluated 85 patients.10 For all 3 trials, patients met DSM-IV and Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KIDDIE-SADS-PL) criteria for major depressive disorder. Patients also had a Childhood Depression Rating Scale, Revised (CDRS-R) score > 40 at baseline, with no greater than a 30% decrease during screening; a Clinical Impressions Severity of Illness (CGI-S) score ≥4; and depressive symptoms for at least 1 month prior to entry into the study. All patients in the active-treatment groups started venlafaxine at 37.5 mg/day for the first week. The dose was then titrated according to weight and response, according to a flexible-dosing regimen. The primary efficacy variable was the CDRS-R total score.

There was no significant difference between venlafaxine XR- and placebo-treated patients for CDRS-R scores in either of the placebo-controlled trials. Venlafaxine XR was found to be safe and well tolerated in all 3 trials, with a safety profile that was similar to that seen in adults with major depression. No patients died in any of the studies. In one placebo-controlled trial,[8] adverse events were the primary or secondary cause for discontinuation of study drug in 13% of venlafaxine XR-treated patients compared with 5% of placebo-treated patients. The adverse events that most frequently caused discontinuation of treatment in the venlafaxine XR group were manic reaction (3%) and suicidal ideation (3%). In the other placebo-controlled trial,[9] adverse events were the primary cause for discontinuation of study drug in 8% of venlafaxine XR-treated patients compared with 1% of placebo-treated patients. The adverse events that most frequently caused discontinuation of treatment in the venlafaxine XR group were hostility (2%) and suicidal ideation (2%).

In a separate preliminary double-blind, placebo-controlled, 6-week study, Mandoki et al[11] evaluated the effectiveness of venlafaxine immediate-release (IR) in the treatment of depression in children or adolescents. The study involved 33 patients (age range, 8-17 years) who met DSM-IV criteria for major depression. Suicidal patients were excluded from the study. Patients were randomized to receive either venlafaxine or placebo (n = 20 each group). The children (aged 8-12) randomized to venlafaxine were titrated during the first week to 12.5 mg t.i.d.; adolescents (aged 13-17) in the venlafaxine group were titrated to 25 mg t.i.d.

Efficacy assessments were obtained weekly by administering the Hamilton Psychiatric Rating Scale for Depression (HAM-D), the Child Depression Rating Scale (CDRS), the Child Behavior Checklist (CBCL), and the Child Depression Inventory (CDI).[11] Safety data were also obtained on a weekly basis.

Both the venlafaxine and placebo groups improved significantly ($P \leq .05$) as measured by the HAM-D, the CDRS, and the CBCL.[11] Significant improvement was not obtained by any group on the CDI. There were no significant differences between treatment groups for any rating scale. In addition, the pattern of improvement over the treatment period was similar for both groups, indicating that there was not a faster onset of action in the venlafaxine group.

A higher percentage of venlafaxine-treated patients reported adverse events than the placebo group at almost every weekly assessment.[11] However, only the incidence of nausea at week 2 (all ages compared) and increased appetite (only adolescents compared) were statistically significantly different from placebo.

Data from these clinical trials indicate that venlafaxine is well-tolerated but is not efficacious for the treatment of depression in children and adolescents.[8-11]

ADHD

Olvera et al[12] conducted a 5-week, open trial of venlafaxine in the treatment of ADHD. Sixteen children and adolescents (ages 8-16 years; mean 11.6 years) meeting DSM-III-R criteria for ADHD (based on the Diagnostic Interview Schedule for Children) participated in the study. The child was also required to have a score of at least 1.5 standard deviations above the mean for the patient's age and sex on the Inattention or Impulsivity/Hyperactivity factor of the CPRS. Venlafaxine was initiated at a dose of 12.5 mg/day for the first week. Based on the patient's tolerability, the daily dose was increased by 25 mg each week until a target dose of 75 mg/day was achieved. For children weighing less than 40 kg, daily venlafaxine doses were increased by 12.5 mg weekly up to a maximum of 50 mg. If a patient experienced side effects, the dosage was reduced to the previous level. The child's parent completed the CPRS, and the child performed the CPT at baseline and at the end of the 5-week trial. In addition, telephone interviews of the child and parent were conducted weekly to assess the effects of venlafaxine treatment on ADHD symptoms.

Of the 16 enrolled patients, 10 patients completed the study (mean venlafaxine dose, 60 mg/day).[12] Two patients were lost to follow-up, 3 discontinued therapy due to an increase in hyperactivity, and one discontinued due to nausea. Of the evaluable patients, treatment with venlafaxine resulted in significant improvement ($P < 01$) in the Impulsivity/Hyperactivity Factor and Hyperactivity Index of the CPRS. However, there were no significant changes in the Conduct Index Factor, nor were there any significant effects of venlafaxine therapy on the CPT. Overall, 44% (7/16) subjects responded favorably to venlafaxine therapy based upon the CPRS.

There were no significant adverse events noted.[12] The most common adverse experiences were drowsiness, nausea, irritability, and worsening of hyperactivity. Other reported adverse events included insomnia, dizziness, decreased appetite, dry mouth, anxiety, and headache. No appreciable effects on blood pressure or heart rate were noted.

The preliminary findings of this study suggest that low doses of venlafaxine appeared to be effective in reducing behavioral but not cognitive symptoms of ADHD in some patients.[12] Further study is necessary to confirm these results.

Autism

Hollander et al[13] conducted an open-label, retrospective evaluation of the treatment responses to venlafaxine in children, adolescents or young adults with autistic spectrum disorders. Ten patients between the ages of 3 and 21 (mean 10.5 ± 5.5) years old who met the DSM-IV criteria for pervasive developmental disorders, including autism and Asperger's Syndrome, were included in the study. Five patients had comorbid disorders including ADHD, body dysmorphic disorder, separation anxiety, obsessive-compulsive disorder, and Tourette's syndrome. Patients were treated with an initial dose of venlafaxine 12.5 mg/day. The venlafaxine dose was gradually increased based on clinical response and adverse events. Efficacy was assessed using the CGI improvement scale. Responders were defined as those patients who obtained a score of 1 (very much improved) or 2 (much improved).

Six of the 10 patients were rated as sustained responders with a CGI improvement score of 1 or 2.[13] The mean endpoint venlafaxine dose in these patients (25 ± 14 mg/day) did not differ from that of the nonresponders. The mean duration of treatment was 4.8 ± 2.5 months. Venlafaxine treatment was noted to improve symptoms in all 3 core dimensions of autism (social deficits, language and communication impairment, restricted interests and repetitive behaviors). Patients were observed to show a decrease in repetitive behaviors and obsessional symptoms. Improvements were also noted in eye contact, socialization, complexity of play, contextual language use, and abnormal vocalizations. According to the investigators, 5 of the 6 responders also showed signs of improvement in features of ADHD including inattention, lack of focus, impulsivity, and hyperactivity.

Venlafaxine appeared well tolerated with the low doses used.[13] Adverse events included polyuria, nausea, inattention and behavioral activation. According to the authors, the behavioral activation symptoms were transient or disappeared with dose reduction in 3 patients, but resulted in withdrawal from the study for 2 patients because of persistent symptoms.

While these preliminary results were positive, randomized controlled studies are necessary to adequately evaluate the safety and efficacy of venlafaxine for autism spectrum disorders.

Conduct Disorder

A randomized, double-blind, third party unblinded, placebo lead-in study of 25 patients (6-16 years of age) was conducted to determine the safety and tolerability of venlafaxine in children with conduct disorder, as well as to evaluate preliminary pharmacokinetic data for venlafaxine in children or adolescents.[15] All patients met the DSM-III R diagnostic criteria for conduct disorder. The study duration was 6 weeks. Venlafaxine was titrated up to targets of 1 mg/kg/day or 2 mg/kg/day.

There were no serious adverse events or deaths reported in this study. There was no significant difference between the venlafaxine- and placebo-treated patients in this trial; however, this was a preliminary trial with insufficient power to detect differences between the treatment groups.

Pharmacokinetics

In an open-label, single-dose study, 18 subjects diagnosed with ADD or ADHD were enrolled to evaluate the pharmacokinetic profile of a single dose of extended-release venlafaxine in pediatric patients.[14] There were 6 subjects each in 3 age groups (6-7 years, 8-11 years, and 12-17 years). The single-dose clearance (normalized-body weight) of venlafaxine and ODV was 2.5-fold to 3.0-fold higher, and plasma concentrations lower, in children and adolescents compared to a historical control of adults who received the same mg/kg dose. It was calculated that children who receive 3.1 mg/kg and adolescents who receive 2.0 mg/kg would have plasma concentrations of venlafaxine and ODV similar to typical adult populations that received 150 mg.

A pharmacokinetic study in 25 children and adolescents with conduct disorder with or without major depression or ADD demonstrated similar findings.[15] The oral-clearance values (normalized for body weight) for venlafaxine were approximately 2.5-fold higher in children and adolescents with conduct disorder that in a historical control of healthy adult subjects who received similar mg/kg doses. It was calculated that children who received3.3 mg/kg/day and adolescents who receive 2.8 mg/kg/day had plasma concentrations of venlafaxine and ODV similar to typical adult populations that received 150 mg (approximately 2.0 mg/kg/day).

Summary/Conclusion

The safety and efficacy of venlafaxine in children or adolescents less than 18 years of age has not been established; therefore, we cannot recommend the use of venlafaxine in this patient population. One randomized controlled trial demonstrated that venlafaxine XR was an effective and well-tolerated treatment for children and adolescents with GAD.[5,6] In a second randomized controlled trial, the improvement in the primary endpoint was greater in the venlafaxine XR group; however, this difference did not reach statistical significance.[7] Data from clinical trials in patients with depression indicated that venlafaxine was well-tolerated but not efficacious for the treatment of depression in children and adolescents.[8-11] Several preliminary investigations into the safety and efficacy of venlafaxine for various other disorders in children and adolescents have been reported.[12,13,15] Larger randomized controlled trials are necessary to establish the safety and efficacy of venlafaxine in these populations.

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B

CLINICAL REVIEW

Executive Summary Section

Clinical Review for NDA 20-151 Supplement SE5-024

Non-Approval Action for Pediatric Supplement for Effexor XR; negative results for Effexor XR in the treatment of Major Depressive Disorder (MDD and negative trial in Effexor XR in the treatment of Generalized Anxiety Disorder) in pediatric patients

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The original supplement for the expanded indications of the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in children and adolescents was submitted September 25, 2002 as Supplement SE5-024 to NDA 20-151. Two of two studies of MDD failed to provide evidence of efficacy over placebo. Only one of two studies provided convincing evidence of efficacy over placebo in the treatment of GAD. It is my view that none of the efficacy results of this negative program for venlafaxine in pediatric MDD and GAD should be noted in labeling. However, there are safety findings of decreased weight gain and growth with venlafaxine use in this pediatric sample and I recommend that they should be added to labeling.

I recommend that the sponsor pool the four, 8-week, placebo controlled studies of MDD and GAD combined and look at the mean changes in weight and height in the venlafaxine treated patients versus the placebo treated patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Effexor and Effexor XR are combination serotonin and norepinephrine reuptake inhibitors that are approved for the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in adults. This supplement was submitted in support of pediatric labeling for Effexor XR in the treatment of MDD and GAD. This supplement presents the results of four studies: two studies in support of a claim for GAD and two in support of a claim for MDD. The MDD studies individually fail to provide evidence that Effexor XR is effective in the treatment of MDD in pediatric patients. Although one of two clinical trials did not individually support the efficacy of Effexor XR in the treatment of GAD, the sponsor proposed that the indication might be approved on the basis of one study.

It should also be noted that the sponsor had sought pediatric exclusivity for this program under FDAMA, and they are given 6 months of additional exclusivity based on the fact that they conducted the studies required under the Written Request. The Written Request stipulated that two positive studies were required to support a claim for MDD and GAD.

Since the proposal was to use the currently approved Effexor XR formulations for this expanded population, there was no need for chemistry or pharmacology reviews. Glenn Mannheim, MD did the primary review of the clinical efficacy and safety data from the clinical group. Fanhui Kong, PhD, from biometrics, also reviewed the efficacy data. Ron Kavanagh, PhD, reviewed the pediatric pharmacokinetic data.

There are two pharmacokinetic studies of venlafaxine in the pediatric population; one is done with the IR formulation (126-US) and one is done with the ER formulation (169-US). 126-US was a multiple dose study and 169-US was a single dose PK study. Dr Kavanagh pointed out that dose normalized AUCs are lower in adolescents than in adults and even lower in preadolescents and younger children. Therefore, Dr. Kavanagh concluded that children, depending on age, might need a 2-4 fold higher dose on a mg/kg/basis as compared to adults. Adolescents needed only a slightly higher mg/kg/dose as compared to adults to achieve equivalent exposures (with the caveat that the exposures to the active metabolites, NDV and NODV, were not considered). However, because effectiveness has not been demonstrated, we will not add pharmacokinetic data for pediatric patients to labeling.

B. Efficacy

Summary of Studies of MDD

Two, 8-week, multi-center parallel group randomized, double blind, placebo controlled flexible dose studies did not provide any evidence of venlafaxine's efficacy in the treatment of MDD in children. These studies employed doses ranging from 37.5 to 225-mg/day. They were adequately powered studies with 161 (103 completing) patients in study 382 and 193 patients (143 completing) in study 394. There were no differences between placebo and drug treatment groups at week eight (8) via the last-observation-carried-forward (LOCF) on-therapy evaluation (382: P=0.338; 394: P=0.386).

Summary of Studies of GAD

The sponsor submitted the results of two 8-week, double blind, placebo controlled, parallel group, flexible dose studies of children aged 6-17 years. Effexor XR demonstrated efficacy in only one of two studies (397-US).

Study 396-US did not separate Effexor XR treatment from placebo at any time point. The following table (Table 9.4.1A) from the sponsor's report shows that there was no time point at which the two treatment groups were significantly different. This difference from study 397-US is difficult to explain. Potential explanations for study failure such as differences in mean ages, placebo responses, drop-out rates, and mean daily doses, were nearly identical across the studies. In the end, drug effect was markedly different between the two studies with a mean adjusted venlafaxine change from baseline in 396-US of -15.5 and in 397-US of -18.7. Treatment separation from placebo was statistically significant starting at week 2 in study 397-US and generally speaking became stronger over the duration of the study. This was not the case in Study 396-US.

Study 396-US Primary Efficacy Variable Analysis Summary

TABLE 9.4.1A. COMPARISON BETWEEN TREATMENT GROUPS FOR C-KIDDIE-SADS GAD 9 DELINEATED ITEMS (INTENT-TO-TREAT PATIENTS) - LOCF ANALYSIS

Week on-therapy	Therapy Group	Number of Patients	Mean Score	Change From Baseline	Adj Change From Baseline	Standard Error	Adj Means (95% CI)	Placebo Minus Ven ER Adj Means (95% CI)	p-Values F-test
Baseline	Placebo	82	30.7				30.5 (30.5,30.5)		
	Venlafaxine ER	78	30.3				30.5 (30.5,30.5)		
Week 1	Placebo	81	35.2	-4.4	-4	0.8	35.5 (34.0,37.0)		0.276
	Venlafaxine ER	74	34.6	-4.7	-5	0.8	34.5 (33.0,36.0)	1.0 (-0.8,2.9)	
Week 2	Placebo	82	31.2	-8.4	-7.9	1.01	31.6 (29.6,33.6)		0.486
	Venlafaxine ER	77	30.4	-8.9	-8.8	1	30.7 (28.8,32.7)	0.9 (-1.6,3.3)	
Week 3	Placebo	82	29.9	-9.8	-9.1	1.06	30.3 (28.1,32.5)		0.257
	Venlafaxine ER	78	28.1	-11.2	-10.7	1.04	28.8 (26.7,30.9)	1.5 (-1.1,4.2)	
Week 4	Placebo	82	29.6	-10.1	-9.6	1.03	29.9 (27.7,32.1)		0.083
	Venlafaxine ER	78	27.2	-12.1	-11.9	1.04	27.6 (25.5,29.7)	2.3 (-0.3,5.0)	
Week 6	Placebo	82	28.6	-11.1	-11.8	1.11	28.7 (26.3,30.1)		0.180
	Venlafaxine ER	78	25.6	-13.6	-13.8	1.18	25.7 (23.4,28.0)	2.0 (-0.9,4.9)	
Week 7	Placebo	82	26	-13.7	-13.9	1.2	25.6 (23.1,28.1)		0.342
	Venlafaxine ER	78	23.7	-15.6	-15.3	1.16	24.2 (21.8,26.6)	1.5 (-1.5,4.5)	
Week 8	Placebo	82	26.7	-13	-12.6	1.17	26.9 (24.4,29.4)		0.060
	Venlafaxine ER	78	23.5	-15.8	-15.5	1.12	24.0 (21.6,26.4)	2.9 (-0.1,5.9)	
Final	Placebo	82	26.8	-12.9	-12.7	1.17	26.8 (24.3,29.3)		0.075
	Venlafaxine ER	78	23.6	-15.7	-15.5	1.12	24.0 (21.6,26.4)	2.8 (-0.2,5.8)	

Study 397-US Primary Efficacy Variable Analysis Summary

TABLE 9.4.1A COMPARISON BETWEEN TREATMENT GROUPS FOR C-KIDDIE-SADS GAD TOTAL (9 DELINEATED ITEMS)
LOCF ANALYSIS

Time on Therapy	Therapy Group	Number of Patients	Mean Score	Adj. Change From Baseline	Standard Error	Adj Means (95% CI)		Placebo Minus Ven ER Adj. Means	p-Value F-test
Baseline	Placebo	77	40.3			40.4	(40.4 - 40.4)		
	Ven-ER	76	40.4			40.4	(40.4 - 40.4)		
Week 1	Placebo	74	36.1	-6.8	0.86	33.5	(31.8 - 35.1)		.683
	Ven-ER	76	35.7	-7.2	0.87	33.1	(31.6 - 34.6)	0.4 (-1.4 - 2.1)	
Week 2	Placebo	77	34.9	-7.1	0.91	33.3	(31.3 - 35.3)		.021
	Ven-ER	76	32.7	-9.8	1.02	30.6	(28.6 - 32.5)	2.7 (0.4 - 5.0)	
Week 3	Placebo	77	32.8	-10.3	1.02	30.1	(27.8 - 32.3)		.005
	Ven-ER	76	29.9	-13.9	1.08	26.4	(24.2 - 28.6)	3.7 (1.1 - 6.2)	
Week 4	Placebo	77	31.7	-12.0	0.93	28.4	(25.9 - 30.8)		.009
	Ven-ER	76	28.2	-15.7	1.19	24.7	(22.3 - 27.0)	3.7 (1.0 - 6.4)	
Week 6	Placebo	77	30.3	-13.0	1.12	27.3	(24.8 - 29.8)		.007
	Ven-ER	76	27.1	-17.0	1.15	23.4	(20.9 - 25.8)	4.0 (1.1 - 6.8)	
Week 7	Placebo	77	30.0	-12.7	1.08	27.7	(25.0 - 30.4)		.002
	Ven-ER	76	25.7	-17.5	1.12	22.8	(20.2 - 25.4)	4.8 (1.8 - 7.9)	
Week 8	Placebo	77	30.2	-12.4	1.13	28.0	(25.1 - 30.8)		<.001
	Ven-ER	76	24.8	-18.6	1.16	21.7	(19.0 - 24.5)	6.2 (3.0 - 9.5)	
Final	Placebo	77	30.2	-12.5	1.19	27.9	(25.1 - 30.7)		<.001
	Ven-ER	76	24.8	-18.7	1.16	21.7	(18.9 - 24.4)	6.2 (3.0 - 9.4)	

Abbreviations: C-KIDDIE-SADS GAD = Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia; LOCF = last observation carried forward, Ven ER = venlafaxine extended release
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Conclusions Regarding Efficacy Data

Given the pediatric PK data, under dosing is a tempting hypothesis to entertain for the reason of the failure of study 396-US in GAD; however, the mean age and mean mg/kg dose across studies 396-US and 397-US are nearly identical. This therefore argues against under dosing alone as an explanation for this inconsistency.

Under dosing likewise is probably not the most likely explanation for the failure of the MDD pediatric studies with Effexor XR. Development programs for MDD in children with the exception of fluoxetine are failing even with adequate dosing. This is not the case with OCD. This is even more mysterious given that in adults only about half the doses of SSRIs that are required to treat Panic, OCD and Social Phobia are necessary to treat MDD.

There are no drugs approved for the treatment of GAD in children. Therefore, it is difficult to say whether or not the treatment response of pediatric patients with GAD will behave more like OCD or MDD. In the tricyclic antidepressant (TCA) era, off-label use of TCAs in the treatment of panic disorder was common but there did not seem to be much utility in using these drugs for GAD. OCD did not respond to TCAs in general with the one exception being clomipramine.

Most people would not have predicted the lack of efficacy of SSRI (and now venlafaxine) antidepressant treatments in children given the experience in adults. This lack of predictability and the historical lack of uniformity in treatment response across the anxiety disorders as a group leads me not to endorse the approval of a pediatric indication for GAD based on one positive study and positive results in adults. Though ultimately with experience it may prove to be sufficient evidence for efficacy, there is not enough experience at this point with GAD for me to come to that conclusion.

C. Safety

The pediatric safety of venlafaxine was explored in four placebo controlled 8-week studies (two in MDD and Two in GAD) and one open label extension study of MDD. One other 6-week phase I-II study of Conduct disorder (Study 126) was included in the sponsor's review of the safety. Thus 339 patients were exposed to Effexor XR in the four 8-week placebo controlled studies and 86 MDD patients received Effexor XR for up to 6-months. This represents 52.2 patient-years of exposure in patients with MDD and GAD.

The safety profile of venlafaxine ER in children and adolescents appears to be generally comparable to the safety profile in adults with some differences. The mean increase from baseline in the total serum cholesterol was higher than adults in the pooled GAD, but, not in the pooled MDD trials. A slightly higher mean pulse rate and ECG heart rate in children and adolescents than in adults was seen. Increases in blood pressure in children were of similar magnitude with adults.

In the pediatric population, a smaller increase in height in children in the pooled GAD studies versus placebo was noted. This was not noted in the MDD group; however, it is surprising that this was noted at all in an 8-week study period. Though height was significantly increased from baseline after 8 weeks of treatment for both venlafaxine ER- treated and placebo- treated patients, the adjusted mean increase at month 2 in the placebo group (1.3 cm) was significantly greater than the venlafaxine ER group (0.4 cm). Mean height in the long term open label treated patients only increased 1.2-cm over 6-months.

Both MDD and GAD patients treated with venlafaxine had mean decreases in weight. The mean weight losses were 0.5 kg (MDD) and 0.6 kg (GAD) over an 8-week period while there was a mean weight gain in the placebo treated MDD and GAD patients. Weight changes in both MDD and GAD patients were statistically significant.

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/s/

Paul Andreason
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Wyeth®

August 22, 2003

Dear Health Care Professional,

Wyeth wishes to inform you about an update to the prescribing information for Effexor® (venlafaxine HCl) Tablets and Effexor® XR (venlafaxine HCl) Extended-Release Capsules to reflect important safety information on the use of venlafaxine in children and adolescents. In clinical studies in pediatric patients (ages 6 to 17), efficacy was not established for major depressive disorder (MDD) or generalized anxiety disorder (GAD), and there were increased reports among those patients on Effexor XR, vs. placebo, of hostility and suicide-related adverse events, such as suicidal ideation and self-harm. Effexor and Effexor XR have not been and are not now recommended for use in pediatric patients. We have updated the prescribing information for Effexor and Effexor XR with the following information shown here in italics:

PRECAUTIONS

Usage in Children/ Pediatric Use

Safety and effectiveness in pediatric patients (individuals below 18 years of age) have not been established.

In pediatric clinical trials, there were increased reports of hostility and, especially in Major Depressive Disorder, suicide-related adverse events such as suicidal ideation and self-harm.

The most common adverse events leading to discontinuation in at least 1% of children and adolescents treated with Effexor XR, and at a rate twice that of placebo, were as follows (percentages listed for Effexor XR and placebo, respectively): MDD studies, hostility (2%, <1%) and suicidal ideation (2%, 0%); GAD studies, abnormal/changed behavior (1%, 0%). In these clinical trials there were no suicides.

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor. Effexor XR Extended-Release Capsules are indicated in adults for the treatment of MDD, GAD, and social anxiety disorder (SAD). Effexor Tablets are indicated in adults for the treatment of MDD.

In light of this important information, you should be alert to signs of suicidal ideation in children and adolescent patients prescribed Effexor or Effexor XR. You may need to reassess the benefit-risk balance when treating individual patients with Effexor or Effexor XR. If a decision is made to discontinue a patient from Effexor or Effexor XR, treatment should not be discontinued abruptly, due to

risk of discontinuation symptoms. A gradual reduction in dose under medical supervision is recommended. Please see the prescribing information for additional information with regard to discontinuation.

Wyeth is committed to global surveillance of all its products and to providing you with current product information, and therefore is sending you this letter. Should you have any questions, or wish to report any adverse event associated with Effexor or Effexor XR, please call Wyeth at 1-800-934-5556. In addition, you can send adverse event information directly to Wyeth Global Safety Surveillance and Epidemiology (GSSE) by fax to 610-989-5544 or by mail to GSSE, 500 Arcola Road, Collegeville, PA 19426.

Adverse event information may also be reported to the FDA's MedWatch Reporting System by phone (1-800-FDA-1088), fax (1-800-FDA-0178), via the MedWatch Web site at www.fda.gov/medwatch, or by mail (using postage paid form) to MedWatch, HF-2, 5600 Fisher's Lane, Rockville, MD 20852-9787.

Enclosed is a copy of the revised labeling for Effexor and Effexor XR.

Sincerely,

Victoria Kusiak

Victoria Kusiak, M.D.
Vice President, Global Medical Affairs and
North American Medical Director for Wyeth Pharmaceuticals

Enclosures

ATTACHMENT D

August 2003 Response Letter

USE OF VENLAFAXINE IN CHILDREN OR ADOLESCENTS

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI).[1,2] Its active metabolite, O-desmethylvenlafaxine (ODV), also inhibits serotonin and norepinephrine reuptake, with similar potency to venlafaxine. Venlafaxine and ODV are weak inhibitors of dopamine reuptake and have no significant affinity for muscarinic cholinergic, H1-histaminergic, or a1-adrenergic receptors in vitro. Effexor XR Capsules are indicated for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD) and social anxiety disorder (SAD). Effexor Tablets are indicated for the treatment of MDD. Please see the prescribing information for recommended dosage and administration.

Summary Points

- The safety and effectiveness of venlafaxine in children and adolescents less than 18 years of age have not been established; therefore, venlafaxine is not recommended in this patient population.[3,4]
- In pediatric clinical trials, there were increased reports of hostility and, especially in MDD, suicide-related adverse events such as suicidal ideation and self-harm.[3,4]
- The safety and efficacy of venlafaxine XR for the treatment of MDD in children and adolescents was assessed in 2 randomized, placebo-controlled trials.[5,6] Venlafaxine XR did not separate from placebo on the primary efficacy variable in either study.
- The safety and efficacy of venlafaxine extended-release (XR) for the treatment of GAD in children and adolescents was assessed in 2 randomized, placebo-controlled trials.[7,8,9] Venlafaxine XR was significantly ($P < .001$) better than placebo on the primary efficacy variable in only 1 of these studies.
- The most common adverse events leading to discontinuation in at least 1% of venlafaxine XR-treated pediatric patients and at a rate twice that of placebo were as follows (percentages listed for venlafaxine XR and placebo, respectively): GAD studies: abnormal/changed behavior (1%, 0%); MDD studies: hostility (2%, <1%) and suicidal ideation (2%, 0%).[10] In addition, the following adverse events were observed at higher incidences than in adult patients: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.
- The long-term safety of venlafaxine XR in pediatrics with MDD was evaluated in a 6-month open-label study.[11] Adverse events were the primary cause of discontinuation for 17% of patients, with hostility (3%) being most common.
- In a 5-week, open trial of 16 patients (ages 8-16) with attention deficit hyperactivity disorder (ADHD), 44% of the patients responded to venlafaxine therapy based on the Conners Parent Rating Scale (CPRS), while no significant effects were found on the Continuous Performance Test (CPT).[12]
- In an open-label, retrospective evaluation of 10 patients (ages 3-21) with autism, 60% of the patients were rated as sustained responders with a Clinical Global Impression (CGI) improvement score of 1 or 2 and showed improvement of symptoms in autism.[13]
- Pharmacokinetic studies demonstrated that the mean clearance (normalized-body weight) of venlafaxine and ODV was 2.5-fold to 3.0-fold higher, and plasma concentrations lower, in children and adolescents compared to adults who received the same mg/kg dose.[14,15]
- The safety concerns and adverse event profile for venlafaxine in pediatric patients are generally similar to those described for adult patients.[10] As with adults, decreased appetite and weight loss, increased blood pressure, and increased cholesterol have been observed. Consequently, the warnings and precautions as described in the prescribing information for adults apply to pediatric patients, including the recommendation for regular monitoring of blood pressure.
- The risks that may be associated with long-term use of venlafaxine in children and adolescents have not been systematically evaluated. In particular, there are no studies that directly evaluate the effects of long-term venlafaxine use on growth, development, and maturation.

Depression

The safety and efficacy of venlafaxine XR for the treatment of depression in pediatric patients ages 6-17 years was assessed in 2 double-blind, 8-week, placebo-controlled trials,[5,6] and one open-label 6-month trial.[11] The double-blind trials included 166 and 201 patients, respectively,[5,6] the open-label trial included 87 patients.[11] For

all 3 trials, patients met DSM-IV and Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KIDDIE-SADS-PL) criteria for major depressive disorder. Patients also had a Childhood Depression Rating Scale, Revised (CDRS-R) score ±40 at baseline, with no greater than a 30% decrease during screening; a Clinical Impressions Severity of Illness (CGI-S) score ±4; and depressive symptoms for at least 1 month prior to entry into the study. All patients in the active-treatment groups started venlafaxine at 37.5 mg/day for the first week. The doses were then titrated according to weight and response, as per the same dosing protocol as the GAD studies described above. The primary efficacy variable was the CDRS-R total score.

There was no significant difference between venlafaxine XR- and placebo-treated patients in CDRS-R scores in either of the placebo-controlled trials. Venlafaxine XR was found to be well tolerated in all 3 trials, with a safety profile that was generally similar to that seen in adults with major depression. No patients died in any of the studies. In one placebo-controlled trial,[5] adverse events were the primary or secondary cause for discontinuation of study drug in 13% of venlafaxine XR-treated patients compared with 5% of placebo-treated patients. The adverse events that most frequently caused discontinuation of treatment in the venlafaxine XR group were manic reaction (3%) and suicidal ideation (3%). In the other placebo-controlled trial,[5] adverse events were the primary cause for discontinuation of study drug in 8% of venlafaxine XR-treated patients compared with 1% of placebo-treated patients. The adverse events that most frequently caused discontinuation of treatment in the venlafaxine XR group were hostility (2%) and suicidal ideation (2%). In the open-label 6-month trial, adverse events were the primary reason for discontinuation for 17% of patients, with hostility (3%) being the most commonly cited event.[11]

In a pooled analysis of the 2 randomized controlled trials in MDD, the most common adverse events leading to discontinuation in at least 1% of venlafaxine XR-treated patients and at a rate twice that of placebo were (percentages listed for venlafaxine XR and placebo, respectively): hostility (2%, <1%) and suicidal ideation (2%, 0%).[10] The most common treatment-emergent adverse events with venlafaxine XR (incidence ≥5% and at least twice that of placebo were abdominal pain (21%) and anorexia (7%).

In another double blind, placebo-controlled, study (N = 40), Mandoki et al[16] found no efficacy difference between venlafaxine immediate-release (IR) and placebo in the treatment of depression in pediatric patients (ages 8-17 years). A higher percentage of venlafaxine-treated patients reported adverse events than the placebo group at almost every weekly assessment.[16] However, only the incidence of nausea at week 2 (all ages compared) and increased appetite (only adolescents compared) were significantly different from placebo.

GAD

The safety and efficacy of venlafaxine XR for the treatment of GAD in pediatric patients ages 6-17 years was assessed in 2 double-blind, 8-week, placebo-controlled trials that evaluated 158 and 164 patients, respectively.[7,8,9] For both trials, patients had symptoms of anxiety for ≥6 months and met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia (C-KIDDIE-SADS) criteria for GAD. Primary efficacy assessments were obtained on days 7, 14, 21, 42 and 49, and safety assessments were obtained at each visit. The primary efficacy variable was the C-KIDDIE-SADS GAD (9 delineated items).

All patients in the active-treatment groups started venlafaxine XR at 37.5 mg/day for the first week. The doses were then titrated according to weight and response using a flexible-dosing regimen. On study day 8, the doses were increased to 75 mg/day for all patients weighing ≥40 kg; the dose increase was optional for patients in the 25-39 kg group. On study day 15, the doses were titrated to a maximum of 75 mg, 112.5 mg, or 150 mg daily for the 25-39 kg group, 40-49 kg group, and ≥50 kg group, respectively. On day 29, the doses were further titrated to a maximum of 112.5 mg, 150 mg, and 225 mg, respectively, for the 25-39 kg, 40-49 kg, and ≥50 kg patient weight groups.

In the first randomized controlled trial, patients in the venlafaxine XR group had a significant mean decrease at week 8 of 18.6 points on the primary efficacy variable compared to the 12.4 point decrease in the placebo group ($P < .001$).[7,8] Adverse events were cited as a cause of discontinuation in 3% and 9% of venlafaxine XR- and placebo-treated patients, respectively. The most common treatment-emergent adverse events for venlafaxine XR (incidence ≥5% and at least twice the placebo rate) were: asthenia (10%), anorexia (10%), hyperkinesia (6%), epistaxis (6%), thinking abnormal (5%), and weight loss (5%).

In the second trial, the decrease from baseline in the C-KIDDIE-SADS GAD was greater in venlafaxine XR- compared with placebo-treated patients (15.8 versus 13); however, this difference did not reach statistical significance (P = .060).[9] The adverse events observed in venlafaxine XR-treated patients were similar to that observed in adult patients with GAD. Adverse events were the primary or secondary cause of discontinuation in 4% of venlafaxine-treated patients and 2% of placebo-treated patients. The most common treatment-emergent adverse events for venlafaxine XR (incidence ±5% and at least twice the placebo rate) were: anorexia (15%), nausea (13%), pain (9%), somnolence (8%), nervousness (8%), dizziness (6%), and dry mouth (5%).

In a pooled analysis of the 2 GAD studies, the most common adverse event leading to discontinuation in at least 1% of venlafaxine XR-treated patients and at a rate twice that of placebo was (percentages listed for venlafaxine XR and placebo, respectively): abnormal/changed behavior (1%, 0%).[10]

Anorexia/Weight Loss in MDD and GAD Trials

In a pooled analysis of the 4 randomized controlled trials of venlafaxine XR in pediatric patients (2 in MDD and 2 in GAD), treatment-emergent anorexia was reported in 10% and 3% of patients (ages 6-17) receiving venlafaxine XR and placebo for up to 8 weeks, respectively.[10] A loss of 5% or more of body weight occurred in 14% of the venlafaxine XR-treated and 1% of the placebo-treated patients in these trials.

ADHD

Olvera et al[12] conducted a 5-week, open trial of venlafaxine in the treatment of ADHD. Sixteen children and adolescents (ages 8-16 years; mean 11.6 years) meeting DSM-III-R criteria for ADHD (based on the Diagnostic Interview Schedule for Children) participated in the study. The patient was also required to have a score of at least 1.5 standard deviations above the mean for the patient's age and sex on the Inattention or Impulsivity/Hyperactivity factor of the CPRS. Venlafaxine was initiated at a dose of 12.5 mg/day for the first week. Based on the patient's tolerability, the daily dose was increased by 25 mg each week until a target dose of 75 mg/day was achieved. For children weighing less than 40 kg, daily venlafaxine doses were increased by 12.5 mg weekly up to a maximum of 50 mg. If a patient experienced side effects, the dosage was reduced to the previous level. The child's parent completed the CPRS, and the child performed the CPT at baseline and at the end of the 5-week trial. In addition, telephone interviews of the child and parent were conducted weekly to assess the effects of venlafaxine treatment on ADHD symptoms.

Of the 16 enrolled patients, 10 patients completed the study (mean venlafaxine dose, 60 mg/day).[12] Two patients were lost to follow-up, 3 discontinued therapy due to an increase in hyperactivity, and 1 discontinued due to nausea. Of the evaluable patients, treatment with venlafaxine resulted in significant improvement (P < .01) in the Impulsivity/Hyperactivity Factor and Hyperactivity Index of the CPRS. However, there were no significant changes in the Conduct Index Factor, nor were there any significant effects of venlafaxine therapy on the CPT. Overall, 44% (7/16) subjects responded favorably to venlafaxine therapy based upon the CPRS.

The most common adverse experiences were drowsiness, nausea, irritability, and worsening of hyperactivity.[12] Other reported adverse events included insomnia, dizziness, decreased appetite, dry mouth, anxiety, and headache. No appreciable effects on blood pressure or heart rate were noted.

Autism

Hollander et al[13] conducted an open, retrospective evaluation of the treatment responses to venlafaxine in children, adolescents or young adults with autistic spectrum disorders. Ten patients between the ages of 3 and 21 (mean 10.5±5.5) years old who met the DSM-IV criteria for pervasive developmental disorders, including autism and Asperger's Syndrome, were evaluated. Five patients had comorbid disorders including ADHD, body dysmorphic disorder, separation anxiety, obsessive-compulsive disorder, and Tourette's syndrome. Patients were treated with an initial dose of venlafaxine 12.5 mg/day. The venlafaxine dose was gradually increased based on clinical response and adverse events. Efficacy was assessed using the CGI improvement scale. Responders were defined as those patients who obtained a score of 1 (very much improved) or 2 (much improved).

Six of the 10 patients were rated as sustained responders with a CGI improvement score of 1 or 2.[13] The mean endpoint venlafaxine dose in these patients (25±14 mg/day) did not differ from that of the nonresponders. The mean duration of treatment was 4.8±2.5 months. Venlafaxine treatment was noted to improve symptoms in all 3 core dimensions of autism (social deficits, language and commu-

nication impairment, restricted interests and repetitive behaviors). Improvements were also noted in eye contact, socialization, complexity of play, contextual language use, and abnormal vocalizations. According to the investigators, 5 of the 6 responders also showed signs of improvement in features of ADHD including inattention, lack of focus, impulsivity, and hyperactivity.

Adverse events included polyuria, nausea, inattention and behavioral activation.[13] According to the authors, the behavioral activation symptoms were transient or disappeared with dose reduction in 3 patients, but resulted in withdrawal from the study for 2 patients because of persistent symptoms.

While the results of this retrospective evaluation were generally positive, randomized controlled studies are necessary to adequately evaluate the safety and efficacy of venlafaxine for autism spectrum disorders.

Pharmacokinetics

Venlafaxine IR

The oral-clearance values (normalized for body weight) for venlafaxine IR were approximately 2.5-fold higher in children and adolescents with conduct disorder than in a historical control of healthy adult subjects who received similar mg/kg doses.[14] It was calculated that children who received 3.3 mg/kg/day and adolescents who receive 2.8 mg/kg/day had plasma concentrations of venlafaxine and ODV similar to typical adult populations that received 150 mg (approximately 2.0 mg/kg/day).

Venlafaxine XR

In an open-label, single-dose study, 18 subjects were enrolled to evaluate the pharmacokinetic profile of a single dose of venlafaxine XR in pediatric patients.[15] There were 6 subjects each in 3 age groups (6-7 years, 8-11 years, and 12-17 years). The results of this study are similar to those reported above for venlafaxine IR. The single-dose clearance (normalized-body weight) of venlafaxine and ODV was 2.5-fold to 3.0-fold higher, and plasma concentrations lower, in children and adolescents compared to a historical control of adults who received the same mg/kg dose. It was calculated that children who receive 3.1 mg/kg and adolescents who receive 2.0 mg/kg would have plasma concentrations of venlafaxine and ODV similar to typical adult populations that received 150 mg.

Summary/Conclusion

The efficacy of venlafaxine in children or adolescents less than 18 years of age has not been established for any indication; therefore, we cannot recommend the use of venlafaxine in this patient population.[3,4]

In depression studies, suicidal ideation and hostility were the most common reasons for discontinuation that occurred at a rate ±1% and at least 2 times that for placebo.[5,6]

Based on studies in MDD and GAD, the safety profile for venlafaxine in pediatric patients is generally similar to those described for adult patients; consequently, the contraindications, warnings and precautions for adults apply to pediatric patients (consult prescribing information).

Preliminary investigations into the safety and/or efficacy of venlafaxine for various other disorders in children and adolescents have been reported.[12,13,15] Larger randomized controlled trials are necessary to establish the safety and efficacy of venlafaxine in these populations.

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Mr. WALDEN. Thank you, Dr. Camardo.

Dr. Olanoff, thanks for being here.

TESTIMONY OF LAWRENCE S. OLANOFF

Mr. OLANOFF. Mr. Chairman, members of the subcommittee, I am Dr. Lawrence Olanoff, executive vice president of Forest Laboratories and head of the Forest Research Institute. I thank the subcommittee for the opportunity to discuss Forest's views on the issues presented in this hearing and in particular to describe our clinical trial registry.

I am a medical doctor. My medical specialty is in clinical pharmacology, and I have devoted my entire career to the development of pharmaceuticals. The topic of today's hearing is the disclosure of clinical trial results. Forest routinely discloses the results of its sponsored clinical trials and believes its practices in this regard have been entirely appropriate and in full compliance with the law.

We also recognize there is great interest in the results of clinical trials by the medical community, and we realize that new approaches are needed to provide physicians and patients with all available relevant efficacy and safety information in a timely manner. To this end, Forest has announced its commitment to make its clinical trial results publicly available on its web site. We have worked with staff of the committee, members of the industry and with the New York State attorney general in developing this approach. Our policy of disclosure is reflected in our recent agreement with the New York State attorney general. We are pleased with the result.

On this registry, Forest will list key ongoing trials for its investigational products. If we are running a trial, the public will know. Forest will provide the results of phase three and four trials for its marketed products regardless of study outcome. When we have results for studies of new uses on products on the market, we will post those results on the web. This registry will include both results for studies going as far back as January 1, 2000 and safety information for even older studies where the information is important to the use of the product. As some physicians may find it cumbersome to research individual company web sites, Forest is also willing to support an industry-wide centralized registry.

Let me now comment about depression in children and Forest actions following the completion of two placebo-controlled trials with Celexa, a drug approved for the treatment of adult depression. Depression, in particular depression in children, is a terrible and dangerous disease which inflicts pain, robs victims of their ability to enjoy their lives and presents a substantial risk of suicide. The loss of a child by suicide is an issue about which Forest and its most senior executives have painful and personal experience. Our personal experience has fueled our commitment to developing and providing the most effective possible treatments for this horrible dis-

ease. This is why Forest is continuing to study its antidepressants in children.

Forest has indicated its serious intent to disclose the results of its clinical trials in a detailed and timely manner. This issue first arose due to questions regarding the past disclosure of pediatric depression trials by the industry. I would like to talk about two studies involving Forest's antidepressant product Celexa. Forest became aware of the results of a European Celexa pediatric depression trial sponsored by its licensor, Lundbeck, and the Forest-sponsored U.S. trial about the same time. The U.S. trial clearly showed that Celexa was superior to placebo treatment whereas the Lundbeck study did not show effectiveness for Celexa. The positive efficacy result achieved for the Forest-sponsored U.S. trial was a significant event. There were 15 placebo-controlled pediatric antidepressant trials reviewed by the FDA. Of these only three were positive, one of which was the U.S. study conducted by Forest with Celexa. It was the importance of the U.S. study outcome and our confidence in the results that led to its presentation and professional meetings and publication in the peer review journal. The Lundbeck study was substantially different in its design compared to the U.S. study, and its unique design features ultimately made it more difficult to fully assess the safety and effectiveness of the drug in this trial.

Despite these differences, Forest determined there were no clinically relevant safety signals in the overall results, including any clinically important or statistically significant increase in suicide-related events. We presented all these data to the FDA, and the FDA reached the same conclusion in its review of our submission. The results of both studies were presented at a prestigious scientific meeting in 2003. Further details of these two studies are provided in my written statement, and the results of both studies will be posted on our clinical trial registry in early 2005.

Mr. Chairman and members of the subcommittee, we at Forest have a deep commitment to doing what is best for patients, particularly children suffering from depression. Forest will continue to search for more effective ways to inform physicians about the clinical trial data on its products. Again, I thank the subcommittee for inviting me to speak, and I am happy to address any questions the subcommittee may have.

[The prepared statement of Lawrence S. Olanoff follows:]

PREPARED STATEMENT OF LAWRENCE S. OLANOFF, EXECUTIVE VICE PRESIDENT, FOREST LABORATORIES, INC.

Mr. Chairman and Members of the Subcommittee, I am Dr. Lawrence Olanoff. I am Executive Vice President of Forest Laboratories and head of the Forest Research Institute. On behalf of Forest, I would like to thank the Subcommittee for the opportunity to discuss our views on the issues presented in this hearing. Among other things, I will discuss our new Clinical Trial Registry.

I am a medical doctor and I have trained as a clinical pharmacologist. I have chosen to devote my career to the development of human pharmaceuticals.

Depression—and in particular depression in children and young people—is a terrible and dangerous disease. It is terrible in that it inflicts terrible pain and it robs victims of the ability to enjoy their lives. It is dangerous because it also presents a substantial risk of suicide. This is an issue about which Forest, and its most senior executives, have painful and personal experience. The book, THE NOONDAY DEMON, authored by Andrew Solomon, is a seminal study of depression and his own depression and in that book Andrew describes his own near suicide. That book

won the National Book Award and is dedicated to his father, who helped to bring him back from the brink of suicide. Andrew's book is dedicated to his father and the dedication reads "for my father who gave me life not once but twice". Andrew's father is our Chairman and Chief Executive Officer, Howard Solomon. In the case of the two most senior executives responsible for the launch and marketing of Celexa®, an antidepressant marketed by us, their child's depression took an even greater toll. Both lost young sons to suicide. One is still a member of our Board and has retired from Forest and now devotes his time to a foundation started by him to prevent suicide among young people.

So we at Forest know all too well that depression, without proper therapy, can be a devastating illness. I tell you about these personal experiences to emphasize our motivation at Forest. We strive to develop and provide the best possible treatment for this horrible disease. Our mission is to alleviate depression and thus help to prevent suicide.

Forest is a medium size pharmaceutical company that primarily markets drugs in the United States. Also, unlike the larger pharmaceutical companies who are members of PhRMA, which we are not, we do not conduct drug discovery activities in-house, but license all our products from other companies, usually European companies which sell the same products in their own markets. Our licensors often have already completed some clinical studies before we license the drug and continue to do studies after we license the drug. In the case of Celexa, for example, the drug was already approved in Europe for six years when we first licensed it. We have also, in the case of most of the drugs we have licensed, performed the additional necessary development activities and clinical trials in the United States to obtain FDA approval of these products.

The basis for a drug's evaluation are the clinical trials in which it is tested. A controlled clinical trial is a method for providing objective evidence about the safety and effectiveness of a drug. In a controlled clinical trial, subjects are divided into different test groups. Most commonly, one group will receive a placebo (a pill with no active drug), while another group will receive the test drug. We attempt to design these studies to assure, to the greatest extent possible, that the only thing that will cause a different result between the two groups is the drug itself. It is essential therefore that the patients in each study group be carefully balanced from the start in as many respects as possible to avoid distorted results. If, for example, one group included more patients with more severe illness, that might affect the results and make it difficult to know whether or not the drug itself was the cause of the study outcome or whether any observed differences arose simply because the study groups were different from the onset. Similar considerations apply in comparisons of the results across different clinical trials if there are different study designs and different patient populations. In addition, the terms that investigators use to describe adverse events and outcome measures may vary among different trials, particularly studies in different countries.

I want to make one additional point about clinical trials of depression and many other psychiatric diseases where the endpoints are not objective measurements like blood pressure but more subjective in nature like, for example, mood. It is well known and accepted in the scientific community that there is typically a relatively high proportion of placebo-treated patients who respond favorably (also called a high placebo response rate) in these studies, particularly because in the environment of a clinical trial, as distinct from clinical practice, drug therapy is accompanied by greater attention to the patient by the investigator and his staff, especially where this was not part of the patient's experience before entering the study. This means that some patients may improve from their condition at the start of the study even though they are not receiving active drug treatment. The high placebo response rate can make demonstration of a therapeutic effect for the test drug difficult when the overall response difference between test groups is compared by statistical analysis. Dr. March, the author of the NIH supported Treatment for Adolescents with Depression Study (TADS), involving Eli Lilly's Prozac and described in the recent JAMA publication, comments in regards to other SSRI/SNRI pediatric depression studies that, "In the 2 earlier fluoxetine studies, the placebo response rates were lower than placebo response rates seen in other pediatric antidepressant trials. Because the response to active drug was comparable, it was the placebo response rate that generally determined the effect size and hence whether a trial was positive or negative." Thus, in many cases studies of drugs intended for the treatment of depression fail to demonstrate a response: i.e., those studies are referred to as "negative" in the scientific literature, although they might be more logically termed "no-effect" studies. In fact, the vast majority of these no-effect studies do show some modest advantage of the test drug compared to the placebo treatment. It is just that the difference between the groups fails to meet the required statistical hurdle that con-

firms that the benefit observed did not simply occur by chance. For the reasons I stated above, the attainment of a positive study is especially notable and this explains why it may take more than one study to achieve a study with a positive outcome. Of the 15 placebo controlled studies in pediatric depression submitted to the FDA, only 3 were considered positive: two fluoxetine studies (which led to the approval of Prozac for pediatric depression) and the Forest sponsored U.S. study with Celexa which is discussed below.

It is clearly essential to determine whether drugs that are safe and effective for use in adults can also be appropriately used in children. This is an important inquiry, because children may be physiologically and psychologically different from adults and they therefore may react differently to drugs. The law therefore currently requires the conduct of pediatric studies where the indications sought for in adults may be applicable to the pediatric population.

Forest supports the goals of the pediatric study law and FDA's implementation of that law with respect to antidepressant drugs. If a drug should not be used in children, doctors should know that. Conversely, if a drug can help some children suffering from depression, it would be a tragedy if doctors and patients were discouraged from its use in that population, condemning those children and their families to unnecessary misery and to a possibly preventable risk of suicide. This places a heavy responsibility on the FDA as it has in so many areas. In our experience we have found the FDA to be unbiased and expert.

So far as we are aware, based on the data available to us and the complexity of the subject, we believe that FDA is trying to achieve the right result.

I want to emphasize that, because the FDA has not approved pediatric labeling for our products, Forest has always been scrupulous about not promoting the pediatric use of our antidepressant drugs, Celexa and Lexapro®. That is the law, and we follow it.

Prior to approval, companies are required to fully disclose the results of all studies related to the indication sought in the NDA to the FDA regardless of their outcome, and Forest has always done so. The FDA reviews those studies and decides what information is necessary in the package labeling which is the ultimate source of information for the physician. The FDA may approve a drug based on two positive studies even if there are negative or no-effect studies in the application, and it may or may not require mention of the no-effect studies in the label because, in large part, the scientific community has accepted that positive studies are generally more informative than no-effect studies. Companies frequently continue to develop drugs despite no-effect studies; the FDA approves drugs even when there are no-effect studies; and journals will often reject no-effect studies for publication.

That brings us to the question of publication and disclosure of the results of clinical trials, both those that show a positive effect and those that fail to detect a positive effect. Aside from the review by the FDA itself, perhaps the most objective review of a pharmaceutical company's clinical studies is the peer review system of prestigious medical journals. It is our experience that journals publish only a small portion of the studies conducted or submitted to their editors, and that they are usually interested in reporting positive studies and are often not interested in publishing studies which are not positive. Positive studies may be breakthrough studies; they are likely to be of greater interest to physicians. No-effect or negative studies, particularly if there are a number of known prior such studies in the same drug category, are often considered of less interest to their physician audience. That is certainly not always the case, but it is understandable that medical journals, like the media in general, want to publish what they believe their readers would be most interested in.

The next question relates to studies for new therapeutic uses completed after the FDA has initially approved the drug for a particular indication. There is no established procedure for disclosure of such study results. The general principle observed by Forest is that information that better enables physicians to treat their patients should be available to them.

Recently much public attention has been directed towards approaches to achieve the timely and full disclosure of all clinical study results for approved and unapproved uses of marketed products. Many have recognized that scientific publications alone cannot serve as the sole vehicle for this purpose for the reasons I have cited above.

Forest has focused on this complicated issue and announced this week the development of detailed procedures to assure that all results of Phase III and IV trials are reported in a Clinical Trial Registry. Forest's Clinical Trial Registry will contain the following information:

Ongoing Studies

Forest's Clinical Trial Registry will include a listing of Forest-sponsored ongoing phase III and phase IV clinical studies for all Forest drugs. In particular, when Forest initiates a Phase III or Phase IV clinical study, the number, title, start date and key objectives will be posted to the Clinical Trial Registry.

Completed Studies

For all phase III and phase IV Forest-sponsored studies relating to currently-marketed Forest products completed since January 1, 2000, Forest will by December 31, 2005 post summaries of the results of these studies on the Clinical Trial Registry. This will include summaries of clinical study reports for clinical studies of the use of Celexa and Lexapro by pediatric patients. These summaries will include results for the protocol-defined efficacy and safety outcomes, as well as a description of the trial design and methodology.

For all phase III studies relating to Forest products completed after today, Forest will post summaries of the results on the Clinical Trial Registry upon the commercial introduction of the product in the United States. For phase IV trials conducted for the approved indications completed after today, Forest will post summaries of the results within a year of study completion.

For studies submitted to scientific peer-reviewed journals whose policies do not permit disclosure of study results prior to publication in these journals, the clinical study summary will be posted at the time of publication. Also, Forest will post a summary on the Clinical Trial Registry of: (a) those Forest-sponsored phase I and phase II studies completed after January 1, 2000 for products which Forest currently markets, and (b) those Forest-sponsored studies completed prior to January 1, 2000 for products which Forest currently actively promotes, which provide additional important information for physicians and the care of patients.

In addition to our own activities in this regard, Forest will participate in and be guided by any industry, legislative, regulatory or medical association initiatives to facilitate this effort.

Now that I have provided the details of our recently announced Clinical Trial Registry, I want to comment on Forest's past practices in disclosing clinical trial results by referring to our three principal products. The first is Namenda, our recently approved drug for the treatment of moderate-to-severe Alzheimer's disease. The product was approved in October, 2003. We have released information on four placebo controlled studies relating to unapproved uses, in each case promptly after we received the study results as these results were judged to be material to investors. In the case of use of this drug in the treatment of patients with mild-to-moderate Alzheimer's disease, we disclosed that one study was positive and that two studies (one of which was performed by a European licensee) showed no effect. We hope to ultimately obtain FDA approval for Namenda in the treatment of mild-to-moderate Alzheimer's disease. The other study related to use of the active ingredient in Namenda in the treatment of neuropathic pain and it also failed to meet the FDA standard for approval even though an earlier study had shown promising results. Again, we promptly disclosed these results. We are continuing to study the drug for that indication and likewise ultimately hope to be able to meet FDA requirements for that indication.

The second drug is Celexa, which was approved for depression in adults in the U.S. in 1998 and which had been first approved in Europe as early as 1989. For this product there are two placebo controlled studies in pediatric-adolescent population. One was a study conducted by our licensor in Europe over a five year period which recruited patients from seven different countries and underwent various modifications in the test protocol over the course of the study in an attempt to improve its slow enrollment rate. We did not originate, design or monitor that study. This study included patients with characteristics that we and other sponsors would not use in our studies of depression and which we believe caused a substantial degree of patient variability and potentially important differences in disease severity between the active and placebo group from the very start of the study. Specifically, the European study allowed for the enrollment of patients without regards to a past history of hospitalization due to psychiatric illnesses, past history of suicide related events or a history of a failure to respond to other antidepressants.

Further, patients were allowed to enter into the study with other co-morbid psychiatric illnesses or on other concomitant psychotropic medications or receiving psychotherapy. This study was unique across the experience of placebo-controlled pediatric trials in that it allowed both hospitalized patients and outpatients to be enrolled. In fact, a third of the patients enrolled had a past history of suicide related events and the patients in the Celexa group had a higher rate of previous psychiatric hospitalizations and a greater number of the Celexa treated patients were

hospitalized due to psychiatric illnesses at the start of the study compared to the placebo group. These design features and potential imbalances between groups make it very difficult to interpret any resultant differences in the incidence of relatively infrequent events such as suicidal ideation or behavior as related to a particular treatment assignment. Finally, this study did not demonstrate effectiveness of Celexa for pediatric use which we believe was due largely to a high placebo response rate, amounting to some 60% of the placebo treated patients.

The second trial was a well-controlled study, designed and monitored by Forest in the United States with investigators and trial centers determined by us, which did demonstrate the efficacy of Celexa for pediatric patients. In contrast to the European study, the U.S. Celexa study was more typical of other pediatric depression studies in that it enrolled only outpatients, did not allow patients to enter with a history of suicidal behavior or treatment resistance, did not allow for concurrent psychotherapy and was far more restrictive in the use of concomitant psychotropic drugs or the presence of comorbid psychiatric illnesses. We felt that this study was important to the medical community as it was the first and only positive study after a string of no-effect studies for all the other modern antidepressants except for two previous positive studies for fluoxetine, which has been approved for the treatment of pediatric depression. When we first unblinded these Celexa studies in 2001, we looked carefully at all the safety data combined across the two studies. We did not see in these results any evidence of a statistically significant or clinically relevant increase in suicide related events (SREs). We fully reported what we believed to be suicide related events under appropriate adverse event descriptive terms in our submission to the FDA in 2002 and the FDA in its review of our submission, while not granting approval for a pediatric indication, did conclude that there were no new safety issues identified in this population which would require labeling. When this issue was raised again in 2003 due to potential concerns over the SSRI/SNRI class as a whole, we reviewed our entire pediatric safety database for any SREs using the FDA's provided algorithm. Our conclusion and the conclusion of the FDA in early 2004, as reflected in the August 16, 2004 memo by Dr. Mosholder, of the FDA, was that the difference between the citalopram and placebo groups in the incidence of SREs was relatively small (risk ratio of approximately 1.4) and not statistically significant. The FDA conducted a new analysis in August based on a reclassification of SREs by experts at Columbia University. After their elimination of questionable cases, this reclassification reduced the number of SREs by some 40% for the citalopram group compared to our own earlier classification. This reclassification led to a new FDA calculated risk ratio of 1.37, also not statistically significant and the lowest of all the risk ratios among the SRI/SNRIs except for Prozac. After adding to this overall Celexa database, the safety experience from the Forest-sponsored and the only pediatric placebo-controlled trial with Lexapro (escitalopram, which is the therapeutically active enantiomer of citalopram), this risk ratio would be reduced to approximately 1.2. The Lexapro trial is relevant as it was conducted in the U.S. according to a protocol design very similar to that of the earlier U.S. pediatric trial for Celexa. When these two U.S. studies are taken together, and separate from the European Celexa trial, the risk of suicide related events is actually two-fold higher in the placebo group compared to these two related SSRIs; however, the numbers of events in these U.S. trials were too low to demonstrate any statistical differences.

As I have previously indicated, these two U.S. trials are in substantial contrast by design to the European trial where event rates were higher in both treatment groups. As stated by the FDA medical reviewer, Dr. Hammad in his review of August 16, 2004, in describing the U.S. and European Celexa trials, "These two Celexa trials varied in almost every aspect. The combination of the differences might have led to higher probability of having higher risk patients in trial 94404."

Forest conducted further analyses to attempt to better understand why certain patients in the Celexa trials experienced SREs. The analyses revealed that such patients generally experienced numerous antecedent psychosocial stress factors and as a group responded substantially less well to treatment, whether they were treated with placebo or active drug, compared to the patients who did not experience SREs.

It was these psychosocial factors and the lack of therapeutic response that appeared to better predict whether a given patient would experience an SRE, rather than their drug or placebo treatment assignment or any prior activation-like side effects.

Dr. March in his recent publication of the TADS results makes the same observation of the patients who experienced what he described as "harm-related adverse events" which included suicide related adverse events. Dr. March states that, "Incident narratives indicate that irritability, agitation/ restlessness, and anxiety were not commonly reported in association with harm-related adverse events, suggesting

that other factors, such as substance use and psychosocial stressors, may be more important in mediating the risk of harm-related adverse events."

Both Celexa studies were completed at virtually the same time, despite the fact that the European study was started four years before our study. In fact, the results of both studies were obtained shortly before we terminated virtually all promotion of Celexa for any use. We stopped promoting Celexa because we had obtained approval for Lexapro, a more potent antidepressant which we considered a superior product. However, the fact that we had a successful study demonstrating efficacy in a pediatric population, after there have been so many no-effect studies for so many other similar antidepressant products was important and something the study investigators felt should be made available to the medical profession. This study was therefore presented at several scientific meetings and accepted by and published in a prominent peer reviewed journal in June, 2004. The no-effect or negative European study results were not hidden by us and were available in several sources including a 2003 presentation at a prestigious meeting of psychiatrists specializing in the care of pediatric and adolescent patients, at which the safety and efficacy findings of both studies were described.

The final example is Lexapro, the antidepressant drug that Forest is currently promoting. We performed a clinical trial of this drug in a pediatric population and that trial failed to show a statistically significant therapeutic effect but did not demonstrate any safety issues for Lexapro in these pediatric patients. We promptly issued a press release disclosing the results of that study. Based on our overall analysis of the study results we are continuing to study Lexapro for that indication. That press release also discussed the positive and no-effect trials of Celexa.

We understand that there is great interest in the issue of disclosure of the results of clinical trials. With respect to Forest, we believe we have consistently acted appropriately and in compliance with all legal and regulatory requirements when informing physicians about out products. As I stated earlier, we are prepared to put into effect a publicly accessible clinical trial registry to facilitate the timely disclosure of our phase III and IV clinical study results for our marketed products.

We at Forest have a deep—and deeply personal—commitment to doing what is best for patients, and particularly children suffering from depression. Our mission is to help heal and treat young people. Forest will continue to search for more effective ways to inform physicians about clinical trial data on its products. I look forward to today's discussion of these important issues.

Mr. WALDEN. Thank you, Doctor.

Dr. Marcus.

TESTIMONY OF RONALD N. MARCUS

Mr. MARCUS. Good afternoon, Mr. Chairman and members of the subcommittee. My name is Dr. Ron Marcus, and I am the executive director of Neuroscience Global Clinical Research at the Bristol-Myers Squibb Pharmaceutical Research Institute. I am also a board certified psychiatrist. Today, I am representing my company to briefly describe our efforts to responsibly report the results of pediatric clinical trials involving our antidepressant, nefazodone, which is also known by its branded commercial name, Serzone.

Serzone was approved almost 10 years ago by FDA. Upon approval, FDA requested the Bristol-Myers Squibb conduct studies to evaluate the use of Serzone in children and adolescents with depression. In response to this request, Bristol-Myers Squibb initiated two pediatric clinical studies involving Serzone. One was a pharmacokinetic and safety study in children and adolescents, and the other was an efficacy and safety study in adolescents. Additionally, in 1999, FDA issued a written request for pediatric studies with Serzone. In response to this request, Bristol-Myers Squibb initiated a third post-approval study, one that examined Serzone's efficacy and safety in pediatric patients.

Bristol-Myers Squibb fulfilled its commitment to FDA and completed all three pediatric trials of Serzone. Each of these studies was carefully designed and the protocols were reviewed by FDA.

The results of the three studies were disclosed in a manner that would appropriately inform the psychiatric community of the studies' results. Specifically, the results of the pharmacokinetic study in children and adolescents were published in the well-respected journal of the American Academy of Child and Adolescent Psychiatry. The results of our efficacy and safety study in adolescents were presented in scientific posters at the annual meeting of the American Psychiatric Association, the premier psychiatric conference in this country, as well as the New Clinical Drug Evaluation Unit conference, otherwise known as NCDEU. Finally, the results of our third study that looked at Serzone's efficacy and safety in pediatric patients were included in the posters detailing the adolescent study presented at the APA and NCDEU meetings.

Bristol-Myers Squibb also submitted the clinical trial results to FDA. After reviewing the clinical trial data, FDA advised the company that the safety and efficacy of Serzone in individuals below 18 years of age had not been established through the clinical trials. The Serzone product label specifically states that the safety and effectiveness in individuals below 18 years of age have not been established.

Bristol-Myers Squibb is committed to the principle that clinical trial results that could have a bearing on patient care and treatment should be made available to physicians making medical decisions regarding the use of our medicines. Our commitment to this principle was most recently highlighted by a response to results of the TIMI-22, or PROVE-IT trial. The trial demonstrated that patients with a recent acute coronary syndrome benefited significantly when treated with an intensive statin regimen using high doses of a competitor's drug when compared to a regiment using standard doses of Bristol-Myers Squibb's statin drug. Clearly, the results could be interpreted as favoring the competitor's product, but because the study data could have an immediate impact on patient care, we worked closely with the investigators to ensure that the presentation and publication of the data were achieved in the shortest possible time.

Consistent with our company's commitment to the principle of disclosure described above, we support the PhRMA principles on the conduct of clinical trials and disclosure of results. Further, we are in the process of developing a mechanism for making these clinical results publicly available. In addition, Bristol-Myers Squibb also registers clinical trials on www.clinicaltrials.gov for life-threatening or serious diseases.

Regarding Serzone, clearly, our company disclosed the results of our pediatric trials in an appropriate manner, and Serzone's label continues to provide a warning to physicians regarding Serzone's use with pediatric patients. Beyond Serzone, Bristol-Myers Squibb is absolutely committed to open and timely reporting of clinical trial results of our medicines when the welfare of patients could be affected. As demonstrated by the company's approach to the TIMI-22 trial on statin drugs, BMS will openly disclose important data, regardless of result, that can have a real impact on patient care.

Thank you for the opportunity to testify on this important issue, and I will be happy to answer any of your questions.

[The prepared statement of Ronald N. Marcus follows:]

PREPARED STATEMENT OF RONALD N. MARCUS, EXECUTIVE DIRECTOR, NEUROSCIENCE GLOBAL CLINICAL DEVELOPMENT, PHARMACEUTICAL RESEARCH INSTITUTE, BRISTOL-MYERS SQUIBB COMPANY

Good morning Mr. Chairman and members of the Subcommittee on Oversight and Investigations.

My name is Dr. Ron Marcus, and I am an executive director of neuroscience global clinical development at the Bristol-Myers Squibb Company's Pharmaceutical Research Institute. I am also a board certified clinical psychiatrist. Today, I am here representing my company to briefly describe our efforts to responsibly report the results of pediatric clinical trials involving our anti-depressant nefazodone, which is also known by its branded commercial name—Serzone.

Serzone was approved almost ten years ago by the FDA. Upon approval, FDA requested that Bristol-Myers Squibb conduct studies to evaluate the use of nefazodone in children and adolescents with depression. In response to this request Bristol-Myers Squibb, initiated two pediatric clinical studies involving Serzone. One was a pharmacokinetic and safety study in children and adolescents, and the other was an efficacy and safety study in adolescents. Additionally, in 1999 FDA issued a Written Request for pediatric studies with Serzone. In response to this request, Bristol-Myers Squibb initiated a third post-approval study—one that examined Serzone's efficacy and safety in pediatric patients.

Bristol-Myers Squibb fulfilled its commitment to the FDA and completed all three pediatric studies of Serzone. Each of these studies was carefully designed and their protocols were reviewed by the FDA.

The results of the three studies were disclosed in a manner that would appropriately inform the psychiatric community of the studies' results. Specifically, the results of the pharmacokinetic study in children and adolescents were published in the well-respected Journal of the American Academy of Child Adolescent Psychiatry. The results of our efficacy and safety study in adolescents were presented in scientific posters at the Annual Meeting of the American Psychiatric Association—the premier psychiatric conference in this country, as well as at the New Clinical Drug Evaluation Unit conference. Finally, the results of our third study that looked at Serzone's efficacy and safety in pediatric patients were included in the posters detailing the adolescent study presented at the APA meeting.

Bristol-Myers Squibb also submitted the clinical trial results to the FDA. After reviewing the clinical trial data, the FDA advised the company that the safety and efficacy of Serzone in individuals below 18 years of age had not been established through the clinical trials. The Serzone product label expressly states that the "safety and effectiveness in individuals below 18 years of age have not been established."

Bristol-Myers Squibb Company is committed to the principle that clinical trial results that could have a bearing on patient care and treatment should be made available to physicians making medical decisions regarding the use of our medicines. Our commitment to this principle was most recently highlighted by our response to the results of the TIMI-22, or "PROVE-IT," trial. The trial demonstrated that patients with a recent acute coronary syndrome benefited significantly when treated with an intensive statin regimen using high doses of a competitor's drug when compared to a regimen using standard doses of—Bristol-Myers Squibb's statin drug. Clearly, the results could be interpreted as favoring the competitor's product. But because the study data could have an immediate impact on patient care, we worked closely with the investigators to ensure that presentation and publication of the data were achieved in the shortest possible time.

Consistent with our company's commitment to the principle of disclosure described above, we support the PhRMA Principles on the Conduct of Clinical Trials and Disclosure of Results. Further, we are in the process of developing a mechanism for making these clinical results publicly available. Bristol-Myers Squibb also registers clinical trials on www.clinicaltrials.gov for life-threatening or serious diseases.

Regarding Serzone, clearly our company disclosed the results of pediatric trials in an appropriate manner, and Serzone's label continues to provide a warning to physicians regarding Serzone's use with pediatric patients.

Beyond Serzone, Bristol-Myers Squibb's is absolutely committed to open and timely reporting of clinical trial results of our medicines when the welfare of patients could be affected. As demonstrated by the company's approach to the TIMI-22 trial on statin drugs, Bristol-Myers Squibb will openly disclose important data, regardless of result, that could have a real impact on patient care.[1]

[1] In a letter dated March 24, 2004, the Committee on Energy and Commerce requested data and background information from BMS from any published and unpublished nefazodone clinical

Continued

ADDITIONAL BACKGROUND

1 OVERVIEW OF THE NEFAZODONE PEDIATRIC STUDIES

On December 22, 1994, FDA approved Serzone® (nefazodone hydrochloride) with a post-approval commitment to conduct studies to evaluate the use of nefazodone in children and adolescents with depression. In response to this commitment and a written Request for pediatric studies with Serzone issued by FDA in 1999, BMS has conducted three nefazodone pediatric studies: CN104-136, CN104-141 and CN104-187.

Study CN104-136: "An Open Label Pharmacokinetic Trial of Nefazodone in Depressed Children and Adolescents"

CN104-136 was a trial designed primarily for the evaluation of pharmacokinetics and the assessment of safety and tolerability in children and adolescents; it is uninformative on the evaluation of efficacy because it is an open-label, uncontrolled trial (i.e., no placebo or comparator arms). BMS submitted the Final Study Report for the Acute Phase to FDA on August 21, 1997; the results were presented at the Annual Meeting of the American Academy of Child and Adolescent Psychiatry in October, 1997. The Final Study Report for the Extension Phase was submitted to FDA on January 20, 1999; these results were published in August, 2000. Findling R.L., Preskorn S.H., Marcus R.N., et al., *Nefazodone pharmacokinetics in depressed children and adolescents,* J. American Academy Child Adolescent Psychiatry 2000; 39;1008-16.

Study CN104-141: "A Multicenter, Double-Blind, Placebo-Controlled Trial of Nefazodone in Depressed Adolescents"

CN104-141 was a double-blind, placebo-controlled trial involving only adolescents designed primarily for the evaluation of efficacy and safety in pediatric patients. The Final Study Report of the Acute Phase and the Ongoing Study Report of the Extension Phase were submitted to FDA on April 16, 2002. The study results were presented in a poster at the Annual Meeting of the American Psychiatric Association, the premier psychiatric conference, on May 20, 2002. M.A. Rynn, R.L. Findling, G.J. Emslie, R.N. Marcus, L.A. Fernandes, M.F. D'Amico, S.A. Hardy, *Efficacy and Safety of Nefazodone in Adolescents with MDD.* The study results were also presented in a poster at the New Clinical Drug Evaluation Unit conference on June 12, 2002. G.J. Emslie, R.L. Findling, M.A. Rynn, R.N. Marcus, L.A. Fernandes, M.F. D'Amico, S.A. Hardy, *Efficacy and Safety of Nefazodone in the Treatment of Adolescents with Major Depressive Disorder.*

Study CN104-187: "A Multicenter, Double-Blind, Placebo-Controlled Trial of Two Dose Ranges of Nefazodone in the Treatment of Children with a Major Depressive Episode"

CN104-187 was a double-blind, placebo-controlled trial involving children and adolescents designed primarily for the evaluation of efficacy and safety in pediatric patients. BMS submitted to FDA the Final Study Report of the Acute Phase and the Ongoing Study Report of the Extension Phase on April 16, 2002. While the results of the study were not formally presented nor published, the two posters for CN104-141 stated: "In a second depression trial in pediatric patients (aged 7-17), nefazodone did not differentiate from placebo." BMS submitted to FDA the Final Study Report of the Extension Phase on September 3, 2004.

2 ADVERSE EVENTS IN THE PEDIATRIC STUDIES

Adverse Events Concerning Worsening Depression, Suicidal Ideation, and Rate of Self-Injury

The risk of worsening depression, suicidal ideation, and rate of self-injury can only, truly, be assessed in the double-blind, placebo-controlled efficacy studies, such as CN104-141 and CN104-187. BMS assessed these risks through the tabulation of adverse events and an analysis of a CDRS-R item related to suicidal ideation.

A review of patient-reported adverse events in the short-term and long-term phases of CN104-141 and CN104-187 was done to evaluate the incidence of worsening depression. Altogether there were two reports of worsening depression in the nefazodone group and no reports in the placebo group, on therapy, in the short-term phase of the efficacy studies; this finding was not statistically significant and therefore did not provide evidence that there is an increased risk of depression with

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trials involving depressed children. On April 12, 2004, BMS submitted the requested data and background information; a copy of that submission (without attachments) is provided as Attachment A.

short-term use of nefazodone. In the long-term phase of CN104-141, there was one patient with worsening depression in the placebo group and no patients in the nefazodone group.

The risk of worsening suicidal ideation was assessed by evaluating the incidence of patients with a baseline score of 1 or 2 on item 13 of the CDRS-R (Suicidal Ideation) that increased to a score of 3 or higher. The results of this analysis show no statistical difference in the incidence of worsening suicidal ideation between nefazodone-treated patients and placebo-treated patients in the short-term phases of CN104-141 and CN104-187. In the long-term phase of CN104-141, no patients on either nefazodone or placebo had worsening suicidal ideation as assessed on item 13 of the CDRS-R.

BMS received a number of requests from FDA beginning on July 2, 2003 for data and information on nefazodone and suicidality in pediatric patients. In response to those requests, BMS has made four submissions to FDA. The review revealed that no suicides occurred in either study. Two nefazodone patients and no placebo patients had on-therapy suicide-related or self-injury events during the short-term phase of the study. One nefazodone patient had self-injurious behavior (minor self-mutilation), during the screening phase, prior to dosing. There were no statistically significant differences between nefazodone and placebo on the incidence of suicidal-related adverse events.

3 COMMUNICATIONS WITH FDA

As discussed above, BMS conducted nefazodone pediatric studies in response to a request from FDA. BMS submitted to FDA the Final Study Reports for CN104-136 on August 21, 1997, and January 20, 1999. BMS submitted to FDA the Final Study Reports for the Acute Phases and the Ongoing Study Reports of the Extension Phases for CN104-141 and CN104-187 on April 16, 2002. Based upon the results of these studies, FDA told BMS that nefazodone is not indicated for use in pediatric patients and the product label specifically notes that the safety and efficacy in individuals below 18 years of age has not been established.

Thank you for the opportunity to testify on this important issue this morning.

Attachment A

RESPONSE TO THE CHAIRMAN OF THE COMMITTEE ON ENERGY AND COMMERCE CONCERNING THE SAFETY AND EFFICACY OF SERZONE® (NEFAZODONE) IN DEPRESSED CHILDREN AND ADOLESCENTS

Bristol-Myers Squibb Company

12-Apr-2004

Approved v2.0 930006704 1.0

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ATTACHMENTS

Attachment	Document	Date Provided to the Serzone NDA #20-152
1.	Marcus RN. An open-label pharmacokinetic trial of nefazodone in depressed children and adolescents (Final Short-Term Phase Clinical Study Report for Protocol No. CN104136). Bristol-Myers Squibb Company, August 1997. BMS Document Control No. 910061068.	Supplement 032 (April 16, 2002)
2.	Fernandes LA. Open-label pharmacokinetic trial of nefazodone in depressed children and adolescents (Final Short-Term Phase Clinical Study Report for Protocol No. CN104136 -Amendment 1). Bristol-Myers Squibb Company, March 2002. BMS Document Control No. 930001515.	Supplement 032 (April 16, 2002)
3.	Findling RL, Preskorn SH, Marcus RN, Magnus RD, D'Amico F, Marathe P, et al. Nefazodone pharmacokinetics in depressed children and adolescents. J Am Acad Child Adolesc Psychiatry 2000;39(8):1008-16, 2000.	N/A
4.	Fernandes LA. A multicenter, double-blind, placebo-controlled trial of nefazodone in depressed adolescents (Final Short-Term Phase Clinical Study Report for Protocol No. CN104141). Bristol-Myers Squibb Company, February 2002. BMS Document Control No. 930001171.	Supplement 032 (April 16, 2002)

LIST OF ATTACHMENTS

Attachment	Document	Date Provided to the Serzone NDA #20-152
5.	Fernandes LA. A multicenter, double-blind, placebo-controlled trial of two dose ranges of nefazodone in the treatment of children and adolescents with a major depressive episode (Final Short-Term Phase Clinical Study Report for Protocol No. CN104187). Bristol-Myers Squibb Company, March 2002. BMS Document Control No. 930001489.	Supplement 032 (April 16, 2002)
6.	Marcus RN. An open-label pharmacokinetic trial of nefazodone in depressed children and adolescents (Final Long-Term Phase Clinical Study Report for Protocol No. CN104136). Bristol-Myers Squibb Company, November 1998. BMS Document Control No. 910070986.	Supplement 032 (April 16, 2002)
7.	Fernandes LA. A multicenter, double-blind, placebo-controlled trial of nefazodone in depressed adolescents (Ongoing Long-Term Phase Clinical Study Report for Protocol No. CN104141). Bristol-Myers Squibb Company, March 2002. BMS Document Control No. 930001464.	Supplement 032 (April 16, 2002)
8.	Fernandes LA. A multicenter, double-blind, placebo-controlled trial of two dose ranges of nefazodone in the treatment of children and adolescents with a major depressive episode (Ongoing Long-Term Phase Clinical Study Report for Protocol No. CN104187). Bristol-Myers Squibb Company, March 2002. BMS Document Control No. 930001468.	Supplement 032 (April 16, 2002)

LIST OF ATTACHMENTS

Attachment	Document	Date Provided to the Serzone NDA #20-152
9.	Fernandes LA. Integrated summary of the efficacy and safety of nefazodone in the treatment of children and adolescents with depression. Bristol-Myers Squibb Company, April 2002. BMS Document Control No. 930001509.	April 16, 2002
10.	Response to FDA request for information regarding pediatric suicidality.	September 5, 2003
11.	Response to FDA request for information regarding pediatric suicidality.	December 17, 2003
12.	General correspondence to FDA.	January 9, 2004
13.	Response to FDA request for information regarding pediatric suicidality.	January 14, 2004

1 INTRODUCTION

The United States House of Representatives Committee on Energy and Commerce, in a letter dated March 24, 2004, requested data and background information from Bristol-Myers Squibb (BMS) from any published and unpublished nefazodone clinical trials involving depressed children. The Committee requested answers to four specific questions; the responses to these questions can be found in sections 3, 4, 5, and 6 of this document. The Committee also requested study reports and data previously submitted to the FDA; please see the list of attachments for a description of these documents.

2 BACKGROUND/OVERVIEW OF THE NEFAZODONE PEDIATRIC STUDIES

BMS has conducted three nefazodone pediatric studies (Table 1). All three studies were conducted in the United States, each with a short-term (8-week) and a long-term (18- or 26-week) phase. One of the studies, CN104136, was an open-label, single-arm, 8-week clinical pharmacology trial at two centers, designed primarily for the evaluation of pharmacokinetics and the preliminary assessment of safety. The long-term phase of study CN104136 was an 18-week, open-label, two-center, outpatient evaluation of the safety and tolerability of nefazodone in children and adolescents with a diagnosis of Major Depressive Episode for patients who had responded to treatment in the short-term phase. Study CN104136 is uninformative on the evaluation of efficacy of nefazodone because it was an open-label, uncontrolled trial (ie, no placebo and/or comparator arms). Two studies, CN104141 and CN104187, were multicenter (15 and 28 sites, respectively), double-blind, placebo-controlled trials designed primarily for the evaluation of efficacy and safety in pediatric patients with a diagnosis of Major Depressive Episode. The diagnosis of Major Depressive Episode was made using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. The designs of the two efficacy studies differed in three important ways. First, only adolescents (12 to 18 years of age) were enrolled in CN104141, whereas both children (7 to 11 years of age) and adolescents (12 to 17 years of age) were enrolled in CN104187. Second, a flexible dose range of nefazodone was compared with placebo in the short-term phase of CN104141, whereas two non-overlapping dose ranges of nefazodone (ie, low and high) were compared with placebo in the short-term phase of CN104187. Third, all patients entering

the long-term phase of CN104141 continued on the same double-blind treatment that they received in the short-term phase, whereas all patients entering the long-term phase of CN104187 received open-label nefazodone. The final clinical study reports for the short-term phases of studies CN104136,* CN104141, and CN104187 are provided in Attachments 1 through 5. The final clinical study report of the long-term phase of study CN104136 and ongoing clinical study reports of the long-term phases of studies CN104141 and CN104187 are provided in Attachments 6, 7, and 8, respectively. Data from these studies have also been summarized as part of a pediatric submission; see Attachment 9.

* Documentation for the short-term phase study CN104136 includes a study report (Attachment 1), an amendment to the study report (Attachment 2), and a publication (Attachment 3).

Table 1: Studies in the Nefazodone Pediatric Program

Study Number	Study Title	Study Dates	Location	Duration of Treatment	Treatment Groups	Nefazodone Dosage (mg/day)	Number of Patients (Safety Sample)
CN104136 (Short-Term Phase)	An Open-Label Pharmacokinetic Trial of Nefazodone in Depressed Children and Adolescents	5-Mar-1996 to 26-Sep-1996	USA	8 weeks	Nefazodone Children Adolescents	 50 – 300 100 - 600	28
(Long-Term Phase)		14-May -1996 to 30-Dec-1996	USA	18 weeks	Nefazodone Children Adolescents	 50 – 300 100 - 600	19
CN104141 (Short-Term Phase)	A Multicenter, Double-Blind Placebo-Controlled Trial of Nefazodone in Depressed Adolescents	29-Oct-1998 to 19-Sep-2001	USA	8 weeks	Nefazodone Placebo	100 - 600	201
(Long-Term Phase)		18-Jan-1999 to 22-Aug-2001	USA	26 Weeks	Nefazodone Placebo	100-600	90

Table 1: Studies in the Nefazodone Pediatric Program

Study Number	Study Title	Study Dates	Location	Duration of Treatment	Treatment Groups	Nefazodone Dosage (mg/day)	Number of Patients (Safety Sample)
CN104187 (Short-Term Phase)	A Multicenter, Double-Blind, Placebo- Controlled Trial of Two Dose Ranges of Nefazodone in the Treatment of Children and Adolescents with a Major Depressive Episode	23-Oct-2000 to 15-Nov-2001	USA	8 weeks			278
					Nefazodone:		
					Low dose		
					Children		
					(< 70 lbs)	100	
					(≥ 70 lbs)	100 - 150	
					Adolescents	200 - 300	
					High dose		
					Children		
					(< 70 lbs)	200	
					(≥ 70 lbs)	200 - 300	
					Adolescents	400 - 600	
					Placebo		
(Long-Term Phase)		5-Jan-2001 to 16-Nov-2001	USA	26 weeks			200
					Nefazodone		
					Children		
					(< 70 lbs)	100 - 200	
					(≥ 70 lbs)	100 - 300	
					Adolescent	100 - 600	

Efficacy was evaluated in 471 patients in the short-term phases of CN104141 and CN104187, and safety was evaluated in 479 patients in CN104141 and CN104187.

Efficacy was evaluated in the short-term phase of the two placebo-controlled, double-blind studies using the following primary and secondary efficacy measures:

- Primary efficacy measure - mean change in the Childhood Depression Rating Scale-Revised (CDRS-R) Total Score from baseline to endpoint;
- Secondary efficacy measure – Clinician Global Impression (CGI) Improvement Score at endpoint;
- Additional efficacy measures – Mean change in the CGI Severity Score from baseline to endpoint; percentage of patients with CGI Response (defined as much or very much improved) at endpoint; and mean change in the Hamilton Depression Rating Scale (HAM-D) Total Score from baseline to endpoint (CN104141 only).

Efficacy results were mixed in the short-term phases of the studies. In CN104141, nefazodone was found to be statistically superior to placebo on all efficacy measures except the primary efficacy measure, the mean change in the CDRS-R Total Score from baseline to endpoint. In CN104187, there were no statistically significant differences on any of the prespecified outcome measures between either low- or high-dose nefazodone and placebo.

The long-term phases of CN104141 and CN104187 were designed to evaluate the safety and tolerability of nefazodone treatment beyond 8 weeks of therapy.

3 RESPONSE TO QUESTION 1A: STUDIES THAT DID NOT SHOW A CLINICAL BENEFIT OF NEFAZODONE OVER PLACEBO - STUDY CN104187

3.1 Short-Term Phase Study Design

Study CN104187 was a multicenter, parallel-group, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of nefazodone in outpatient children (aged 7 to 11 years) and adolescents (aged 12 to 17 years) with a DSM-IV diagnosis of major depressive episode. All patients entered a baseline phase of 2 to 4 weeks to assure

that they met eligibility criteria. Patients who continued to meet eligibility criteria were then randomized to receive one of the following three treatments, for 8 weeks:

- Low-dose nefazodone (children 100 to 150 mg/day; adolescents 200 to 300 mg/day)
- High-dose nefazodone (children 200 to 300 mg/day; adolescents 400 to 600 mg/day)
- Placebo

Efficacy was evaluated weekly during the short-term phase using the CDRS-R and the CGI Improvement and Severity Scales.

3.2 Short-Term Phase Efficacy Results

A summary of the efficacy results from the short-term phase of CN104187 is presented below in Table 2. There were no statistically significant differences between placebo and either of the nefazodone treatment groups in the mean CDRS-R Score at endpoint, mean CGI Improvement Score at endpoint, the CGI response rate at endpoint, or the mean change in CGI Severity Score from baseline to endpoint.

Table 2: Summary of Efficacy Results at Endpoint (Week 8 LOCF): CN104187

Variable	Placebo (N = 93)	Nefazodone Low (N = 90)	Nefazodone High (N = 90)	Significance vs Placebo Nefazodone Low	Significance vs Placebo Nefazodone High
PRIMARY EFFICACY ENDPOINT					
CDRS-R Total Score					
Mean Baseline	58.3	61.2	61.0	0.014	0.023
Mean Change from Baseline[a]	-21.6	-23.2	-20.6	0.430	0.654
Treatment Difference (95% CI)[b]	--	1.7 (-2.5;5.8)	-0.9 (-5.1;3.2)	--	--
SECONDARY EFFICACY ENDPOINT					
CGI Improvement[c]					
Mean Score	2.6	2.4	2.6	0.263	0.861
Treatment Difference (95% CI)	--	0.2 (-0.1;0.5)	0 (-0.3;0.3)	--	--
OTHER EFFICACY ENDPOINTS					
Patients with CGI Response[d]					
N (%)	44 (47)	52 (58)	47 (52)	0.186	0.719
Relative Risk (95% CI)	--	1.2 (0.9;1.7)	1.1 (0.8;1.4)	--	--
CGI Severity Score[e]					
Mean Baseline	4.4	4.5	4.6	0.151	0.039
Mean Change from Baseline[a]	-1.3	-1.4	-1.4	0.633	0.635
Treatment Difference (95% CI)[b]	--	0.1 (-0.3;0.4)	0.1 (-0.3;0.4)	--	--

[a] Negative values indicate improvement.

[b] Positive differences favor nefazodone.

[c] CGI Improvement: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse.

[d] Response = Much or very much improved.

[e] CGI Severity: 1 = Normal, not ill at all; 2 = Borderline mentally ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; 7 = Among the most extremely ill patients.

4 RESPONSE TO QUESTION 1B: STUDIES THAT DID SHOW A CLINICAL BENEFIT OF NEFAZODONE OVER PLACEBO - STUDY CN104141

4.1 Short-Term Phase Study Design

Study CN104141 was a double-blind, multicenter study of nefazodone in adolescent outpatients who met DSM-IV criteria for a Major Depressive Episode. This study was originally designed for 12- to 18-year-old patients; however, after the study had been initiated, the FDA requested that the study be conducted in 12- to 17-year-old patients and the study was amended to comply with this request.

All patients entered a baseline phase of 2 to 4 weeks to assure that they met eligibility criteria. Patients who continued to meet eligibility criteria were then randomized to either placebo or nefazodone (100 - 600 mg/day). Patients received 8 weeks of double-blind treatment.

4.2 Short-Term Phase Efficacy Results

A summary of the efficacy results from the short-term phase of CN104141 is presented below in Table 3. For the primary efficacy measure of CDRS-R, there was a greater mean change from baseline for the nefazodone group (-25.8) compared with the placebo group (-22.1) for the Primary Efficacy Sample (12- to 18-year olds); however, the difference between the groups was not statistically significant (P = 0.077). For the Secondary Efficacy Sample (12- to 17-year olds), the mean change from baseline was greater for the nefazodone group (-26.5) compared with the placebo group (-22.5), and the difference between the groups approached significance (P = 0.055). On the secondary efficacy measure of mean CGI Improvement Score, nefazodone showed statistically significantly greater improvement for both the Primary and Secondary Efficacy Samples. On all other efficacy measures, nefazodone was statistically significantly superior to placebo. In summary, nefazodone was superior to placebo on all of the efficacy measures except for the primary efficacy measure, where it just missed statistical significance.

Table 3: Summary of Key Efficacy Results at Endpoint: Week 8 LOCF (CN104141)

Variable	Placebo	Nefazodone	Treatment Difference (95% CI)	P-Value
Number of Patients				
Primary Efficacy Sample (12 - 18 Year Olds)	96	102		
Secondary Efficacy Sample (12-17 Year Olds)	92	95		
PRIMARY EFFICACY ENDPOINT				
CDRS-R Total Score				
Primary Efficacy Sample				
Mean Baseline	61.6	60.2	1.5 (-1.0;3.9)	0.237
Mean Change from Baseline[a]	-22.1	-25.8	3.7 (-0.4;7.8)	0.077
Secondary Efficacy Sample				
Mean Baseline	61.7	60.3	1.4 (-1.2;4.0)	0.280
Mean Change from Baseline[a]	-22.5	-26.5	4.0 (-0.1;8.1)	0.055
SECONDARY EFFICACY ENDPOINT				
Mean CGI Improvement Score[b]				
Primary Efficacy Sample	2.8	2.4	0.4 (0.1;0.8)	0.013
Secondary Efficacy Sample	2.8	2.3	0.4 (0.1;0.8)	0.012
OTHER EFFICACY ENDPOINTS				
Percentage of Patients with CGI Response[c]				
Primary Efficacy Sample	44	63	(1.1;1.9)[d]	0.004
Secondary Efficacy Sample	46	65	(1.1;1.8)[d]	0.005
HAM-D Total Score				
Primary Efficacy Sample[e]				
Mean Baseline	16.7	16.6	0.1 (-1.1;1.3)	0.883
Mean Change from Baseline[a]	-8.0	-9.9	1.9 (0.2;3.5)	0.025
Secondary Efficacy Sample[f]				
Mean Baseline	16.6	16.6	0 (-1.2;1.2)	0.983
Mean Change from Baseline[a]	-8.2	-10.0	1.9 (0.3;3.5)	0.023

[a] Negative values indicate improvement. Positive differences favor nefazodone.

[b] CGI Improvement: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse.

[c] CGI Response = Very much or much improved. Confidence intervals on the relative risk. Primary Efficacy Sample RR = 1.4; Secondary Efficacy Sample RR = 1.4.

[d] Confidence interval on relative risk. Primary Efficacy Sample RR = 1.4; Secondary Efficacy Sample RR = 1.4.

[e] Placebo (N = 95); nefazodone (N = 99).

[f] Placebo (N = 91); nefazodone (N = 93).

5 RESPONSE TO QUESTION 1C: STUDIES WITH RESULTS THAT COULD BE INTERPRETED AS INCREASING THE RISK OF DEPRESSION, SUICIDAL IDEATION, AND THE RATE OF SELF-INJURY

There are no BMS nefazodone studies with results that could be interpreted as increasing the risk of depression, suicidal ideation, and the rate of self-injury. The data and analyses that support this conclusion are presented in Section 6.

6 RESPONSE TO QUESTION 1D: STUDIES WITH RESULTS THAT COULD NOT BE INTERPRETED AS INCREASING THE RISK OF DEPRESSION, SUICIDAL IDEATION, AND THE RATE OF SELF-INJURY

The risk of worsening depression, suicidal ideation, and rate of self-injury can only, truly, be assessed in the double-blind, placebo-controlled efficacy studies. An assessment of the risk of worsening depression, suicidal ideation, and rate of self-injury was done by analyses of the CDRS-R and the tabulation of adverse events.

6.1 Risk of Depression as Assessed by Adverse Events

A review of patient-reported adverse events in the short-term phases of studies CN104141 and CN104187 were done to evaluate the incidence of worsening depression. Altogether there were two reports of worsening depression in the nefazodone group and no reports in the placebo group, on therapy, in the short-term phase of the efficacy studies (Table 4). This finding was not statistically significant and therefore did not provide evidence that there is an increased risk of depression with short-term use of nefazodone. The two reports occurred in the low-dose arm in study CN104187.

Table 4: Incidence of the Adverse Event of "Worsening Depression" in Patients: Short-Term Phases of CN104141 and CN104187

Study	Placebo n/N (%)	Nefazodone n/N (%)	P-Value*
CN104141	0/99	0/102	N/A
CN104187	0/94	2/184 (1.1)	0.55
CN104141 and CN104187	0/193	2/286 (0.7)	0.52

*Fishers Exact Test

A review of patient-reported adverse events in the long-term phase of study CN104141 (placebo-controlled) was also done to evaluate the incidence of worsening depression. There was one patient with worsening depression in the placebo group and no patients in the nefazodone group (Table 5).

Table 5: Incidence of the Adverse Event of "Worsening Depression" in Patients: Long-term Phase of CN104141

Study	Placebo n/N (%)	Nefazodone n/N (%)
CN104141	1/41 (2.4%)	0/49

6.2 Risk of Suicidal Ideation as Assessed by the CDRS-R

The risk of worsening suicidal ideation was assessed by evaluating the incidence of patients with a baseline score of 1 or 2 on item 13 of the CDRS-R (Suicidal Ideation) that increased to a score of 3 or higher (Suicidal Ideation Scores: 1 = understands the word "suicide" but does not apply term to himself/herself; 2 = sharp denial of suicidal thoughts; 3 = has thoughts about suicide, or of hurting himself/herself; 5 = has recurrent thoughts of suicide; 7 = has made a suicide attempt within the last month or is actively suicidal). The results of this analysis show no statistical difference in the incidence of worsening suicidal ideation between nefazodone-treated patients (10.3%) and placebo-treated patients (9.5%) in the short-term phases of studies CN104141 and CN104187 (Table 6). All of the patients who showed a worsening in suicidal ideation in the short-

term phase of the two efficacy studies had a maximum score of 3, with the exception of two nefazodone patients and three placebo patients, who had maximum scores of 4.

Table 6: Incidence of Patients with a Baseline Score of 1 or 2 on Item 13 on the CDRS-R who had a Score of 3 or Higher on Treatment: Short-Term Phases of Studies CN104141 and CN104187

Study	Placebo n/N (%)	Nefazodone n/N (%)	P-value
CN104141	10/96 (10.4)	9/102 (8.8)	0.81
CN104187	8/93 (8.6)	20/180 (11.1)	0.67
CN104141 and CN104187	18/189 (9.5)	29/282 (10.3)	0.88

* Fishers Exact Test

In the long-term phase of study CN104141 (double-blind, placebo-controlled) no patients on either nefazodone or placebo had worsening suicidal ideation as assessed on item 13 of the CDRS-R (Table 7).

Table 7: Incidence of Patients with a Baseline Score of 1 or 2 on Item 13 on the CDRS-R who had a Score of 3 or Higher on Treatment: Long-Term Phase Study CN104141

Study	Placebo n/N (%)	Nefazodone n/N (%)	P-value
CN104141	0/41	0/49	N/A

6.3 Risk as Assessed by the Identification of "Suicide-Related Events"

Bristol-Myers Squibb received a number of requests from FDA beginning on July 2, 2003 for data and information on nefazodone and suicidality in pediatric patients. In response to these requests BMS has made four submissions to FDA, dated September 5, 2003, December 17, 2003, January 9, 2004, and January 14, 2004; these four submissions are provided in Attachments 10, 11, and 12, and 13, respectively.

6.3.1 Identification of "Suicide-Related Events"

The FDA response followed the recommendations of FDA in defining the studies and criteria for identifying suicidal adverse events. All adverse events occurring within 30 days of the last dose of drug were included in the search. The search excluded adverse events that occurred before dosing or more than 30 days after the last dose of drug. The adverse event terms that were searched were: 'ATTEMPT', 'CUT', 'GAS', 'HANG', 'HUNG', 'JUMP', 'MUTILAT', 'OVERDOS', 'SELF', 'DAMAG', 'HARM', 'INFLICT', 'INJUR', 'SHOOT', 'SLASH', 'SUIC', and 'DEATH'.

In addition, at the request of FDA all serious adverse events from the short-term phases of the two studies were reviewed by a physician blinded to the treatment code to identify any additional cases related to suicidality or self-harm.

6.3.2 Incidence Rate of Suicide Attempts/Suicide-Related/Self-Injury Events

All pediatric data were reviewed to identify any death caused by suicide or overdose. No deaths occurred in either study.

Four patients had a suicide attempt/gesture, suicidal ideation, or intentional cutting/injury during the short-term phase of the study or within 30 days of completing the short-term phase of the study. The incidence rate of suicide attempts/suicide-related/self-injury events on treatment or within 30 days of last dosing is presented in Table 8. Three of the patients were treated with nefazodone (104187-18-322, 104141-3-1065, and 104141-5-1279). The fourth patient (104187-17-405) received placebo. It should be noted that patient 104187-17-405 (randomized to placebo) completed the short-term phase without incident but reported suicidal ideation 5 days after starting nefazodone in the long-term phase. The patient's nefazodone medication was raised and the event resolved the next day. The narratives for these patients are provided in Attachment 11.

The incidence rate of suicide attempts/suicide-related/self-injury events on treatment is presented in Table 9. Table 9 reflects that there were no on-therapy suicide-related or self-injury events for placebo in the short-term phases of the studies. Table 10 presents the physician term and the primary adverse event term that it was coded to in the adverse

event dictionary for patients with suicide attempts/suicide-related adverse events on treatment or within 30 days of last dosing.

The blinded review of serious adverse events did not identify any additional suicidal-related events.

Table 8: FDA-Requested Incidence Rate of Suicide Attempts/Suicide-Related/Self-Injury Adverse Events on Treatment or Within 30 days of Last Dosing in Studies CN104141 and CN104187

		Placebo	Nefazodone	P-value**
CN104-141	n/N (%)	0/95 (0)	2/95 (2.1)	0.50
	n/person years (rate)	0/12.5 (0)	2/13.6 (0.15)	
CN104-187	n/N (%)	1/94 (1.1)	1/184 (0.5)	1.00
	n/person years (rate)	1/12.9 (0.08)	1/25.4 (0.04)	
Total	n/N (%)	1/189* (0.5)	3/279* (1.1)	0.65
	n/person years (rate)	1/25.4 (0.04)	3/39.0 (0.08)	

* As requested by the FDA, this analysis does not include 4 placebo patients and 7 nefazodone patients for study CN104141 who were 18 years old. There were no events in these patients.
**Fishers Exact Test

Table 9: Incidence Rate of Suicide Attempts/Suicide-Related/Self-Injury Adverse Events on Treatment in Studies CN104141 and CN104187

		Placebo	Nefazodone	P-value**
On-therapy	n/N (%)	0/189* (0)	2/279* (0.7)	0.52
	n/person years (rate)	0/25.4 (0)	2/39.0 (0.05)	

* As requested by the FDA, this analysis does not include 4 placebo patients and 7 nefazodone patients for study CN104141 who were 18 years old. There were no events in these patients.
**Fishers Exact Test

Table 10: Identification of Primary Term and Physician Adverse Event Term for Patients with Suicide Attempts/Suicide-Related/Self-Injury Adverse Events on Treatment or Within 30 days of Last Dosing in Studies CN104141 and CN104187

Patient Number	Treatment	Primary Term	Physician Adverse Event Term
104187-17-405	Placebo*	Suicidal thoughts	Suicidal ideation
104187-18-322	Nefazodone**	Overdose	Overdose
		Suicide attempt	Suicide gesture
102141-3-1065	Nefazodone	Accidental injury	Minor self-mutilation, superficial cutting
104141-5-1279	Nefazodone	Pre-dosing	Pre-dosing
		Accidental injury	Cut arm/leg with razor
		On treatment	On treatment
		Accidental injury	Cuts to right arm

* Patient treated with placebo in short-term phase; reported suicidal ideation 5 days after starting nefazodone in the long-term phase.
** Suicide attempt 4 days after discontinuing treatment.

7 SUMMARY

In summary, 286 pediatric patients were treated with nefazodone in two double-blind, placebo-controlled, short-term (8-week) studies in children with major depressive disorder (MDD). There were no differences between nefazodone and placebo in the risk of worsening depression as assessed by adverse event reports of "worsening depression."

There were no statistically significant differences between nefazodone and placebo in the risk of worsening suicidal ideation as assessed by item 13 (Suicidal Ideation) on the CDRS-R, nor were there statistically significant differences between nefazodone and placebo on the incidence of suicidal-related adverse events.

Mr. WALDEN. Thank you, Dr. Marcus.
Mr. Osinsky.

TESTIMONY OF PATRICK J. OSINSKY

Mr. OSINSKY. Good afternoon, Congressman Walden, Congresswoman DeGette and members of the subcommittee. I am Patrick J. Osinsky, vice president and general counsel of Organon USA, Inc., on whose behalf I appear before you today.

At the outset, Organon would like to thank the subcommittee for inviting us to participate in today's hearing. Organon shares the subcommittee's concern about the safety of antidepressants in children. In response to the subcommittee's letter of March 24, Organon compiled data and other information about clinical trials involving the use of Organon's Remeron, mirtazapine tablets, for the treatment of major depressive order in children.

On April 14, Organon submitted this information to the subcommittee and updated it on July 16. The following is a brief summary of that information. Organon conducted two studies, both of which were subsequently submitted to FDA on May 1, 2001 as part of Organon's supplemental new drug application for pediatric exclusivity of Remeron tablets. One of these two studies was a safety and efficacy study of the use of Remeron for the treatment of depression in pediatric patients. In terms of safety, the conclusion was that Remeron was well tolerated and safe. In terms of efficacy, however, there was no statistically significant difference detected between the placebo and treatment groups. That study was the subject of two presentations, one made in September of 2001 in Pittsburgh at a consortium entitled, "Pharmacological Update in Children and Adolescents," and one made at a symposium held at American Academy of Child and Adolescent Psychiatry Conference in October 2001.

The second study that Organon sponsored and submitted to FDA as part of its supplemental NDA was a pharmacokinetic study. The conclusion of that study was that Remeron was relatively well tolerated and safe. That study was the subject of a manuscript, portions of which were presented at a March 2002 annual meeting of the American Society of Clinical Pharmacology and Therapeutics in an abstract entitled, "Single Dose Pharmacokinetics and Mirtazapine and Demethyl Metabolite in Depressed Children and Adolescents," which was published in a 2002 issue of Clinical Pharmacology Therapeutics. A summary of the PK study was also disseminated as part of a poster session at the October 2001 American Academy of Child and Adolescent Psychiatry Conference and subsequently included in the compilation of conference materials.

Grants were provided for two additional studies conducted on the use of Remeron in children. The first was an open label study that was conducted in Finland to evaluate the antidepressant efficacy and safety of Remeron in adolescents suffering from major depression. Based on the results of that study, it was concluded that Remeron may be a safe and effective treatment for major depression adolescents. This study is the subject of an article entitled, "Mirtazapine in the Treatment of Adolescents with Major Depression," in an open label multicenter pilot study, which is expected

to be published in the third week of this month in the Journal of Child and Adolescents Psychopharmacology.

The study subject to a grant was a study on the safety and efficacy of Remeron for the treatment of social phobia in children. The conclusion of that study was that Remeron was associated with significant improvement in social phobia and was well tolerated. This study was the subject of an abstract provided at two separate conferences: The Society of Biological Psychiatry in May 2003 and the New Clinical Drug Evaluation Unit, a scientific conference sponsored by the National Institute of Mental Health in June 2003.

And, finally, Organon is aware of one additional study in pediatric patients. That study, though neither sponsored nor funded by the company, was the subject of an abstract at the 21st CINP Congress in Glasgow, Scotland in 1992. That abstract states that significant improvements of depressive symptoms on nine of the DSM-4 criteria were found with no serious adverse effects being reported. This then is a brief summary of the information that Organon has concerning studies on the use of Remeron in children for the treatment of major depressive disorders. Each of the studies was discussed in varying detail at scientific and professional meetings and published in scientific journals in either abstract or full manuscript form.

On behalf of Organon, I thank you again for the opportunity to be here this afternoon. Organon looks forward to continuing to work with you and to provide you with any additional information that you might require.

[The prepared statement of Patrick J. Osinsky follows:]

PREPARED STATEMENT OF PATRICK J. OSINSKI, ON BEHALF OF ORGANON USA INC.

Good morning Congressman Walden, Ranking Minority Member Deutsch, and Members of the Subcommittee. I am Patrick J. Osinski, Vice President and General Counsel of Organon USA Inc. ("Organon"). I appear before you today on behalf of Organon, in connection with the Subcommittee's inquiry concerning the publication and disclosure of studies related to the safety of anti-depressants in children.

At the outset, Organon would like to thank the Subcommittee for inviting us to participate in today's hearing. Organon shares the Subcommittee's concern about the safety of antidepressants in children.

By letter dated March 24, 2004, the Subcommittee requested that Organon provide it with data and other information of published and unpublished clinical trials involving the use of Organon's prescription drug product, Remeron® (mirtazapine) Tablets, for the treatment of major depressive disorder in children. In response to the Subcommittee's request, on April 14, 2004, Organon compiled and submitted this information, which was updated on July 16, 2004. The following is a summary of that information.

Organon conducted two studies—both of which were subsequently submitted to FDA on May 1, 2001, as part of Organon's submission of a supplemental New Drug Application (sNDA) for pediatric exclusivity of Remeron® Tablets. Neither of these studies raised any safety concerns, though it was determined that no efficacy was indicated in either trial.

One of these two studies was a safety and efficacy study of the use of Remeron® for the treatment of depression in pediatric patients. In terms of safety, the conclusion was that Remeron® was well-tolerated and safe. In terms of efficacy, however, there was no statistically significant difference detected between the placebo and treatment groups. That study was the subject of two oral presentations with slides, one made in September 2001 in Pittsburgh, Pennsylvania at a consortium entitled "Pharmacological Update in Children and Adolescents" and one made at a symposium held at an American Academy of Child and Adolescent Psychiatry Conference in October 2001.

The second study that Organon sponsored and submitted to FDA as part of its May 2001 sNDA was a pharmacokinetic, or PK, study. The conclusion of that study

was that Remeron® was relatively well-tolerated and safe. That study was the subject of a manuscript, portions of which were presented at a March 2002 annual meeting of the American Society of Clinical Pharmacology & Therapeutics, and an abstract entitled, "Single-Dose Pharmacokinetics (PK) of Mirtazapine (M) and its Demethyl Metabolite (MET) in Depressed Children and Adolescents," which was published in a 2002 issue of Clinical Pharmacology Therapeutics. A summary of the PK study was also disseminated as part of a poster session at the October 2001 American Academy of Child and Adolescent Psychiatry Conference, and subsequently included in a compilation of Conference materials prepared by the Academy.

Grants were provided for two additional studies conducted on the use of Remeron® in children.

The first was an open label study that was conducted in Finland to evaluate the antidepressant efficacy and safety of Remeron® in adolescents suffering from major depression. Based on the results of that study, it was concluded that Remeron® may be a safe and effective treatment for major depression in adolescents. This study is the subject of an article entitled "Mirtazapine in the Treatment of Adolescents with Major Depression: An Open-Label, Multicenter Pilot Study," which is expected to be published in September 2004 in the Journal of Child and Adolescent Psychopharmacology.

The second study subject to a grant was a study on the efficacy and safety of Remeron® for the treatment of social phobia in children. The conclusion of that study was that treatment with Remeron® was associated with significant improvement in social phobia and was well-tolerated. This study was the subject of an abstract provided at two separate conferences—the Society of Biological Psychiatry in May 2003 and the New Clinical Drug Evaluation Unit—a scientific conference sponsored by the National Institute of Mental Health—in June 2003.

And finally Organon is aware of one additional study in pediatric patients. That study, though neither sponsored nor funded by the Company, was the subject of an abstract at the 21st CINP Congress in Glasgow, Scotland in 1998. The abstract states that significant improvements of depressive symptoms on 9 of the DSM IV criteria were found with no serious adverse effects being reported.

This, then, is a brief summary of the information that Organon has concerning studies on the use of Remeron® in children for the treatment of major depressive disorder. Each of the studies was discussed in varying detail at scientific and professional meetings and published in scientific journals in either abstract or full manuscript form.

On behalf of Organon, I thank you again for the opportunity to be here this morning. Organon looks forward to continuing to work with you and to provide you with any additional information that you might require.

Mr. WALDEN. Thank you, Mr. Osinsky.

Dr. Clary, welcome.

TESTIMONY OF CATHRYN M. CLARY

Ms. CLARY. Thank you. Good afternoon, Mr. Chairman and members of the subcommittee. I really thank you for the opportunity to testify today on this important topic, and I respectfully request that this testimony be included in the record.

Mr. WALDEN. Absolutely.

Ms. CLARY. My name is Cathryn Clary. I am a physician, also a board certified psychiatrist and the vice president for Psychiatry and Neurology in the U.S. Medical Department at Pfizer. I am here today to testify about disclosure and communication of results with Pfizer's antidepressant, Zoloft, in the pediatric population.

During my 13 years in private practice of psychiatry before joining Pfizer, I treated hundreds of people, both teenagers and adults, who were suffering from psychiatric illness, including major depression. As you have heard from many others today and as some of the subcommittee has also stated, pediatric depression is a devastating illness. It is one of the most serious public health problems facing the adolescent population in America.

Childhood depression affects 10 percent of all children under 18 every year and can result in suicide, tragically. It is the third leading cause of death in this age group, as you have also heard. I joined Pfizer in 1996 because of its commitment to developing innovative medicines to treat psychiatric illnesses such as depression as well as its commitment to educating physicians about its medicines in a full way, such as Zoloft.

In my testimony today, there are three points that I would like to make. First of all, Pfizer has conducted extensive and valuable research in the pediatric population with our antidepressant, Zoloft. Second, the data from this clinical research program has been communicated to the FDA, all of it, it has been published in peer review journals, and it has been presented at multiple scientific meetings. Third, in conjunction with FDA, changes have been made to the Zoloft label to reflect the findings from this pediatric research program.

One thing that I wanted to say clearly is that Pfizer began studying Zoloft for a disorder called obsessive-compulsive disorder back in 1991. This was around the time of the drug's approval, and it was not based on any type of legislation or a request from FDA. It was based on the fact that Pfizer determined there was unmet medical need in children suffering from obsessive-compulsive disorder, which can be quite debilitating. By the mid-1990's, Pfizer had completed several studies, and it obtained safety, tolerability as well as dosing information from the studies of these children and teenagers suffering from obsessive-compulsive disorder, also called OCD. And in 1997, after submitting the results of these studies to the FDA, Zoloft was approved by the FDA for treatment of OCD in pediatric patients. So since 1997, there has been pharmacokinetic dosing data and safety data in the label for Zoloft as well as one indication for pediatric obsessive-compulsive disorder.

Several years later, with a written request under FDAMA, Pfizer began to study Zoloft in pediatric patients who were suffering from major depressive disorder, or MDD. From December 1999 through May 2001, Pfizer conducted, in the terms of the written request, two identical placebo-controlled studies in children and teenagers with major depression. While the studies were underway and before the results were known, the result of neither individual study was known, we did not know which children were on Zoloft, which children were on placebo, and because of new information that was being obtained as the results of other studies came in, Pfizer decided to combine these two studies for the purpose of the analysis. We felt that would provide the most scientifically sound and reliable result. It would improve our ability to detect the difference between Zoloft and placebo if one existed.

The combined analysis did demonstrate the benefit of Zoloft in treating the symptoms of depression in the pediatric population. There was a statistically significant difference between Zoloft and placebo, although small. There was a small difference. This combined analysis study report was submitted to FDA in December 2001 along with the results of the individual studies and full individual study reports, as per the written request. Although FDA made a determination that the submitted data did not support approval for pediatric depression, the Zoloft label was updated in Sep-

tember 2003 to include additional safety information derived from these studies. And in addition, the label did state that efficacy had not been established in children under the age of 18 in major depressive disorder. I do want to emphasize that Pfizer does not promote the use of Zoloft in pediatric MDD. In addition, the Zoloft label has recently been updated to reflect the new warning.

In total, Pfizer has completed nine pediatric studies with Zoloft. Every one has been submitted to the FDA. In addition, seven have been published in peer review journals, including our pediatric MDD data, which were published in JAMA. The eighth study has been submitted to a peer review journal and is undergoing peer review. The only study that Pfizer has conducted with Zoloft in the pediatric population not published in a peer review journal, although of course submitted to FDA, is an open label continuation of a dose finding study, an early pharmacokinetic study. We, of course, filed this with FDA. Given the current interest in transparency of all results of pediatric trials, we are now preparing this study for submission to a peer review journal.

In addition, Pfizer is committed to working with PhRMA, with AMA, journal editors and all interested stakeholders to determine the optimal means for disseminating information from all of our trials that will have an impact on prescribing decisions in public health. Pfizer's participation in the recently announced PhRMA data base is a first step in that direction, and I understand you will hear more about that this afternoon.

In conclusion, I want to emphasize my belief, as a physician and vice president at Pfizer, that our company has been and continues to be committed to generating and communicating meaningful information to physicians about the appropriate use of Zoloft in the pediatric population. Thank you, and I will be happy to take any questions.

[The prepared statement of Cathryn M. Clary follows:]

WRITTEN TESTIMONY

OF

PFIZER INC

Submitted to the

House Committee on Energy and Commerce

Subcommittee on Oversight and Investigations

Regarding

Zoloft Studies in the Pediatric Population

Cathryn M. Clary M.D.

Vice President, U.S. Medical

Neuroscience and Customer and Market Development

Pfizer Global Pharmaceuticals

Pfizer Inc

235 E 42nd Street

New York NY 10017

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Summary of the Major Points of the Written Testimony of Pfizer Inc

Depression among children and teenagers is a serious medical condition with significant public health implications.

- Suicidal thinking and behavior often accompany major depression, particularly in the young, who are ill equipped to manage the illness.
- Suicide is the third leading cause of death among children and teenagers ages 10-19, and when it occurs, it is often due to untreated depression.

Pfizer has conducted a clinical program with Zoloft in the pediatric population.

- In 1997, FDA approved Zoloft for the treatment of Obsessive-Compulsive Disorder in the pediatric population. Although Zoloft was not approved for the treatment of major depression in this population, Pfizer's studies yielded important information that was added to the Zoloft label.
- There were no patients who committed suicide in the Zoloft pediatric studies.
- The number of suicide-related events in the Zoloft pediatric studies is small, and, because none of these numbers are statistically significant, no conclusion can be drawn that treatment with Zoloft in these studies is associated with an increased risk of suicidal behaviors.

Pfizer has disclosed the results of the Zoloft pediatric studies.

- Seven of the nine completed Zoloft pediatric studies have been published in peer reviewed journals and one has been submitted to a peer-reviewed journal for publication. A manuscript is currently being completed for the ninth study that also will be submitted to a peer review journal. Prior to publication, the results of these studies have been presented in posters and abstracts at scientific meetings. Pfizer has also shared information about the Zoloft pediatric program with doctors and the public in the form of "Medical Information" letters.
- The Zoloft pediatric studies have led to a series of important changes in the Zoloft label, informing doctors about the valuable information learned from those studies.
- Pfizer is committed to communicating the results of all Phase 3 and 4 controlled clinical trials of marketed products, regardless of outcome. Pfizer is participating in a PhRMA initiative to develop a clinical trial results database to contain summaries of studies that fall within the scope of the PhRMA Principles on the Conduct of Clinical Studies and the Communication of Clinical Study Results.

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A Introduction

This written testimony is submitted in support of the oral testimony to be provided by Cathryn M. Clary, M.D., Vice President, U.S. Medical, Neuroscience and Customer and Market Development, Pfizer Inc, before the United States House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, Hearing on Publication and Disclosure Issues in Antidepressant Pediatric Clinical Trials on September 9, 2004. This document summarizes the completed clinical trials that Pfizer has conducted in the pediatric population with Pfizer's selective serotonin reuptake inhibitor (SSRI) medicine, Zoloft® (sertraline HCl), with particular emphasis on Pfizer's public disclosure of these studies in publications and presentations at scientific meetings, medical information letters, and the addition of information to the Zoloft label (package insert)[1].

A.1 The History of Zoloft Approvals in the United States

The clinical development program for Zoloft began in the early 1980s, and Pfizer received its first approval for Zoloft from the U.S. Food and Drug Administration (FDA) in 1991 for the treatment of Major Depressive Disorder (MDD) in the adult population. Since 1991, Pfizer has received five additional approvals for Zoloft for the treatment of other mood and anxiety disorders, which are chronic and often debilitating psychiatric illnesses.

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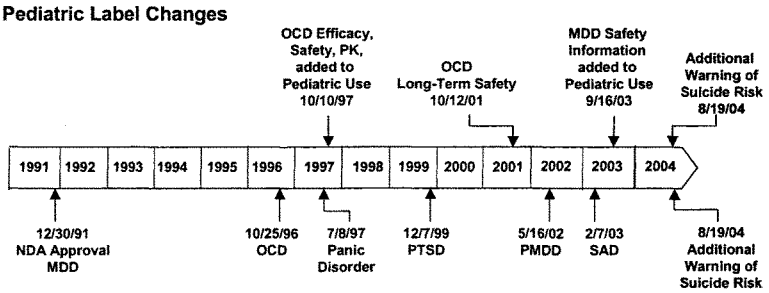
[1] This document does not address studies conducted as Independent Research Grants by researchers outside of Pfizer and funded or otherwise supported by Pfizer or studies that were neither supported nor sponsored by Pfizer.

For each of the approved indications in adults—Major Depressive Disorder (MDD), Obsessive-Compulsive Disorder (OCD), Panic Disorder, Posttraumatic Stress Disorder (PTSD), Premenstrual Dysphoric Disorder (PMDD), and Social Anxiety Disorder (SAD)—Pfizer submitted to the FDA two or more double-blind studies in patients with the indicated illness that demonstrated that Zoloft was more effective than placebo. Because Zoloft had been approved for adult OCD, only a single positive placebo-controlled trial was required by and submitted to FDA for the pediatric OCD labeling. OCD is the only approved use for Zoloft in the pediatric population.

The following diagram illustrates the chronology of adult approvals for Zoloft, as well as the addition of pediatric information to the Zoloft label.

Zoloft Regulatory Overview*



NDA: New Drug Application
PK: Pharmacokinetics
MDD: Major Depressive Disorder
OCD: Obsessive-Compulsive Disorder
PTSD: Posttraumatic Stress Disorder
PMDD: Premenstrual Dysphoric Disorder
SAD: Social Anxiety Disorder

*Not every label change is reflected in this schematic

A.2 Prevalence, Symptoms and Impact of Major Depressive Disorder in the Pediatric Population

Major depressive disorder is a significant public health issue for American children and teenagers. The annual prevalence of depression is estimated to be 2–3% in children aged 8–12 years and 4–8% in those aged 11 ½ to 18 years[2], as compared with a rate of 6.6% in adults aged 18 and older[3]. It is estimated that one in five adolescents has had an episode of MDD by the age of 18[2]. Studies have demonstrated that each successive generation since 1940 is at higher risk for MDD and that the disorder is being experienced earlier in life than it had been previously[2].

The Diagnostic and Statistical Manual of Mental Disorders version IV with revisions (DSM)[4] is used to diagnose depression. As the Manual states, "Major Depressive Disorder may begin at any age." The diagnostic criteria for a Major Depressive Episode are five or more of the following symptoms during the same two-week period:

- Depressed or irritable mood
- Lack of interest or pleasure in activities
- Sleep disturbance
- Appetite/weight changes
- Concentration and attention difficulties
- Fatigue or loss of energy
- Psychomotor agitation or retardation
- Cognitive changes: worthlessness, excessive guilt, hopelessness
- Recurrent thoughts of death, suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

The criteria used to diagnose children and adolescents are similar to those used to diagnose adults, with the exceptions that DSM notes that children and adolescents may exhibit an irritable mood, rather than a depressed mood, and that a child's failure

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[2] American Academy of Child and Adolescent Psychiatry (1998), Practice Parameters for the Assessment and Treatment of Children and Adolescents with Depressive Disorders. *J Amer Acad Child Adolesc Psychiatry* 37 (10 suppl).

[3] Kessler RC et al. The epidemiology of Major Depressive Disorder; results from the National Comorbidity Survey Replication (NCS-R) *JAMA* 2003; 289: 1395-1305.

to make expected weight gains should be considered. In all age groups, suicidal thinking or behavior is one of the diagnostic criteria.

Depression in children is a devastating disease. Children and teenagers who suffer from MDD frequently experience thoughts of guilt, shame, and self-criticism that may leave them feeling worthless, helpless, and hopeless. As described in the Surgeon General's Report on Mental Health[5]: "Depressed children are sad, they lose interest in activities that used to please them, and they criticize themselves and feel that others criticize them. They feel unloved, pessimistic, or even hopeless about the future; they think that life is not worth living, and thoughts of suicide may be present. . . .. Associated anxiety symptoms, such as fears of separation or reluctance to meet people, and somatic symptoms, such as general aches and pains, stomachaches, and headaches, are more common in depressed children and adolescents than in adults with depression." Children with MDD frequently experience functional impairment such as a drop in school performance, family tension/problems, and conflicts with friends. They are also at risk for other psychiatric disorders, substance abuse, anxiety disorders, and disruptive behavior disorders[2]. In addition, follow-up studies have found that 20% to 40% of teenagers with MDD will go on to develop bipolar I disorder (a disorder which is characterized by episodes of depression alternating with another clinical state called mania) within a period of 5 years after the onset of depression[6].

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[4] Diagnostic and Statistical Manual of Mental Disorders version IV with revisions (DSM-IV TR) p353-354.

[5] Mental Health: A Report of the Surgeon General, published 1999, (David Satcher, Surgeon General). p150-152.

[6] Birmaher B; Ryan ND, Williamson DE, etal. Childhood and Adolescent Depression: A Review of the Past 10 Years. Part I, *J Amer Acad Child Adolesc Psychiatry* 1996 35(11):1427-1439.

Exacerbating the distressing nature of MDD is the risk of suicidal behavior that often accompanies the disease, particularly in the young, who are ill equipped to manage the illness. Suicide is the third leading cause of death among young people aged 10-19 years and the incidence of suicide attempts peaks during the mid-adolescent years[7]. An ongoing surveillance of health-risk behaviors in young people reported in 2003 that among high school students nationwide in the preceding year, 28.6% had felt so sad and hopeless that they stopped doing some of their usual activities; 16.9% had seriously considered, and 16.5% had made a plan to attempt, suicide; and 8.5% had actually attempted suicide, 2.9% to the extent that they needed medical attention[8].

The evidence is strong that over 90% of children and adolescents who commit suicide have a mental disorder[9]. As then-Surgeon General David Satcher noted in his Report on Mental Health in 1999, "Children, and particularly adolescents, who suffer from depression are at much greater risk of committing suicide than are children without depression"[9]. Approximately half of all teenagers with MDD attempt suicide at some time during their lives, and among children with MDD there is a 4- to 5-fold higher lifetime risk of suicide attempt, compared with healthy children without depression[10] [11] [12]. At the beginning of a study in outpatient youths with MDD, 66% of patients

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[7] Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS) [Online]. (2003). National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (producer). Available from: URL: www.cdc.gov/ncipc/wisqars. 30 Aug 2004.

[8] Youth Risk Behavior Surveillance System – United States, 2003; Volume 53/SS-2.

[9] Mental Health: A Report of the Surgeon General, published 1999 (David Satcher, Surgeon General). p150-152.

[10] Rao U, Weissman MM, Martin JA and Hammond RW (1993) Childhood depression and risk of suicide: a preliminary report of a longitudinal study. *J Am Acad Child Adolesc Psychiatry* 32:21-27.

[11] Weissman MM, Wolk S, Goldstein RB *et al* (1999a). Depressed adolescents grown up. JAMA 281:1701-1713.

acknowledged a history of suicidal ideation, and 9% had already made at least one suicide attempt. The rate of suicide attempts in this study reached 24% by age 17[13]. Because mood disorders such as depression substantially increase the risk of suicide, suicidal behavior is a matter of serious concern for clinicians who deal with the mental health problems of children and adolescents. Given this background, it can be difficult to disentangle the causal factors for a suicide attempt when a child is being treated for MDD, regardless of the type of treatment.

Studies in children and teenagers have shown that a typical episode of MDD lasts 2-9 months, although episodes may last much longer. Even after remission, which is defined as the complete absence of symptoms, *i.e.*, recovery from the episode of depression, there is a high probability that the disease will return: up to 40% within 2 years and 70% by 5 years[9]. These rates are similar to the rates of recurrence that have been reported for adults[14].

A.3 Treatment Options for Major Depressive Disorder in the Pediatric Population

The options for the treatment of MDD in children and adolescents have historically been limited. Prior to the advent of the SSRIs, tricyclic antidepressants (TCAs) were the most commonly used medications for MDD treatment. Although TCAs were associated with some improvement in small open studies in children, more rigorous controlled studies failed to demonstrate that TCAs were more effective than placebo.

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[12] Weissman MM, Wolk S, Wickramaratne P *et al* (1999b). Children with prepubertal-onset major depressive disorder and anxiety grown up. *Arch Gen Psychiatry* 56:794-801.

[13] Kovacs M, Goldston D, and Gatsonis C (1993). Suicidal behaviors and childhood-onset depressive disorders: A longitudinal investigation. *J. Am. Acad. Child & Adol. Psychiatry* 32(1):8-20.

TCAs also pose certain safety risks in children, specifically, cardiac arrhythmias and a potential lethality in overdose[2]. The high degree of acceptance of SSRIs for the treatment of adult MDD, together with their low incidence of side effects, easy once-a-day administration, and safety when taken in overdose made it natural that physicians, faced with the need to treat patients suffering from MDD, would prescribe these in younger patients, even though most of these products had not been approved by FDA in that population. Fluoxetine (Prozac®), approved in January 2003,[15] is the only SSRI that has been approved by FDA for the treatment of pediatric MDD.

Psychotherapy, also used in the treatment of MDD, may take the form of individual, group, or family therapy; cognitive behavioral therapy; or interpersonal-, problem-solving-, or play therapy. There are, however, few controlled studies with psychotherapy. In small studies, cognitive-behavioral therapy has been shown to have some benefit in treating depression, but this treatment by itself does not appear to be as effective for episodes of depression with more severe symptoms[2].

The American Academy of Child and Adolescent Psychiatry currently recommends psychotherapy, SSRI treatment, or both combined, for first-line acute treatment of MDD in children and adolescents[2].

A recently published study[16] of adolescents with major depression showed that of the treatments studied, the combination of fluoxetine and cognitive behavioral therapy

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[14] Birmaher B; Ryan ND, Williamson DE, et al. Childhood and Adolescent Depression: A Review of the Past 10 Years. Part I, *J Amer Acad Child Adolesc Psychiatry* 1996 35(11):1427-1439.

[15] http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01187.html [FDA Talk Paper announcing approval of Prozac for MDD].

[16] Treatment for Adolescents with Depression Study (TADS) team (2004). Fluoxetine, Cognitive Behavioral Therapy, and their combination for adolescents with depression. *JAMA* 292:807-820.

was the most effective treatment, and that therapy alone was not more effective than placebo, while fluoxetine alone was also effective, though less so than combination treatment.

Despite reports that antidepressants are being widely prescribed for America's youth, prescription data show that only 4% of antidepressant prescriptions are for the treatment of individuals younger than 18 years old[17]. It is interesting to note that concurrently with the introduction and usage of SSRIs, which is associated with higher diagnosis and treatment rates of depression, there has been a reduction in suicide rates among both the adult and pediatric populations. Epidemiological studies in both adults[18] and adolescents[19] addressed rates of suicide since the introduction of SSRIs. Each of these studies demonstrated that as the rate of SSRI usage increased, the rate of completed suicides decreased. The adolescent study, which entailed the assessment of a large managed-care database over the last decade, showed that as the use of antidepressants has increased, there has been an overall decrease in the suicide rate. These data can also be expressed as a risk reduction for adolescent suicide of 0.23/100,000 population per year with only a 1% increase in antidepressant usage[19].

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[17] Scott-Levin MAT, May 2004.

[18] Hall WD, Mant A, Mitchell PB et al (2003). Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. *BMJ* 326:1008-1012.

[19] Olfson M, Shaffer D, Marcus SC et al (2003). Relationship between antidepressant medication treatment and suicide in adolescents. *Arch. Gen. Psychiatry* 60:978-982.

B Pfizer's Zoloft Pediatric Program

B.1 Introduction

Clinical trials may be conducted as 'open-label' studies, in which there is no comparison group and patients and investigators know that all the patients are receiving the drug under study, or as 'double-blind' studies, in which patients are randomly assigned to receive study drug or placebo (an inert sugar pill made to look exactly like the study drug), with the treatment assignment unknown to everyone until the study is completed. The presence of a placebo comparison group and the anonymity of the treatment assignment, to both patients and investigators, lend an additional level of rigor to the data from these studies.

Mental illnesses pose a unique challenge to researchers as they try to document the severity of the symptoms and the degree of change in these symptoms over time. In contrast to infections or physiological illness, mental illnesses, such as depression, do not have a simple laboratory test or physician finding that can accurately measure and quantify the changes in the illness. Instead, researchers must rely on responses to specific questions and on observations. The organization of this information into standard rating scales that are validated as meaningful and sensitive to treatment effects over time is the standard in the field of psychopharmacology research.

Because the responses to such questions are inherently subjective (based on the patient's own feelings, thoughts, and willingness and ability to describe those feelings and thoughts accurately), psychiatric rating scales may show more differences between subjects and different investigators than tests used to measure other illnesses. In addition, patients with disorders such as depression can often get better due to their

hopefulness about treatment, their faith in the doctor or research institution, or just the passage of time. When this occurs in patients who are randomized to placebo in a clinical trial, then the improvement is called a "placebo response." The distinction between a placebo response and a real treatment effect presents an additional challenge in clinical research.

B.2 Studies Conducted by Pfizer

Pfizer began a pediatric program for Zoloft in 1991 with studies in obsessive-compulsive disorder (OCD). Since then, Pfizer has completed nine studies and has two studies still in progress in the pediatric population (ages 6-18 years), demonstrating its commitment to understanding the safety, efficacy and tolerability profile of Zoloft in this population. Table 1 lists all 11 studies conducted or being conducted by Pfizer in the pediatric population. Six of these studies are open-label and five of these studies are double-blind.

Table 1. Summary of Pediatric Studies Conducted with Zoloft

Study (Objective)	Study Design	Indication	Age Range	No. Of Patients	
				Zoloft	Placebo
Early Open Label Studies					
90CK21-0525 (Pharmacokinetics and tolerability)	Open Label, 6-week, fixed–dose (200mg)	OCD/MDD	6-17 yrs	n=61	n/a
91CK21-0550 (extension* of 0525 to collect safety data)	Open Label, 24- week, flexible–dose* (50-200mg)	OCD/MDD	6-18 yrs	n=43	n/a
Studies in Obsessive-Compulsive Disorder					
90CE21-0498 (Efficacy and Safety)	Double Blind, 12- week, flexible–dose (50-200mg)	OCD	6-17 yrs	n=92	n=95
91CE21-0536 (extension of R-0498 to collect long-term data)	Open Label, 52- week, flexible–dose (50-200mg)	OCD	6-17 yrs	n=137	n/a
Studies in Depression					
R-0246 (Pilot study for efficacy, Safety and Tolerability	Open Label, 22- week, flexible–dose (50-200mg)	MDD	13-18 yrs	n=53	n/a
STL-CDN-94-002 (Safety and Tolerability)	Open Label, 24- week, flexible–dose (50-200mg)	MDD/Dysthymia	11-18 yrs	n=27	n/a

Study (Objective)	Study Design	Indication	Age Range	No. Of Patients	
				Zoloft	Placebo
A0501001 (Efficacy and Safety)	Double Blind, 10- week, flexible –dose (50-200mg)	MDD	6-17 yrs	n=97	n=91
A0501017 (Efficacy and Safety)	Double Blind, 10-wk, flexible–dose (50-200mg)	MDD	6-17 yrs	n=92	n=96
A0501015 (extension of A0501001 and A0501017 to collect long-term data)	Open Label, 24- week, flexible–dose (50-200mg)	MDD	6-17 yrs	n=226	n/a
Ongoing Studies					
A0501061 (Efficacy and Safety)	Double Blind, 10- week, flexible--dose (50-200mg)	PTSD	6-17 yrs	160 projected 73 enrolled (Aug 2004)	
A0501033 (Efficacy and Safety)	Double Blind, 9-month, flexible--dose (50-200mg)	OCD	6-17 yrs	324 projected 25 enrolled (Aug 2004)	

MDD: Major Depressive Disorder; OCD: Obsessive-Compulsive Disorder; PTSD: Posttraumatic Stress Disorder
* extension studies are continuations of initial studies under a new protocol to allow collection of additional, long-term data; patients who complete the initial study have the option of continuing in the extension
* flexible dose: dosage individualized based on patient response

The early studies, 90CK21-0525 and its extension, 91CK21-0550, were open-label studies conducted to collect preliminary safety and tolerability data and to understand whether Zoloft dosing in young people was similar to adults.

Study 90CE21-0498 and its extension, 91CE21-0536, were the basis of Zoloft's approval for treatment of children and adolescents with OCD. Pfizer also conducted two early pediatric depression studies. Study R-0246 was an open-label study in 53 adolescents with MDD conducted to fulfill Pfizer's post-approval commitment to FDA following the 1991 approval of Zoloft for MDD in adults. Study STL-CDN-94-002 was a small (27-patient) open-label study conducted by Pfizer Canada to evaluate the safety and tolerability of Zoloft in the treatment of adolescents.

The placebo-controlled studies, A0501001 and A0501017, form the core of Pfizer's program to understand the effectiveness of Zoloft in the treatment of pediatric depression and are described in further detail in the following section. Their open-

label extension, Study A0501015, gathered additional information about long-term treatment.

Because of the current interest in clinical studies of SSRIs in pediatric patients with MDD, this document will describe in some detail Pfizer's studies of Zoloft in this population. However, in the following Section C, we discuss the dissemination of the clinical trial results of all of the studies in the Zoloft pediatric program.

B.3 Design and Conduct of the Zoloft Pediatric Depression Program

In April 1999, the FDA issued a Written Request[20] for Pfizer to conduct pediatric depression studies with Zoloft. The FDA required that Pfizer conduct two trials, each enrolling equal numbers of children and adolescents, and using the Children's Depression Rating Scale-Revised to measure efficacy. Pfizer was required to submit the data from these studies within three years of FDA's Written Request, and did so.

B.3.1 Study Design Issues

To comply with the requirements of the Written Request, Pfizer conducted two identical, double-blind, flexible-dose, multicenter studies of Zoloft in children and adolescents with MDD. Study A0501001 was conducted from December 1999 to May 2001, and Study A0501017 was conducted from February 2000 to March 2001. Patients were required to have a current episode of MDD. As is typical in such depression studies, patients who had previously attempted suicide or who posed a

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[20] In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA), intending in part to ensure that medicines that could benefit children were properly evaluated in the pediatric population. It allowed the FDA to issue Written Requests to manufacturers of these medicines to conduct the relevant trials within a specified time. Clinical trials in children are more difficult to conduct than trials in adult populations. To provide incentive for manufacturers to

serious suicidal or homicidal risk were excluded from the studies. In both studies an equal number of children and adolescents received Zoloft and placebo.

The Children's Depression Rating Scale-Revised (CDRS-R) was agreed upon with FDA as the primary outcome measure in the study, *i.e.*, the way to measure depressive symptoms. At the time Pfizer began these studies, the CDRS-R was emerging in the psychiatric field as the gold-standard depression rating scale for the pediatric population, although it had only been validated in children, not adolescents. It had also not previously been used in any multicenter study. With this scale, both the children and their parents are asked to rate the severity of the depressive symptoms being experienced by the child. The clinical investigator then combines the patient and the parent scores to derive a composite score for the patient. A higher score represents more severe symptoms; a decrease in score indicates improvement. It is a somewhat difficult scale to utilize, and there can be variability in ratings from investigator to investigator. To ensure greater consistency in the use of the CDRS-R, all investigators performing the CDRS-R evaluations were required to participate in a training session at the startup of the study, and to demonstrate proficiency in using this scale.

An important element in the design of any clinical trial is the estimation of the number of patients to be included. Statisticians determine this number by looking at the data from previous similar trials to obtain information regarding the extent to which differences between treatment groups represent a true effect of treatment or might be due to random variability between patients. The larger the number of

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conduct such trials and to balance their cost, sponsors could be eligible for a 6-month patent extension upon submission of the complete package of required data to the FDA.

patients, the greater the confidence that an effect observed in a study accurately reflects the true effect. However, in a homogeneous group it can be expected that a smaller sample will be representative, whereas, if the whole group is diverse and has greater variability, a larger sample is required in order to see an effect, if one is there.

Pfizer determined the number of patients needed for its two pediatric MDD studies by examining data from a small (96 patients) *single center* study of fluoxetine (Prozac®) in children and adolescents with MDD, the only published placebo-controlled study of an SSRI utilizing the CDRS-R at the time[21]. Based on these data, Pfizer estimated that 160 subjects would be required to provide reasonable confidence that an observed effect would represent a true situation.

At the time Pfizer was designing its two multicenter studies, there had been no published *multicenter* trial that had used the CDRS-R to demonstrate efficacy, and hence no data to provide information regarding any additional variability, between subjects and between sites, that might be expected in a larger, multicenter trial. To address the concern that the random variability in such a study might be greater than in a small well-controlled single-site study, the two studies were designed to be identical in order to allow a combined analysis. Indeed, before the studies were completed, and before the blind was broken (before investigators or Pfizer researchers knew what treatment anyone was taking) Pfizer decided to pool the two studies, in order to have sufficient power to show a difference, if one existed.

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[21] Emslie GJ, Rush AJ, Weinberg WA *et al* (1997). A double-blind, randomized, placebo controlled trial of fluoxetine in children and adolescents with depression. *Arch. Gen. Psychiatry* 54:1031-1037.

B.3.2 Results

Efficacy

Table 2 shows the results from the two MDD studies for the primary measurement of efficacy (reduction in CDRS-R score from the start of the study). In each study, the improvement in the Zoloft group was greater than in the placebo group, but the difference was not statistically significant (statistical significance in these studies required a p-value less than 0.05), except for a greater proportion of responders on Zoloft in Study A0501017. However, when the two studies were pooled, thus providing an adequate sample size to test if there were true differences, the treatment effect of Zoloft compared to placebo, although modest in size, was shown to be statistically significant.

Table 2. Efficacy Outcome for Primary Endpoint in Zoloft Pediatric MDD Studies

		Zoloft	Placebo	P-value
Study A0501001	N=	93	88	
CDRS-R: Total Score, Baseline → Endpoint		64.2→38.1	63.8→41.9	0.08^
CDRS-R: Responders* %		62.4%	56.8%	0.46
Study A0501017	N=	92	91	
CDRS-R: Total Score, Baseline → Endpoint		64.4→36.1	65.4→39.3	0.17
CDRS-R: Responders* %		75.0%	60.4%	0.03
Combined Data: (A0501001 + A0501017)	N=	185	179	
CDRS-R: Total Score, Baseline → Endpoint		64.3→37.1	64.6→40.6	0.03
CDRS-R: Responders* %		68.7%	58.7%	0.05

* Responders were individuals who had a 40% decrease in the adjusted CDRS-R total score from baseline to endpoint.
^ P <0.05 indicates statistical significance

Although the difference between Zoloft and placebo was not statistically significant in the two individual studies, this does not mean that Zoloft did not bring about an improvement in depressive symptoms. In fact, on average, CDRS-R scores were almost halved, and approximately two thirds of the patients responded to treatment

with Zoloft, a rate similar to that seen in adults. However, the patients receiving placebo *also* showed a substantial improvement from baseline. This is known as the 'placebo effect,' and its occurrence is not unusual in clinical studies of depression. In these studies the placebo effect was so high that in the individual, uncombined studies there was not a statistically significant difference between the effect seen with Zoloft and that seen with placebo.

Research suggests that two psychological variables significantly increase the placebo effect: high suggestibility, and high expectancy[22] [23] [24]. Children are known to be more suggestible than adults, and the younger the children, the more suggestible they tend to be. Children also show higher expectancy effects, i.e., a treatment effect produced from the belief or expectation that the doctor and the treatment will help them, compared to adults, especially when treated in the novel setting of a treatment research office, often in an academic center. In addition, the time that their parents or caregivers take in bringing them to the office and speaking with the clinical staff about their disorder can, in itself, be therapeutic. It is worth noting that when the combined data from the Studies A0501001 and A0501017 were analyzed separately for children (6-12 years) and adolescents (13-17 years), the children's group had a higher placebo response than the adolescent group. In fact, the adolescents treated with Zoloft had a statistically significant greater improvement in CDRS-R scores than

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[22] De Pascalis V, Chiaradia C, Carotenuto E. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. *Pain* 2002;96:393-402.

[23] Leigh R, MacQueen G, Tougas G, Hargreave FE, Bienenstock J. Change in forced expiratory volume in 1 second after sham bronchoconstrictor in suggestible but not suggestion-resistant asthmatic subjects: a pilot study. *Psychosom Med* 2003;65:791-795.

[24] Vase L, Robinson ME, Verne GN, Price DD. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients. An empirical investigation. *Pain* 2003;105:17-25.

placebo-treated adolescents[25]. In contrast, in the children's group, although the Zoloft-treated patients also had greater improvement than the placebo-treated patients, the higher placebo effect resulted in the difference not meeting statistical significance.

Safety

In the Zoloft pediatric depression program, as well as in the other pediatric studies, safety data, including time and severity of adverse events, vital signs, laboratory test values, electrocardiograms, and other events occurring during the trial were systematically collected and analyzed. This information was submitted to FDA as part of the clinical study reports and a summary of this information was also disclosed in the clinical trial publications. In addition, the safety of pharmaceutical drug products, such as Zoloft, is evaluated through an ongoing analysis of Pfizer's spontaneous adverse event report database.

We have not included general safety data about Zoloft in this Testimony, although Pfizer is willing to provide such information to the Committee. Instead, because of current discussion and debate surrounding the issue, we are focusing our comments about Zoloft safety on the issue of suicide-related behaviors from the pediatric controlled trials. This issue will also be discussed at a joint meeting of the FDA Pediatric Advisory Committee and the Psychopharmacologic Drugs Advisory Committee scheduled to take place on September 13 and 14, 2004.

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[25] Donnelly C et al. A comparison of the response to sertraline in children and adolescents with major depressive disorder; NCDEU 2003 (poster) and Donnelly C et al. A comparison of the response to sertraline in children and adolescents with major depressive disorder (submitted to *J Am Acad Child Adolesc Psychiatry*).

Suicide-Related Behaviors in the Controlled Pediatric Studies

There were no suicides in these studies, nor were there suicides in any of Pfizer's other pediatric trials with Zoloft. In addition, a comprehensive evaluation conducted by Pfizer of the Zoloft placebo-controlled trials shows that the risk of suicide-related behavior in children and adolescents treated with Zoloft in clinical trials of MDD is no greater than that with placebo.

In the MDD program, in Study A0501001, one patient in the Zoloft-treated group was classified by the investigator as having made a suicide attempt. In Study A0501017, two patients in the Zoloft-treated group and two patients in the placebo-treated group made a suicide attempt. One patient in the placebo-treated group attempted suicide twice. Three cases of suicidal thinking (also called "ideation") were reported in MDD study A0501001, and one in the OCD program (90CE21-0498), none of which were deemed by the investigator to be related to the study drug. The following tables summarize the incidence of suicide attempts and suicide ideation in the placebo-controlled Zoloft pediatric trials.

Table 3. Incidence of suicide attempts in placebo-controlled studies of Zoloft in children and adolescents

	Zoloft		Placebo	
Diagnosis	**n/N**	**Incidence % [95% CI]**	**n/N**	**Incidence % [95% CI]**
MDD (A0501001)	1/97	1.0% [0.03 – 5.61%]	0/91	0.0% [-]
MDD (A0501017)	2/92	2.2% [0.26 – 7.63%]	2*/93	2.2% [0.26 – 7.55%]
MDD Combined	3/189	1.6% [0.33 – 4.57%]	2*/184	1.1% [0.13 – 3.87%]
OCD (90CE21-0498)	0/ 92	0% [-]	0/95	0% [-]
All Combined	3/281	1.1% [0.22 – 3.09%]	2/279	0.7% [0.09 – 2.57%]
Combined Ages 12–17	1/158	0.6% [0.02 – 3.48%]	2/151	1.3% [0.16 – 4.70%]
Combined Ages 7–11	2/123	1.6% [0.20 – 5.75%]	0/128	0% [-]

* there were 3 attempts in 2 patients

Table 4. Incidence of suicidal ideation in placebo-controlled studies of Zoloft in children and adolescents

	Zoloft		Placebo	
Diagnosis	**n/N**	**Incidence % [95% CI]**	**n/N**	**Incidence % [95% CI]**
MDD	3/189	1.6% [0.33 – 4.57%]	0/184	0% [-]
OCD	0/92	0% [-]	1/95	1.1% [0.03 – 5.73%]
All Combined	3/281	1.1% [0.22 – 3.09%]	1/279	0.4% [0.01 – 1.98%]

Table 5. Incidence of suicide attempts and suicidal ideation in placebo-controlled studies of Zoloft in children and adolescents

	Zoloft		Placebo	
Diagnosis	**n/N**	**Incidence % [95% CI]**	**n/N**	**Incidence % [95% CI]**
MDD	6/189	3.2% [1.17 – 6.78%]	2/184	1.1% [0.13 – 3.87%]
OCD	0/92	0% [-]	1/95	1.1% [0.03 – 5.73%]
All Combined	6/281	2.1% [0.79 – 4.59%]	3/279	1.1% [0.22 – 3.11%]

In the tables above, it is clear that the number of events is very small, and because none of these numbers are statistically significant, no conclusion can be drawn that treatment with Zoloft in these studies is associated with an increased risk of suicidal behaviors.

These data, which are congruent with the classification of the Zoloft cases conducted by the Columbia University researchers, as requested by FDA, will be discussed in more detail at the upcoming FDA Advisory Committee meeting on September 13 and 14.

C Pfizer's Disclosure of the Zoloft Pediatric Studies

As a research-based pharmaceutical company, Pfizer recognizes that the availability of meaningful clinical trial results is critical to the communication of important new information for the medical profession, patients and the public. Pfizer is committed to the timely communication of meaningful results of Pfizer sponsored hypothesis-testing clinical trials (essentially all Phase 3 and 4 trials), regardless of outcome, for Pfizer's marketed prescription medicines. In short, Pfizer is dedicated to making public the results of all clinical trials that have the potential to improve patient care. Pfizer's practices conform to the PhRMA Principles on the Conduct of Clinical Studies and Communication of Clinical Trial Results and are also codified in Pfizer's Policy on Public Disclosure of Clinical Trial Results which is available on Pfizer's website[26] (http://www.pfizer.com/are/about_public/mn_about_ethical_trials.html).

Pfizer continues to examine ways to improve accessibility to meaningful clinical trial information. To that end, Pfizer is actively participating in and supports a recent PhRMA initiative to develop a centralized database to provide access to clinical trial results on studies that fall within the scope of the PhRMA Principles. Pfizer believes that the development of a single database containing summaries of studies sponsored

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[26] Publication of findings from Zoloft pediatric studies predates the formulation of the current disclosure policy, but is concordant with all the principles embraced in the policy.

by all participating PhRMA member companies will facilitate healthcare providers' accessibility to clinical trial results and positively impact patient care.

Important safety and efficacy information generated from clinical trials can be publicized and disseminated in a number of ways:

- Through abstracts, posters and presentations at scientific meetings,
- Through publication in peer-reviewed journals,
- Through inclusion in "Medical Information" letters, and
- Through filing to regulatory authorities and subsequent inclusion in the product label.

Most frequently, clinical data from studies are presented first as abstracts and posters at scientific meetings. This is useful since it is relatively rapid, provides opportunity for questions and discussion and, because scientific meetings may be attended by many thousands of individuals, has the potential to reach a large audience. The more rigorous system of publication in a peer-reviewed journal may take longer due to the time involved in peer review and journal publication dates, but benefits from the thoughtful scrutiny of subject-matter experts. These peer reviewers are appointed by the journal and, working independently and anonymously, may suggest additions or deletions, as well as challenge analyses and suggest new ones, as pre-requisites for publication.

C.1 Pfizer's Publication of Zoloft Pediatric Data at Scientific Meetings and in Peer-Reviewed Journals

Information obtained from the Zoloft pediatric program has been made public in numerous ways. Seven of the nine completed studies have been published in respected journals, and one has been submitted for publication to the Journal of Child and Adolescent Psychopharmacology, where it has recently undergone peer review.

Some of the Zoloft pediatric trials have provided data for multiple publications. For example, large placebo-controlled studies like A0501001 and A0501017 with extensions (like A0501015, in which some patients were followed for up to 34 weeks) are rich in data and have provided the opportunity to understand the results better through subset analyses. The data from Studies A0501001 and A0501017 have been used to revise and validate efficacy scales (CDRS-R and PQ-LES-Q) for use in adolescent populations and provided technical advances in this field of research[27].

Table 6 lists the nine completed studies and a selection of the posters and publications they have generated. In addition, a comprehensive review of Zoloft safety data, including the individual efficacy results of the two pediatric depression studies, was presented at a special invited session during the annual meeting of the American Academy of Child and Adolescent Psychopharmacology in October, 2003.

Table 6. Zoloft Pediatric Studies: Selected Abstracts, Posters, and Publications

Study # Indication	Abstract/Poster	Publication
90CK21-0525 MDD/OCD 6 weeks, Open Label	Alderman J et al. Sertraline treatment in children and adolescents: tolerability, efficacy, and pharmacokinetics. APA, 1996 (poster); also Eur Neuropsychopharmacol 6 (suppl 3) June 1996 (abstract)	Alderman J et al. Sertraline treatment of children and adolescents with obsessive-compulsive disorder or depression: pharmacokinetics, tolerability, and efficacy. **J Am Acad Child Adolesc Psychiatry** 1998; 37 (4): 386-394
91CK21-0550 MDD/OCD 24 weeks, Open Label, continuation of 90CK21-0525		Manuscript being prepared for submission
90-CE21-0498 OCD 12 weeks, Double Blind	Wolkow R et al. Sertraline in pediatric OCD: a multicenter controlled trial; World Congress of Biological Psychiatry, June 1997 (poster) Wolkow et al. A placebo-controlled trial of sertraline for pediatric OCD; APA, 1997 (abstract)	March J et al. Sertraline in children and adolescents with Obsessive-Compulsive Disorder. **JAMA** 1998; 280 (20): 1752-1756 Wilens TE et al. Absence of cardiovascular adverse effects of sertraline in children and adolescents. **J Am Acad Child Adolesc Psychiatry** 1999; 38 (5): 573-577

[27] See Endicott J et al. Reliability and validity of the CDRS – Revised in children and adolescents treated with sertraline; NCDEU 2002 (poster) and Endicott J et al: The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q): Reliability and Validity (submitted to *J Am Acad Child Adolesc Psychiatry*, April 2004).

Study # Indication	Abstract/Poster	Publication
91CE21-0536 OCD 52 weeks, Open Label, continuation of 90-CE21-0498	Wagner KD. Safety and efficacy of sertraline in long-term pediatric OCD treatment: a multicenter study; NCDEU 1999 (poster) Cook E et al. Obsessive-compulsive disorder: Long-Term Sertraline in Children and Adolescents, AACAP, 1999 (poster) Wagner KD et al. Long-term sertraline treatment for pediatric OCD: remission rates and functional status; APA 2002 (poster)	Cook E et al. Long-term sertraline treatment of children and adolescents with obsessive-compulsive disorder. **J Am Acad Child Adolesc Psychiatry** 2001; 40 (10): 1175-1181 Wagner KD et al. Remission status after long-term sertraline treatment of pediatric obsessive-compulsive disorder. **J Child Adolesc Psychopharmacol** 2003; 13 (Suppl 1): S53-60
R-0246 MDD 22 weeks, Open Label	Presented at AACAP, 1997 (poster)	Ambrosini P et al. Multicenter open-label sertraline study in adolescent outpatients with major depression. **J Am Acad Child Adolesc Psychiatry** 1999; 38 (5): 566-572
STL-CDN-94-00 MDD/Dysthymia 24 weeks, Open Label	Simeon JG et al. Sertraline in adolescent depression and dysthymia: a 6-month open trial. APA 1998 (poster)	Nixon MK et al. Sertraline effects in adolescent major depression and dysthymia: a six-month open trial. **J Child Adolesc Psychopharmacol** 2001; 11 (2): 131-142
A0501001 and **A0501017** MDD 10 weeks, Double Blind	Donnelly C et al. Efficacy and safety of sertraline in the treatment of pediatric major depressive disorder; ACNP 2001 (poster) Wagner KD et al. Efficacy and safety of sertraline in the treatment of pediatric major depressive disorder; APA 2002 (poster); ECNP 2002 (poster) Endicott J et al. Reliability and validity of the CDRS – Revised in children and adolescents treated with sertraline; NCDEU 2002 (poster) Donnelly C et al. A comparison of the response to sertraline in children and adolescents with major depressive disorder; NCDEU 2003, AACAP 2003 (poster) Wagner KD et al. Efficacy of sertraline in anxious subgroup in youth with major depression; APA 2004, NCDEU 2004 and CINP 2004 (poster)	Wagner KD et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. **JAMA** 2003; 290 (8):1033-1041 and reply in **JAMA** 2004; 291 (13): 1561-2 Donnelly C et al. A comparison of the response to sertraline in children and adolescents with major depressive disorder (submitted to **J Am Acad Child Adolesc Psychiatry)** Endicott J et al: The Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q): Reliability and Validity (submitted to **J Am Acad Child Adolesc Psychiatry**, April 2004)
A0501015 MDD 24 weeks, Open Label, continuation of 1001 and 1017	Rynn MA et al. ACNP 2002 (poster) Rynn MA et al. Long-term safety and tolerability of sertraline in children and adolescents with major depression; APA 2003, ECNP 2003, ACNP 2003 (poster)	Rynn, M (submitted to **J Child Adolesc Psychopharmacol)**

JAMA: Journal of the American Medical Association
AACAP: American Academy of Child and Adolescent Psychopharmacology
APA: American Psychiatric Association
NCDEU: New Clinical Drug Evaluation Unit Meeting –sponsored by National Institute of Mental Health
ACNP: American College of Neuropsychopharmacology;
ECNP: European College of Neuropsychopharmacology
CINP: Collegium Internationale Neuro-Psychopharmacologicum

The only study that Pfizer has not published, although the data from the study have been submitted to FDA, is open-label extension study 91CK21-0550. Because this was a small, open-label study—32 patients with depression, 10 patients with OCD, and one patient with OCD and depression—and its results were consistent with known data about Zoloft in this population, Pfizer did not seek to have it published. However, given the current interest in SSRI data in the pediatric population, Pfizer is preparing a manuscript of this study for submission and publication. Since this was also an extension study, all of these 43 patients had participated in the parent study (90CK21-0525) that was published by the Pfizer researchers who conducted the study[28].

C.2 Dissemination of Information by Medical Information Letters

Medical Information letters are another means by which pharmaceutical companies provide important information about their products to interested healthcare practitioners and the public. These letters generally respond to unsolicited inquiries about a particular drug from health care professionals, patients or others. Healthcare professionals employed by the pharmaceutical company prepare these letters after an extensive review of the particular topic to be addressed.

There are two letters in the Pfizer Medical Information database that are related to the Zoloft pediatric program. One letter reviews data related to the two Zoloft pediatric depression trials, as well as related published data. It should be noted that in this letter, Pfizer clearly states that Zoloft is not approved by the FDA for the treatment of

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[28] Alderman J et al. Sertraline treatment of children and adolescents with obsessive-compulsive disorder or depression: pharmacokinetics, tolerability, and efficacy. *J Am Acad Child Adoles.*

MDD or dysthymic disorder in pediatric patients and that Pfizer does not recommend the use of Zoloft for these conditions. The second letter provides all available information on suicide-related adverse events in children and adolescents from Pfizer's pediatric program for Zoloft, as well as from independently conducted (non-Pfizer) studies. In this letter, Pfizer also provides a review of the case reports in the scientific literature as well as position statements concerning the topic of suicidal behavior in children and adolescents with major depression.

C.3 Changes to Zoloft Labeling

In today's demanding and complex healthcare system, doctors lack the time, and often the capacity, to review, analyze and evaluate the enormous quantity of clinical data that is generated for the enormous number of drug products that are on the U.S. market, as well as the many others that are in clinical development. Because of this, the FDA, by virtue of its statutory authority, conducts comprehensive reviews of the data related to each drug to make determinations about its overall Risk/Benefit profile and approvability. The FDA objectively evaluates the wealth of data that are gathered in the preclinical and clinical development programs of a new drug, as well as the ongoing clinical research that expands knowledge of approved medications. The output of its review is the product label, which, through its consistent presentation of data, allows doctors to objectively compare drugs in a therapeutic class and make the best decisions for their patients. The product label is arguably the most important vehicle for the dissemination of information about drug safety and efficacy.

Psychiatry 1998; 37 (4): 386-394.

The nine completed Zoloft pediatric studies have all been submitted to the FDA. Together with the extensive written reports and complete analyses for each study, the FDA also receives all the efficacy and safety data collected in these trials, allowing its medical and statistical reviewers to conduct additional analyses and checks. In addition, the FDA routinely receives safety data in the form of Annual Reports. These mandated reports require a drug sponsor to summarize, for each drug in development or already on the market, the safety information from trials in progress or completed in the previous year, including tabular summaries of adverse events, information about patients who dropped out of a study for adverse events, and any new information that is learned relating to a drug's actions. These studies have led to a series of important changes in the Zoloft Package Insert (PI) and have consequently informed doctors about valuable information learned from those studies.

In October 1997, on the basis of data from Studies 90CK21-0525 and 90CE21-0498, Zoloft was approved for the treatment of pediatric OCD. Text added to the label informed doctors about how the blood levels observed in children and adolescents compared with those in adults, described the conduct of the double-blind clinical trial, the magnitude of the improvement observed, noted adverse events that had been recorded, and gave specific dosing recommendations for children and adolescents. In October 2001, additional text was added to the label that described the one-year continuation study in pediatric OCD (Study 91CE21-0536) providing information on the long-term safety of Zoloft in pediatric use. Since the study supporting this label change was open label, no long-term efficacy information was added.

In September 2003, the Zoloft label was again modified to add safety information gained from the pediatric MDD trials, Studies A0501001 and A0501017 and the long-term extension, Study A0501015. Specifically, the added text advised doctors that weight loss had been observed in the first ten weeks of treatment, although with longer treatment weight gain was again as expected. Regular monitoring of weight and growth in children treated with Zoloft was recommended. An indication for the use of Zoloft in pediatric MDD was denied since Pfizer had not fulfilled the requirement for two positive trials (individually the two studies were not each positive, and the pooled efficacy analysis, albeit positive, constituted just a single trial). The FDA chose not to describe the studies in the label, stating in their letter to Pfizer that: "*Given the fact that negative trials are frequently seen, even for antidepressant drugs that we know are effective, we do not feel that it would be useful to describe these negative trials in labeling, since this may be misinterpreted as evidence that Zoloft does not work in this population. Rather, we feel that the existing language, suggesting simply that efficacy has not been established in this population, is still most appropriate*"[29].

In August 2004, the Warnings section of the Zoloft label was amended to advise doctors that adult and pediatric patients with MDD could experience a worsening of their illness that might include thoughts of suicide. The Warning further advised that patients should be carefully monitored, especially when starting treatment with an antidepressant or changing dose levels. The label also advised that caregivers should

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[29] Correspondence from FDA to Pfizer, September 30, 2002.

be told to be watchful for changes in symptoms and notify healthcare providers if they notice a change in symptoms.

In summary, there have been four additions to the Zoloft label relating to pediatric use:

(1) the original pediatric use for OCD on 10/10/97
(2) the pediatric OCD long-term safety inclusion on 10/12/01
(3) safety information inserted as a result of the pediatric MDD trials on 9/16/03
(4) Warning to monitor for suicidality on 8/19/04

These four important label changes to the Zoloft label served to provide new information about Zoloft to healthcare professionals and in particular to those responsible for prescribing Zoloft.

D Conclusions

Pfizer has conducted a rigorous pediatric program for Zoloft, consisting of nine completed studies and two studies still in progress. In 1997, FDA approved Zoloft for the treatment of Obsessive-Compulsive Disorder in the pediatric population. Although Zoloft was not approved for the treatment of major depression in this population, Pfizer's studies yielded important information that was added to the Zoloft label.

There were no patients who committed suicide in the Zoloft pediatric studies.

The number of suicide-related events in the Zoloft pediatric studies is small, and, because none of these numbers are statistically significant, no conclusion can be drawn that treatment with Zoloft in these studies is associated with an increased risk of suicidal behaviors.

Pfizer submitted all of the completed studies to the FDA, resulting in several important changes to the Zoloft label, providing doctors with important safety and efficacy information from those studies.

Moreover, Pfizer sought a wider dissemination of the safety and efficacy results of its pediatric program through its publication of study results. The results of eight of Pfizer's pediatric studies have been shared with the medical and scientific community in the form of abstracts, posters, and presentations at scientific meetings as well as publication in respected peer-reviewed journals. Publications based on the databases generated in the Zoloft pediatric trials have not only served to disclose the findings from the studies, but have also contributed to the understanding and evaluation of devastating psychiatric illnesses in a vulnerable patient population.

Mr. WALDEN. Thank you very much, Dr. Clary. We appreciate all of you being here today and testifying as we look at how all this information is made public. Dr. Clary, your company performed two pediatric studies with Zoloft in depressed children; is that correct?

Ms. CLARY. That is correct.

Mr. WALDEN. These study reports were submitted then to the FDA in December 2001, right?

Ms. CLARY. Yes, that is correct.

Mr. WALDEN. And is it correct that neither study showed efficacy?

Ms. CLARY. It is correct that neither study showed a statistically significant difference between Zoloft and placebo.

Mr. WALDEN. And, therefore, Zoloft is not approved, as you said, for use in depressed kids, correct?

Ms. CLARY. Yes.

Mr. WALDEN. On the label.

Ms. CLARY. Yes.

Mr. WALDEN. Neither of these depression studies that you did in children were published on a stand-alone basis, right?

Ms. CLARY. That is correct, because Pfizer had made a determination before the blinds were broken that the pooled analysis was really what was needed in order to really have reliable results.

Mr. WALDEN. If you always sort of planned on pooling the studies, why is the Zoloft pooling article published 1½ years after the study reports were completed?

Ms. CLARY. Well, I would like to just—that brings up really a question about sort of the peer review process——

Mr. WALDEN. Sure.

Ms. CLARY. [continuing] and the length of time that it can take to get an article into publication. It often may take a year to a year and a half for submission of a manuscript. Then the article is sent out by journal editors to a group of anonymous peer reviewers, experts in the field review the information, review the study, often will ask for new analyses, they may ask for things to be taken out of the article or additional information to be placed in the article. It is then sent back to the authors, the authors respond and possibly rewrite the article. It goes back, it is reviewed again. There are still editorial decisions that have to be made. So it can take a while for——

Mr. WALDEN. And that is what happened in this case?

Ms. CLARY. Yes. Yes.

Mr. WALDEN. That is why the delay?

Ms. CLARY. Yes. This manuscript was submitted very soon after we had the information.

Mr. WALDEN. Could you turn to tab 48, please? This is the pooled analysis article that was published in the Journal of American Medical Association in August of 2003. Nowhere in this article does it make clear that the two separate trials by themselves did not show efficacy. Do you know why that wasn't included?

Ms. CLARY. That was because Pfizer had made a determination that the best way——

Mr. WALDEN. Was to pool?

Ms. CLARY. [continuing] was to pool. We have a signed analysis plan demonstrating that. This was certainly not anything that the

editors, the peer reviewers didn't know. As a matter of fact, there was a lot of exchange between the editors and Pfizer about exactly what should be in the article, as is common in these peer reviewed articles.

Mr. WALDEN. Sure. Now, I guess as I read the JAMA from August 27, 2003, it talks about comment, and it says, "In the trials reported here, Sertraline was found to be more effective than placebo for treatment of pediatric MDD with statistically greater improvement occurring as early as week 2. Of these three randomized double blind placebo-controlled trials of an SSRI in pediatric MDD that have been published to date, only one," that was Prozac, I believe, "the study by Emslie, et al., of fluoxetine reported statistically significantly better results for the prospectively defined primary end point, and this was a comparatively small single center trial. Thus, our trials," and these would be the ones Pfizer did, "describe the largest positive psychopharmological study of pediatric MDD using an international multicenter study design."

Now, when it says here the largest positive study for pediatric MDD and yet where I am confused is if the two individual studies showed no efficacy, how do you arrive at this conclusion that it is the largest positive study for pharmacological pediatric MDD?

Ms. CLARY. I think in a paper like this, and, again, in the methodology section of the paper, it was described that there were two trials that were pooled. This decision was made to pool prior to the breaking of the blind, so no one, the investigators nor Pfizer statisticians or anyone knew who was on medicine——

Mr. WALDEN. Sure.

Ms. CLARY. [continuing] and who was on placebo, but the word, "study," is often used in an article like this to describe the paper was about a combined analysis.

Mr. WALDEN. Do you think, though, that that article implies that Zoloft works in kids, and, if so, do you think that accurately is based on what the two studies showed independently?

Ms. CLARY. I think that the article states—in a scientific article, what you state is the conclusion from the data that is presented in that article, and it states that—I just wanted to read you exactly what the last part of that—it talked about some limitations, whether there might be lower dosages that could be needed or whether longer-term treatment was effective or unknown, that was not known. It did say the results reported here, so the results in this study, these two pooled studies, support the conclusion that Sertraline is an effective, safe and well-tolerated short-term treatment. And, indeed——

Mr. WALDEN. Treatment for pediatric MDD?

Ms. CLARY. Yes, for children and adolescents with MDD. Those are the conclusions from this particular analysis, which——

Mr. WALDEN. But you said earlier the independent study showed it really didn't have an efficacy in pediatric MDD, right, the two studies on their own?

Ms. CLARY. There was not a statistical difference. In both studies, Zoloft-treated patients showed more improvement than placebo-treated patients.

Mr. WALDEN. Now, I want to go to tab 67 because this is the review and evaluation of clinical data by the Food and Drug Adminis-

tration. The reviewer was Andrew D. Mosholder, MPH, and it was completed on August 13, 2002. And in the executive summary Dr. Mosholder says, and I quote, "The sponsor's proposed claim for the treatment of pediatric major depressive disorder is not supported by the data in this submission. Both pivotal studies failed to distinguish Sertraline from placebo on the primary outcome measures. The sponsor has proposed pooling the data from the two trials to yield a statistically significant result on the basis the trials were conducted under identical protocols. This, however, would be a major departure from our usual policies discouraging pooling of efficacy data." And then it goes on to say some other things, but that is the primary point. How did your company respond to Dr. Mosholder's comments?

Ms. CLARY. Well, when we received the indication from the FDA that they would not approve the drug for pediatric depression, we had to accept that.

Mr. WALDEN. Sure.

Ms. CLARY. We believed that the pooled analysis was the most valid, scientifically accurate way to show the data, but we of course accepted that, and eventually that did end up in our label that efficacy was not established. In addition, we have not promoted the use of Zoloft for pediatric MDD. Physicians who inquire about the use of Zoloft in MDD will receive information, medical information letter stating that Zoloft is not approved for use in MDD in pediatrics.

Mr. WALDEN. And in fact after our conversation yesterday, sometime this afternoon, Pfizer provided us with the letter that is sent out when someone does inquire about use of Zoloft for pediatric depression. And I note that, if I recall correctly, at least in the cover letter, it doesn't say that it is—it actually says Zoloft is indicated for the treatment of major depressive disorder, obsessions and compulsions in patients with OCD, panic disorder, et cetera, et cetera. So in the cover letter it doesn't say it is not approved for pediatric MDD; however, it does say that when you go over to the next page. But then it goes on in the summary to talk about how well it is tolerated in children and all kinds of open label studies and other uses in adolescents. And then it makes a reference to a retrospective study. "Sertraline demonstrated clinical benefits in treating depression in children and adolescents." It sure—I mean I am not a doctor, but it sure would leave me with the impression that it is not only safe to use in adolescents for pediatric MDD but may actually do some good.

Ms. CLARY. So there are a couple of ways I would like to respond to that.

Mr. WALDEN. Yes, please.

Ms. CLARY. First of all is that, again, going back to 1997, the FDA concluded that Zoloft was a safe medication to use in the pediatric population, ages 6 to 17. So that has been in the label since——

Mr. WALDEN. Safe but no efficacy.

Ms. CLARY. Safe and effective for obsessive-compulsive disorder.

Mr. WALDEN. Okay, for OCD, right.

Ms. CLARY. Right. We have no reason to think the safety—so the basic safety information has been there. The way that these letters

are constructed, and there is a very clear process with our Medical Information Department, is that they do a literature search of all literature. You will note here that there is literature, most of it open label because there really haven't been a lot of large placebo-controlled studies until FDAMA was passed, which really did encourage controlled studies to be done, but a comprehensive search. So every study is put into these letters, positive or negative, that is in the literature.

Mr. WALDEN. I should have submitted this letter for the record, and so I would like to do that without objection at this time.

[The information referred to follows:]

U.S. Medical Information
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

Pfizer Pharmaceuticals Group

February 10, 2004

401 Parnassus Ave Box F
San Francisco, CA 94143-9911

Dear

Our colleague, Jennifer Glassman, has referred to Medical Information your request for information regarding Zoloft® (sertraline hydrochloride). Your request concerned use in pediatric depression.

Zoloft (sertraline hydrochloride) is indicated for the treatment of major depressive disorder, obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), panic disorder with or without agoraphobia, post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder (also known as social phobia) in adults. It is also indicated for obsessions and compulsions in pediatric patients with OCD aged 6 to 17 years.

I hope this information is helpful. Thank you for your interest in Pfizer. If you would like additional assistance, please call 1-800-438-1985.

Sincerely,

Ellen Shulman.

Ellen Shulman, RPh
Medical Information Product Specialist
Pfizer U.S. Medical Information

SHULMANE/10106137

Encl.

use in pediatric depression
Zoloft (sertraline hydrochloride) Package Insert

INTRODUCTION

Two double-blind, placebo-controlled studies were conducted to evaluate the efficacy and safety of sertraline in children and adolescents with major depressive disorder (MDD; also known as major depression). In September of 2003, Pfizer received approval from the Food and Drug Administration to include the safety information from the 2 depression trials into the Zoloft labeling.

Zoloft is not approved by the Food and Drug Administration for the treatment of depression in pediatric patients or for the treatment of dysthymia. Also, the safety and effectiveness of sertraline in pediatric patients below the age of 6 have not been established.[1]

Approximately 600 patients with MDD or obsessive-compulsive disorder between 6 and 17 years of age have received sertraline in clinical trials, both controlled and uncontrolled. The adverse event profile observed in these patients was generally similar to that observed in adult studies with sertraline. As with other selective serotonin reuptake inhibitors, decreased appetite and weight loss have been observed in association with the use of sertraline. Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with a selective serotonin reuptake inhibitor is to be continued long-term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.[1]

SUMMARY

- Results of the pooled analysis from 2 identically designed, double-blind, placebo-controlled, multicenter, 10-week studies found sertraline to be well tolerated and more effective than placebo in children and adolescents with major depression. A significantly greater proportion of sertraline-treated patients were considered responders at study endpoint.

- Sertraline was safe and well tolerated in a subset of children and adolescents with MDD who participated in 1 of the acute-treatment, 10-week studies and continued into the 24-week open-label extension study. The clinically important weight loss observed in the acute-treatment studies was reversed during the 24-week open-label treatment. Patients continued to maintain symptomatic improvement for up to 24 weeks of the study. In addition, most patients no longer met DSM-IV criteria for MDD at study endpoint.

- An open-label study examined the efficacy and safety of sertraline continuation treatment in chronically depressed adolescent outpatients who responded to the acute 10-week sertraline therapy. Sertraline demonstrated improvements in both clinician- and patient-rated depression efficacy measures that were maintained during the continuation treatment.

- In another small open-label study, the long-term treatment with sertraline (up to 24 weeks) in adolescents with major depressive or dysthymic disorder was effective and well tolerated; high response rates were maintained through Week 24 in patients with depression, but not in patients with dysthymic disorder.

- In a prospective, open-label, 12-week study of adolescents hospitalized for the treatment of a depressive episode, sertraline demonstrated significant improvements on most depression

efficacy scales. Sertraline treatment was well tolerated, with the exception of a high frequency of sleep disturbances, which were usually manageable.

- In a retrospective study, sertraline demonstrated clinical benefits in treating depression in children and adolescents. Some patients reported adverse events, which included gastrointestinal adverse events, fatigue, sedation, and behavioral adverse events.

LITERATURE SEARCH

As of August 2003, a computerized search of the medical literature has identified several articles that discuss the use of sertraline in the treatment of pediatric depression. A review of some of these articles is provided below. This communication contains summaries of articles that were not published by Pfizer Inc. Therefore, the summaries should not be viewed as an endorsement or validation of the reporting or of the methodology used by authors of these articles.

DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES

Wagner et al evaluated the safety and efficacy of sertraline in the treatment of 367 outpatient children aged 6 to 11 years and adolescents aged 12 to 17 years with a DSM-IV diagnosis of MDD. The data was pooled from 2 identically designed, double-blind, placebo-controlled, multicenter, flexible-dose, 10-week studies. The exclusion criteria were as follows: current primary DSM-IV-defined diagnosis of attention-deficit hyperactivity disorder, conduct disorder, or panic disorder; history of bipolar disorder; any currently psychotic features or autistic spectrum disorders; patients who had previously attempted suicide or who were judged to pose a significant suicidal or homicidal risk. Nearly 40% of patients had at least 1 comorbid psychiatric disorder, with the most common being oppositional defiant disorder, anxiety, adjustment reaction and phobic disorders. The primary efficacy measure was the Children's Depression Rating Scale-Revised (CDRS-R), a validated 17-item, clinician-rated instrument that measures the severity of patients' depressive symptoms, with total possible scores ranging from 17 to 113. The mean baseline CDRS-R score±SD was 64.3±11 in sertraline-treated patients and 64.6±11 in patients receiving placebo. Secondary outcomes measures are provided in Table 1 below.[2]

Table 1. Secondary Outcomes Measures

Responder Criteria Based on the Following Scales	CGI Rating Scales	Anxiety Scale	Quality of Life/Social Functioning Scales
CDRS-R (defined as a 40% decrease in the adjusted CDRS-R total score) **CGI-I responders** (defined as patients with a CGI-I score ≤2 ["very much" improved or "much" improved])	CGI-S CGI-I	MASC	PQ-LES-Q CGAS

CGAS=Children's Global Assessment Scale; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; MASC=Multidimensional Anxiety Scale for Children; PQ-LES-Q=Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

The CDRS-R and CGI-S scales were administered at screening visits and, along with the CGI-I, at the end of Weeks 1, 2, 3, 4, 6, 8, and 10 of double-blind treatment (or at the time of early discontinuation). All other secondary assessments were made at baseline and at the end of Week 10 of double-blind treatment (or at the time of early discontinuation). Safety data, including vital signs, body weight, and adverse events, were collected.[2]

Patients were randomized to receive a flexible dose of either sertraline (50-200 mg/day; N=189) or placebo (N=187) for 10 weeks. Sertraline treatment commenced with 25 mg/day for 3 days, followed by 50 mg/day; increases of 50 mg/day every 2 weeks thereafter were allowed for a maximum dose of 200 mg/day, based on tolerability and clinical response. One hundred and eighty-five sertraline-treated patients and 179 placebo patients were included in the efficacy analysis.[2]

The mean sertraline dose at endpoint (Week 10) for completers was 131 mg/day. Sertraline-treated patients showed significantly greater improvement than placebo-treated patients on the primary efficacy measure (CDRS-R total score mean change at Week 10 was -30.24 versus -25.83, respectively [p=0.001]; an overall mean change of -22.84 versus -20.19, respectively [p=0.007]). Significantly greater improvement was noted with sertraline treatment for 5 of the 17 items, including irritability (p<0.001), low self-esteem (p=0.02), excessive weeping (p=0.003), listless speech (p=0.005), and hypoactivity (p=0.03). No statistically significant difference was noted between treatment groups for suicidal ideation (p=0.78). Additionally, in sertraline completers, the mean changes in CGI-S and CGI-I scores were statistically significant (p=0.001 and p=0.009, respectively) versus placebo. Significantly greater improvement was seen as early as Week 1 for the CGI-I and Week 3 for the CGI-S and CDRS-R (p<0.05 for all). A greater proportion of sertraline-treated patients (69%) compared to placebo-treated patients (59%) met the CDRS-R responder criteria (p=0.05). Additionally, 63% of sertraline-treated patients met CGI-I responder criteria compared with 53% of patients in the placebo group (p=0.05). The mean changes from baseline for the secondary outcomes measures, including MASC, PQ-LES-Q, and CGAS, were

numerically greater for sertraline compared to placebo; however, the differences did not reach statistical significance.[2]

Sertraline was generally well tolerated; the majority of adverse events were mild to moderate in severity. Adverse events that occurred in >5% of sertraline-treated patients and twice that of placebo-treated patients included insomnia, diarrhea, anorexia, vomiting, agitation, urinary incontinence, and purpura. There was no increase in the rates of suicide or suicide attempts in patients treated with sertraline versus placebo.[2] At baseline the mean weight for children was 39.0 kg for sertraline and 38.5 kg for placebo. At baseline the mean weight for adolescents was 61.4 kg for sertraline and 62.5 kg for placebo. There was a bigger difference between sertraline and placebo in the proportion of outliers for clinically important weight loss in children than in adolescents. For children, about 7% had a weight loss greater than 7% of body weight compared to none of the placebo patients; for adolescents, about 2% had a weight loss greater than 7% of body weight compared to about 1% of the placebo patients.[1] The mean change in body weight from baseline to the final visit was -0.38 kg in sertraline-treated patients and +0.78 kg among placebo-treated patients (p=0.001). There were no clinically important differences between the 2 treatment groups with respect to laboratory tests, vital signs, or electrocardiographic findings. The authors concluded that sertraline was statistically superior to placebo in the treatment of pediatric MDD.[2]

PROSPECTIVE, OPEN-LABEL STUDIES

Rynn et al assessed the safety and tolerability of sertraline in an open-label, multicenter, 24-week trial of 226 patients (109 children, 6-11 years of age; 157 adolescents, 12-18 years of age) with MDD who completed 1 of the 2 double-blind, placebo-controlled, 10-week trials summarized above. Safety was assessed by adverse event reports, clinical laboratory tests, and vital signs. The primary efficacy parameter was the CDRS-R (Best Description of Child), which is based on the highest (most severe) rating provided for each scale item. Secondary outcome measures were the same as in the acute double-blind study summarized above, except there were 2 additional responder criteria (listed in Table 2) that were prospectively defined in the open label study.[3]

Table 2. Additional Responder Criteria

Remitters: proportion of subjects no longer meeting DSM-IV criteria for MDD as determined by the Affective Disorder Supplement of the Kiddie Schedule for Affective Disorder and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL).
Responding remitters: proportion of patients no longer meeting criteria for MDD, as defined above, and who responded as defined by CDRS-R.

Overall, 62.4% of patients completed 24 weeks of treatment. The mean dose at study endpoint was 113.8 mg/day for patients who were previously exposed to sertraline in the double-blind study (sertraline/sertraline group) and 106.8 mg/day for patients newly exposed to sertraline in the open-label study (placebo/sertraline group). Patients treated with sertraline for up to 24 weeks continued to show symptomatic improvement of MDD as measured by the changes in CDRS-R Best Description of Child and CGI-S total scores (p<0.0001 from baseline to endpoint).

Additionally, statistically significant improvements were observed on secondary outcome measures including the CGI-I, MASC, CGAS, and PQ-LES-Q. A vast majority of patients treated for up to 24 week with open-label sertraline met all 4 responder criteria.[3]

Most adverse events were mild or moderate in severity. The most frequent adverse events, which occurred in ≥10% of patients, were upper respiratory infection, pharyngitis, headache, insomnia, vomiting, and dizziness. Only 4.1% of patients discontinued the study due to adverse events related to medication. There were no clinically significant changes in electrocardiogram, vital signs, pulse, or blood pressure noted over the course of the study. Additionally, there were no clinically important changes in weight noted for males or females treated with sertraline.[3] A mean weight loss of approximately 0.5 kg was seen during the first 8 weeks of treatment for subjects with first exposure to sertraline during the open-label extension study, similar to mean weight loss observed among sertraline-treated subjects during the first 8 weeks of the randomized controlled trials. The subjects continuing in the open-label study began gaining weight compared to baseline by Week 12 of sertraline treatment. Those subjects who completed 34 weeks of sertraline treatment (10 weeks in a placebo-controlled trial plus 24 weeks open-label, N=68) had weight gain that was similar to that expected using data from age-adjusted peers.[1] Patients maintained their overall percentile for age-adjusted body weight between baseline and study endpoint (Week 24). The authors concluded that sertraline was safe and generally well tolerated for up to 24 weeks in the range of 50 to 200 mg/day in children and adolescent with MDD.[3]

Ambrosini et al reported on a prospective, multicenter trial of sertraline therapy in 53 adolescents (12-19 years of age) with MDD. Patients were enrolled in a single-blind, placebo-controlled, 2-week assessment period followed by an open-label, acute-treatment, 10-week phase with sertraline. Patients meeting response criteria (≥50% reduction in the 21-item Hamilton Depression Rating Scale [HAM-D-21], Beck Depression Inventory [BDI], or 17-Item Depression Rating Scale derived from the Mini-SADS [M-SADS], or CGI-I score of ≤2) were eligible to continue sertraline treatment for an additional 12-week period. At the end of the single-blind placebo phase, sertraline dosing began at 50 mg once daily in all patients. The first dose increment of 50 mg was allowed, if clinically indicated, at Week 3, and the dose could be titrated in increments of 50 mg to a maximum daily dose of 200 mg for those patients continuing to show an inadequate response. Therefore, by the end of Weeks 3, 6, and 7, the maximum dose could be 100, 150, or 200 mg/day, respectively. Doses could be decreased at any time due to adverse events. Visits to evaluate therapeutic response and adverse events were scheduled at Weeks 2, 3, 4, 6, 8, and 10. In addition, assessments were completed at Weeks 14, 16, 18, 20, and 22 for patients who entered the continuation phase. Efficacy measures included M-SADS and the 17-Item Depression Rating Scale derived from the M-SADS. Additionally, the HAM-D-21, 21-item BDI, CGI-I, CGI-S, and CGAS scales were administered.[4]

Forty-one patients completed at least 6 weeks of sertraline treatment and 34 patients completed at least 10 weeks. Twenty-six patients were defined as CGI responders and entered the 12-week continuation phase; 22 patients completed treatment. The mean sertraline dose was 93.3±20 mg at Week 6 and 127.2±45 mg at Week 10. Response rates for the HAM-D-21, CGI-I, 17-Item Depression Rating Scale, and BDI scales increased from Weeks 6 to 10, although the magnitude of the increase was different for each parameter. Response rates at the end of Weeks 8 and 10 were similar to rates reported using the same assessment criteria in adult patient antidepressant trials. Twenty-six of 47 patients (55.3%) had a reduction of at least 50% in HAM-D-21 scores

from baseline to endpoint. For all response criteria, a higher proportion of patients responded at Week 10 than at Week 6. All 4 measures of depression severity showed statistically significant improvement from baseline at Weeks 2, 4, 6, 8, and 10. The degree of improvement across the latter weeks was highest at Week 10 for all measures (p=0.0001). In the continuation phase, mean HAM-D-21 and BDI scores were recorded at baseline and at Weeks 10, 14, 18, and 22. All scores showed a significant change from baseline values (p=0.0001) at all time points. Sertraline was well tolerated, and most adverse events were considered mild to moderate in severity. The most frequent adverse events, which occurred in ≥10% of patients, were headache, insomnia, nausea, dizziness, flue-like symptoms, diarrhea, fatigue, agitation, and somnolence. None of the patients developed manic-like activation or mania. The authors concluded from this open-treatment study that sertraline appeared to be a therapeutically beneficial and generally well-tolerated antidepressant in a group of chronically depressed adolescent outpatients with moderate to severe major depressive disorder.[4]

Nixon et al evaluated the efficacy, safety, and tolerability of sertraline in the long-term treatment of MDD and dysthymia. Twenty-one psychiatric outpatients aged 12 to 18 years were evaluated in a noncomparative, open-label, single-arm, 6-month study. Of these, 13 patients had MDD defined by DSM-IV and a score of ≥18 on the first 17 items of the HAM-D for at least 3 months and 8 patients had dysthymic disorder (HAM-D score ≥13) for at least 1 year. Three patients were diagnosed with both disorders. A secondary diagnosis of anxiety or attention deficit hyperactivity disorder was allowed. Patients receiving psychoactive medication except methylphenidate underwent a washout period preceding study treatment. Clinical assessments included the HAM-D, CGI-I, CGI-S, and Hamilton Anxiety Rating Scale (HAM-A). Sertraline was administered for a period of 24 weeks, starting at 50 mg/day for at least 2 weeks and titrated in 50 mg/day increments at 2-week intervals, up to a maximum dose of 200 mg/day.[5]

A total of 9 patients (6 with MDD; 3 with dysthymic disorder) completed the full 24-week study period. Both patient groups showed a clinically significant improvement in HAM-D, HAM-A, and CGI-S scores. Patients with MDD had maximal response rates of 76.9% on the HAM-D at Weeks 12 and 24 and 69.2% on the CGI-I at Week 12, increasing to 76.9% at Week 20, and maintained through Week 24. Patients with dysthymic disorder had maximal response rates of 100% on the HAM-D and 75% on the CGI-I at Week 6. These rates did not remain elevated over time, with only 2 of 3 study completers responding to treatment at Week 24. Adverse events were mild to moderate; nausea and headache were the most commonly reported. The authors concluded that sertraline might be effective in the treatment of major depressive and dysthymic disorders and in the continued treatment of MDD in adolescents. They also emphasized the importance of longer-term studies for evaluating antidepressant therapy in adolescents with MDD and dysthymia.[5]

In a prospective, open-label study, McConville et al evaluated the effects of sertraline in 13 adolescents (12-18 years of age; mean 15.1 years) who were hospitalized for treatment of a major depressive episode. Patients were evaluated in an inpatient setting for a length of stay of 9 to 38 days (mean 18.7 days), with follow-up evaluations after discharge for a total of 12 weeks. Sertraline was flexibly dosed from 25 to 200 mg/day depending on the clinical response. The mean sertraline dose at Week 12 was 110 mg/day. The following rating scales were administered at baseline and weekly through Week 12: HAM-D, Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression Scale adapted for Depression (CGI-D), CGAS,

and Family Global Assessment Scale (FGAS). Additionally, 14 items from the K-SADS-II-R Major Depression Module were also administered to assess dimensional changes in individual symptoms of depression. Sertraline treatment resulted in statistically significant reductions in HAM-D ($p=0.027$) and MADRS ($p=0.022$) scores from baseline to Week 12. There was a small but statistically significant improvement on the CGAS between baseline and Week 12 ($p=0.011$); however, no significant change on the FGAS from baseline to Week 12 was observed. Based on the K-SADS-P assessment, all individual symptoms of depression, except for hypersomnia, increased appetite, and anorexia, decreased significantly over the 12-week period. Following 12 weeks of sertraline treatment, the most common adverse events were insomnia (69%), drowsiness (61%), weight change (46%), nightmares (39%), feeling tense and restless (31%), loss of appetite (31%), and headache (31%). There were significantly fewer adverse events at Week 12 compared to Week 1, suggesting diminution in these adverse events over time or a decrease in the severity of depressive symptoms. The authors concluded that sertraline might be useful in treating adolescents with major depression; however, further double-blind studies are needed in this patient population.[6]

RETROSPECTIVE STUDY

Tierney et al retrospectively evaluated the therapeutic and adverse effects of sertraline 25 to 200 mg/day in 33 children and adolescents aged 8 to 18 years with DSM-III-R-defined MDD. Of the 33 children and adolescents, 3 were diagnosed with MDD with psychotic features. All patients received no other psychotropic medication. Patients were evaluated by CGI-S and CGI-I scales. Among the 21 patients who received sertraline treatment for a mean of 45 days (range=2-10 weeks), the mean CGI-S score changed from 5.8 at baseline to 3.4 at endpoint (6=severely ill, 3=mildly ill). At study endpoint, the mean dose for these 21 patients was 100±53 mg/day. Of the 17 patients who could be assessed for CGI-I scores, 11 (65%) had a substantial clinical response (i.e., CGI-I score of 1=very much improved or 2=much improved), 5 patients (29%) showed slight improvement, and 1 showed no change. Adverse effects occurred in 16 of 33 patients and 8 patients discontinued sertraline therapy due to adverse effects. Of the 33 patients, 5 reported gastrointestinal adverse events (nausea, vomiting, stomach ache, decreased appetite), 5 patients reported fatigue and sedation, 3 patients reported headache, and 1 reported insomnia. Seven (21%) patients experienced behavioral adverse events (2 patients developed mania and 5 patients developed other types of behavioral activation). None of the patients exhibited suicidality, or aggressive or violent behavior. As noted by the authors, the absence of the control group limits the ability to determine whether the apparent adverse events were drug-related. The authors concluded that some children and adolescents with MDD might respond to sertraline; however, further controlled studies evaluating the efficacy and safety of sertraline in children and adolescents are needed.[7]

Refs.

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2. Wagner KD, Ambrosini P, Rynn M, et al. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: 2 randomized controlled trials. *JAMA* 2003;290:1033-1041.
3. Rynn M, Wagner KD, Donnelly C, et al. Long-term safety and tolerability of sertraline in children and adolescents with MDD (poster). Presented at the 156th Annual Meeting of the American Psychiatric Association; May 17-22, 2003; San Francisco, CA.
4. Ambrosini PJ, Wagner KD, Biederman J, et al. Multicenter open-label sertraline study in adolescent outpatients with major depression. *J Am Acad Child Adolesc Psychiatry* 1999;38:566-572.
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7. Tierney E, Joshi PT, Llinas JF, et al. Sertraline for major depression in children and adolescents: preliminary clinical experience. *J Child Adolesc Psychopharmacol* 1995;5:13-27.

Mr. WALDEN. One final question—I have blown past my time limit here—do you have—what is the objection to publishing studies in full as stand-alone? Some of you, I think, your companies at least have begun to do that. It would seem to me that it would be in everyone's best interest as we all try and get information to make these studies published stand-alone, fully available to the public without us having to mandate that legislatively. I noted today that the various medical journals are now requiring additional standards in terms of what they are going to accept to be published, I think, in part, because of these hearings, but can you just quickly say if your company does support publication of stand-alone studies, making them available on your web sites of all pediatric MDD studies? Dr. Wheadon?

Mr. WHEADON. Well, as I think I stated in my opening statement, we have taken that process starting in June 2004 to post on our web site the study results for the pediatric studies. So that is a process that we have undertaken for the——

Mr. WALDEN. But when you say study results, is that a summary of them or will you also make the full study available if someone were to want to access that?

Mr. WHEADON. Actually, on this particular web site, we are posting the study reports.

Mr. WALDEN. Is that whole thing?

Mr. WHEADON. The whole thing, right.

Mr. WALDEN. Okay.

Mr. WHEADON. As well as the protocols.

Mr. WALDEN. Yes. Dr. Hayes?

Mr. HAYES. I am not completely clear what you mean by stand-alone. Do you mean as——

Mr. WALDEN. Some of them are published as summaries or as pooled studies.

Mr. HAYES. I see. So if a study is done, a study with a particular identifier, yes, we do that regularly.

Mr. WALDEN. So not only just a summary but you also make the full study available.

Mr. HAYES. Yes. In the format which is usually acceptable in the scientific journals, is that what you mean? Yes.

Mr. WALDEN. Okay. Dr. Hayes?

Mr. CAMARDO. I am Dr. Camardo.

Mr. WALDEN. I am sorry.

Mr. CAMARDO. That is all right.

Mr. WALDEN. I keep—these names are all one off, my apologies. Dr. Camardo.

Mr. CAMARDO. That is okay. At Wyeth, we would like to support—we do support the PhRMA proposal and favor having a centralized data base which I believe would be somewhat more easily searchable for a physician, which is one important criteria.

Mr. WALDEN. But PhRMA's is a summary, not full data.

Mr. CAMARDO. Yes, it is. It is actually designed to be a standardized format summary which is pretty extensive and readable review of the designs, the methods, the analysis, the safety and the efficacy. It is a standardized relatively extensive summary. I think if that is found to be inadequate, we don't have an objection to publishing, certainly to making more available, but, as Dr. Woodcock

pointed out, it can get pretty wordy if you let it keep going, and this summary is a pretty standard format that all of us——

Mr. WALDEN. Would that include the Effexor?

Mr. CAMARDO. It would, yes. I mean when the data base is opened, we can put our summaries on that data base.

Mr. WALDEN. And you will do that?

Mr. CAMARDO. Yes. Yes.

Mr. WALDEN. Okay. Dr. Olanoff?

Mr. OLANOFF. Yes. I would support the previous statements and also state we have already committed to doing this by way of a clinical trial registry. And, again, I think what we have committed to at this point is we are posting summaries. The summaries are very extensive. These are under an international agreed upon format, and these can run 5 to 10 pages of fairly detailed information. As Dr. Woodcock explains, some of our study reports run thousands of pages. I am not sure—our concern would be that they would actually obfuscate the ability of the physician to get to the clear information.

Mr. WALDEN. It would seem to me you can publish the study summaries and then make available for people who want to do that——

Mr. OLANOFF. Clearly, if that is where this is going, we have no objection to that.

Mr. WALDEN. Dr. Marcus?

Mr. MARCUS. We are committed to following the PhRMA proposal and would be putting the Serzone pediatric studies as individual summaries on that data base.

Mr. WALDEN. Mr. Osinsky?

Mr. OSINSKY. Yes, we support the PhRMA and we would be putting our information, which is already published, on that web site.

Mr. WALDEN. And Dr. Clary?

Ms. CLARY. Yes. Pfizer also worked very closely with PhRMA, and we are committed to putting all the individual study summaries. We share the concern expressed by Dr. Olanoff that perhaps—we really want to have a dialog. What we encourage is that everyone get together and really talk about what really is the best form of the information that needs to be there. I think we have heard that there is a cry for a lot more information than there has been, and we really do support having that discussion with industry, with government, with AMA, with FDA and really all the stakeholders in this.

Mr. WALDEN. I appreciate the tolerance of the committee, as I have overrun my time. I would now defer to the gentlelady from Colorado.

Ms. DEGETTE. Thank you, Mr. Chairman. I actually thank the chairman because he asked my first question for me. As you can see, I have actually got the PhRMA guidelines in my hand, and I guess I think it is a commendable first step by the pharmaceutical companies and PhRMA to agree to communicate the results. I think the concern a lot of us share, and I am sure you share it too, is how will those be meaningfully made available to patients and their physicians, and that is the line of questioning I would like to ask about.

Dr. Woodcock talked about the number of studies out there. She used the number 11,000, and my concern is let us say we get this web site set up and there are all these clinical studies on it. I want to know how that information is going to be meaningful to people. Now, Dr. Wheadon, I think it is your organization, as a result of the agreement with Mr. Spitzer, the attorney general of New York, you folks are putting now information on the web; is that correct?

Mr. WHEADON. In terms of all of our marketed products since the time of the merger, so that is since 2000, we are establishing a clinical trial registry that will have studies—in this case, summaries of studies posted on that particular web site.

Ms. DEGETTE. And would that include the document I referred to earlier during Dr. Woodcock's testimony? I don't know if you were in the room and heard about that. There was a summary right here. It is a summary about Paxil. We actually got it off your web site, so I assume that is kind of the information you intend to put——

Mr. WHEADON. That is the sort of information. Paxil is not on that web site yet, because Paxil has its own web site that we posted prior to initiation of the clinical trial register for all of our marketed products.

Ms. DEGETTE. All right. Now, is that also going to be posted on this PhRMA web site?

Mr. WHEADON. Well, the process of how individual web sites, our web site in particular, will either populate the PhRMA web site or refer to the PhRMA web site or vice versa hasn't been worked out yet.

Ms. DEGETTE. So it might not be on the PhRMA web site?

Mr. WHEADON. No. We fully expect that whatever the agreement is within the industry and PhRMA about that web site, we will either download our information to PhRMA or have a link——

Ms. DEGETTE. Oh, okay.

Mr. WHEADON. [continuing] that would link to the web site and the information.

Ms. DEGETTE. I guess I had thought there was already an agreement in place. Is that not accurate? I can ask the PhRMA people that when they——

Mr. WHEADON. Right. I think Dr. Loew will be testifying later about that.

Ms. DEGETTE. So you don't know—the details haven't been worked out; is that fair to say?

Mr. WHEADON. That is correct.

Ms. DEGETTE. Does anybody here know when those details will be worked out and all this information will be available through the web site?

Ms. CLARY. Well, I do understand the web site should be operational in October, but I don't—it will be quite a while, I think, before all the results get posted.

Ms. DEGETTE. All right. I will ask the PhRMA folks about that. Now, Dr. Camardo, you testified that some of the things that Wyeth has done on Venlafaxine?

Mr. CAMARDO. Venlafaxine.

Ms. DEGETTE. Venlafaxine is changing the label and a letter to physicians that this drug is really not recommended for a prescription to children for depression, correct?

Mr. CAMARDO. Yes.

Ms. DEGETTE. Now, let me ask the rest of you for whom your product has not been indicated for children, have you changed your label and have you sent a letter to physicians? And I guess we can start with you, Dr. Wheadon.

Mr. WHEADON. Well, we have amended our label as has everyone at the table based upon the FDA class labeling that was required of all antidepressant sponsors a few months ago, which references the issue of suicidality associated with depression, whether or not someone is undergoing antidepressant treatment.

Ms. DEGETTE. Does it talk about the use in pediatric populations?

Mr. WHEADON. Our labeling indicates that Paxil does not have the indication for pediatric depression.

Ms. DEGETTE. Does it talk about the studies that you talk about on your web site that shows it has some—well, that Paxil was not statistically superior to placebo with respect to efficacy? Does it say it hasn't been proven to work?

Mr. WHEADON. The specific references to the individual studies are not presently in the label.

Ms. DEGETTE. But does it say that it has not been proven to work in pediatric populations?

Mr. WHEADON. I think the language is that it has not been shown to be effective or is not an indicator. I can't remember the exact language, but it clearly indicates that the FDA has not given their regulatory purview that the drug has been shown to be effective.

Ms. DEGETTE. Now, did you all send a letter out to physicians saying the same thing?

Mr. WHEADON. A letter has gone to physicians on two occasions, one with the FDA talk paper in 2003 that initially referenced the metaanalysis in terms of the suicidality data, and then with the label change, a letter went to health care professionals——

Ms. DEGETTE. Okay.

Mr. WHEADON. [continuing] indicating that Paxil is not approved for pediatric depression.

Ms. DEGETTE. Okay. Who is next? Dr. Hayes? No, you have been approved, so you are off the hook. Dr. Camardo, you already talked. Dr. Olanoff. This panel is so big it is hard to keep all the drugs separate.

Mr. OLANOFF. In response to your question, Congresswoman DeGette, we have changed our label. We were very quick to adopt the changes.

Ms. DEGETTE. And what does your label now say?

Mr. OLANOFF. The label expressly provides warnings regarding the potential for suicidality in both adult and pediatric patients, especially in the early course of disease, with or without antidepressant treatment. In addition, the labels has always stated that the drug has not been shown to be safe and effective in pediatric patients.

Ms. DEGETTE. Okay. Did you send a letter out to physicians?

Mr. OLANOFF. No, we have not as yet.

Ms. DEGETTE. Do you intend to do that?

Mr. OLANOFF. We can, yes.

Ms. DEGETTE. That would be a good idea. Okay. Next.

Mr. MARCUS. We pretty much made the same change. I think all the companies made the same change, so——

Ms. DEGETTE. And, again, why did you make that change?

Mr. MARCUS. We were asked by the FDA to make the change as part of class labeling.

Ms. DEGETTE. Okay. And what does your label now say?

Mr. MARCUS. I can tell you in a second. I think it is pretty much standardized across most of the labels.

Ms. DEGETTE. Okay. Did you send a letter out to physicians?

Mr. MARCUS. I would have to double check, but I believe we did.

Ms. DEGETTE. Mr. Stupak points out, and for all of you, this label is not actually on the medication itself; it is sent out to physicians, right? Dr. Olanoff, you are nodding. Is that correct?

Mr. OLANOFF. That is correct. As Dr. Woodcock indicated, sometimes when you get your prescription it is attached to the bottle. It depends on how the pharmacist packages it. But, yes, the primary——

Ms. DEGETTE. Well, this is the instructions to the physicians. This isn't on the bottle that is given out to the patients.

Mr. OLANOFF. That is correct.

Ms. DEGETTE. Now, do you have any—Doctor, do you have any objection to this language being put on the bottle that is given to the patients?

Mr. OLANOFF. I think it is something for consideration. We would have to discuss in general how patient labeling would be done in this regard for all potential safety or efficacy——

Ms. DEGETTE. Well, I mean if you have got a drug that is being widely prescribed off-label for a population for which it hasn't been shown to be efficacious, for the most part, and, worse, could cause increased suicide, it would seem that would be a warning that might be appropriate to be put on the label for consumers, right?

Mr. OLANOFF. I think in the context of whether the drug was approved and being used and utilized in that regard, it could be something considered, but the product is not approved for use in that pediatric population.

Ms. DEGETTE. Right, so given the fact it is being so widely prescribed, don't you think that would be a good thing to have on the bottle, especially since you have it on the label that is given to physicians anyway?

Mr. OLANOFF. I think it is important that that information be provided to the physician and the physician so instruct the patient in terms of the potential benefits and risks of the product. I am not sure that the description in the warning in a label, at least in a very limited space on a box or on a bottle, would be sufficient to really instruct the patient as to all considerations to the benefits and risks of the product.

Ms. DEGETTE. Well, I don't know. I mean it hasn't been approved by the FDA for us in these populations, and the reason is because it hasn't been proven to be efficacious. So what would the use be for the pediatric populations? I don't mean to be difficult.

Mr. OLANOFF. No, no. I am afraid I am not entirely understanding your point either.

Ms. DEGETTE. Well, does anybody here think it would be a good idea to put it right on the bottle that was given out to the patients? Dr. Wheadon? You need to turn your mic. Thanks.

Mr. WHEADON. I think we need to refer back to the statement that Dr. Woodcock made earlier today, and that is it is important not to undercut or negate the relationship between the prescriber and the patient, the learned intermediary. As we all know, and, again, as Dr. Woodcock very, I think, appropriately pointed out, the issue of depression in pediatric patients is extraordinarily complex and very important to be treated in the same way that adults are being treated for depression, seriously and by appropriate prescribers. So it is our belief that the information concerning the state of affairs for the studies is most appropriately in the label for physicians that can understand the limitations of the data as opposed to potentially sullying the relationship between the patient and the physician.

Ms. DEGETTE. Well, I hear your point, but part of the whole rationale for like these new PhRMA rules and for the things the FDA is talking about is so that we can have more information out, not just to doctors but also to the families of these children who are really suffering some serious psychological problems so they can know, they can be a participant. These are not adults making independent decisions for themselves. These are parents making—as you well know, they are making decisions for their kids, and part of the whole goal of getting the information out there is to let people know.

I was talking to some of my colleagues up here. Even some Members of Congress who sit on committees like this one were under the misimpression that if the FDA does not approve a drug for a population, then it can't be prescribed. That is what they thought. They were stunned to know that physicians are actually prescribing these medications off-label. They wouldn't even know for their own children. And that is why part of the goal is to get this information out to the general population as well as physicians, and it would seem to me if you are putting it in the labeling, you wouldn't object to putting it on the bottle.

Mr. WHEADON. Well, unfortunately——

Ms. DEGETTE. And let me just add——

Mr. WHEADON. Unfortunately, in the best of all possible worlds, that would be a wonderful thing to do, but let us also keep in mind where we are in terms of the acceptance and the willingness for people to recognize that children are suffering from a mental illness, from a psychiatric illness. So the important context is for the physician to be able to counsel the parent and the patient about the disorder, about how to treat the disorder and about the things that need to be watched for in terms of the evolving nature of the disease and the potential side effects of the drug.

Now, by putting a host of very confounded data on a patient label about negative studies, that could potentially, potentially do more harm than good, and I think that is what we are all struggling with——

Ms. DEGETTE. Right.

Mr. WHEADON. [continuing] is how do we do most of all good and provide the context for the physician and patient to make the right decision for treating the disease.

Ms. DEGETTE. And you know what? I agree with you, which is why we are giving all this information to the physician, but we should give it to the parents too. And let me just make one more point. I support pediatric exclusivity, a concept under which all of your companies have made a lot of profits. I support research for these drugs for juvenile populations. I think it is terrible that we only have one drug approved by the FDA for treatment of depression. I think we should have more drugs, be we need more studies to do that. But in the meantime, parents who for whatever reason whose physicians don't understand or don't care that these drugs are not indicated for pediatric populations, they should also be able to find out. That is my only point. Thank you very much for your comity. I appreciate it, Mr. Chairman.

Mr. BASS [presiding]. The Chair thanks the gentlelady from Colorado and recognizes himself for 10 minutes. I have a series of questions for Dr. Olanoff and before I ask them, though, I just want to ask the witnesses to think about a single question and perhaps respond at the end of my line of questioning of Dr. Olanoff if there is time.

I don't understand why a pharmaceutical manufacturer wouldn't want to put every possible bit of information out on the table, be it positive or negative. Certainly, the potential liability, legal liability, for withholding bad or negative trial studies and so forth exists. I understand that there is an interest in expanding markets and sales and so forth and finding new and giving doctors the ability to provide these medications off-label, but not to be totally forthcoming with every conceivable piece of information is beyond me.

I don't want members to answer now but members of the panel can think about that and give me any reason why the public shouldn't have access to as much data as possible. When I see an ad for a pharmaceutical on television these days, 20 of the 26 seconds is spent describing how it is going to kill you instead of cure you, and I think that is part of the process, but in this instance, in the professional community where really trained professionals, the people who should be doing the prescribing, aren't getting all the information potentially that they need in order to make informed decisions.

Dr. Olanoff, Forest Labs conducted two random controlled trials in pediatric patients. One showed no efficacy and one showed efficacy. Do you agree with that?

Mr. OLANOFF. I agree with it except for the comment that actually one of the studies was conducted by our licensor, Lundbeck, independent of Forest.

Mr. BASS. Fair enough. If you could turn to tab 15 in the—tab 15, and this is a journal article that was published in June 2004 on the one Celexa study that showed efficacy. I want to make sure you have the same tab that I do.

Mr. OLANOFF. Yes, we do.

Mr. BASS. Do you have it?

Mr. OLANOFF. Yes, I do.

Mr. BASS. Good. Why didn't the article also reference the fact that another Celexa study in depressed children showed no efficacy? Do you think that admission could be misleading?

Mr. OLANOFF. First of all, let me state that we disclosed the results of both studies prior to the publication of this journal article. They were disclosed. Both the efficacy and safety results of both studies were disclosed by Forest at the American Academy of Adolescent and Child Psychiatrists in 2003. The focus of this particular article was the U.S. study, and if you read through the article and into the discussion section, you can see that the tone of the article was more in line with what studies are out there that suggest that SRIs might work. It wasn't intended as a full review of all studies that have been done with antidepressants or all positive or negative studies. It really was a focus on one study. And I should state that this study was a single study, it was planned as a single study, it was unequivocally positive, was so recognized by the FDA.

Mr. BASS. What was the last sentence you said, it was what?

Mr. OLANOFF. It was unequivocally positive and it was so recognized by the FDA.

Mr. BASS. One of the studies was.

Mr. OLANOFF. Yes, that is right.

Mr. BASS. But in this article it says in the conclusions that, "In this population of children and adolescent treatment with," whatever it is, "reduced depressive symptoms to a significantly greater extent than placebo treatment and was well tolerated. It doesn't say anything about any negative trial at all; is that correct?

Mr. OLANOFF. That is correct, but it doesn't say anything about any negative data for any of the other antidepressants. The focus of the article was more on what data is out there that suggests that any of these drugs may work.

Mr. BASS. But it is about your drug. It is not all drugs, it is about your drug.

Mr. OLANOFF. That is correct.

Mr. BASS. And it only says the good stuff about your drug; isn't that true?

Mr. OLANOFF. It was the intent of the authors and the focus of the article to concentrate on this particular study. There were other venues in which you can talk about the multitude of studies that are out there. They could have been referenced in this article, there was no prohibition for that, but that wasn't the tone and focus of this article. I think that in large part addresses why publications on their own are an imperfect way of disclosing information and in large part gets us back to why we have gone forward and really got out in front of the industry in regards to clinical trial disclosure.

Mr. BASS. Let us finish this up. If you had to do this again, would you do it any differently today?

Mr. OLANOFF. I think given the interest and the general consensus of the community, we have in fact taken steps internally to try to make sure that at least topline results are mentioned in all our scientific presentations and publications. But that wasn't the general thrust of how these papers were put together in the past.

Mr. BASS. Okay. Why don't we turn to tab 18 for a second, if you could? Got it?

Mr. OLANOFF. Yes, I do.

Mr. BASS. Tab 18 is the slide show presentation by Dr. Jonas at Forest Labs, and its presentation is focused more on safety results than on efficacy, don't you agree?

Mr. OLANOFF. It is, but as you can see from the speaker notes, the speaker specifically referred to the fact that one study was positive and one study was negative. I would like to put this presentation in context. The presentation was primarily focused on safety, and it was really a direct replica of what we presented to the FDA in response to their request to review all suicide-related events according to an algorithm they provided. We thought this was useful information, and we wanted to get it out to the specialists in this care are as soon as possible. And this came out only a few months after we provided the data to the FDA.

Mr. BASS. Well, as you know, this particular slide show has a one-line reference to the fact that the study showed no efficacy, and do you think that that is sufficient disclosure to the medical community and the public as to the efficacy results of Celexa in depressed children?

Mr. OLANOFF. Well, it also has a one-line reference to the fact that the U.S. study did show efficacy, and that, again, was just because of the way this presentation was put together. It was a focus on safety issues, not on efficacy. But we did disclose the topline results.

I think another context which is important is that the problem with no-effect studies or sometimes called negative studies is that they don't rise to a statistical hurdle that demonstrate clear and unequivocal efficacy. We are alone, aside from Prozac, in being able to demonstrate case study that does show efficacy. When you have a no-effect study it is not particularly informative if you can't determine why there was no efficacy in that particular study.

Mr. BASS. Did you make any effort to get the no-efficacy study published in any peer review journal?

Mr. OLANOFF. We have asked our colleagues at Lundbeck to do so.

Mr. BASS. Okay. Moving to Lexapro for a second, are you attempting to get the Lexapro trial, which did not show efficacy and was recently completed and submitted to the FDA, published?

Mr. OLANOFF. Yes, we are, and we have disclosed those results in a very short time at the time we unblinded the study.

Mr. BASS. How come it took over a year until October 2003—you may have answered this question with a previous questioner—even to mention publicly the fact that one of the studies was negative?

Mr. OLANOFF. We didn't put as much emphasis on the European study for a number of reasons; main reason being that we didn't find the study particularly informative. There was a 60 percent placebo response in this study, which makes it very difficult to interpret why we didn't show efficacy. We believe there were some imbalances in the groups at the beginning, which may have explained this, but we couldn't provide useful information on a negative study. We also knew that it is very difficult to publish negative studies. Just as a coincidence, around the same time, we had finished a study in geriatric patients, in very old population of geriatric patients, greater than 75 years old. In many ways, it was a

groundbreaking study in that it employed many other research techniques, such as MRIs and extensive psychometric testing, and we applied to have that published in a journal. We gave the data base over to our investigators, they send in the publication, and we had great difficulty getting that published.

Mr. BASS. Moving on to your settlement with the AG, is there any reason—tell us why you entered into a settlement with the New York attorney general when he hadn't even filed a complaint against you?

Mr. OLANOFF. We entered into an agreement with the attorney general. His office had started an inquiry. We responded to that inquiry. It became apparent to us as we were working out our own internal policies for a clinical trial registry that this was a great interest of the Attorney General's Office. We were able to discuss that with the office. They provided significant input into what they believed should be in a clinical trial registry. We were able to incorporate that registry. We are very pleased with the results. That led to the core of the agreement.

Mr. BASS. In a minute or so can you give us a couple of specifics on the trial registry that you are obligated to create under your consent agreement? What types of trials and drugs are included, the timeframe in which results must be posted, summaries or are they actual studies and any enforcement mechanisms if you don't post something or it is incomplete? Can you address those?

Mr. OLANOFF. Under the agreement with the New York Attorney General's Office, we will be providing not only summaries of our clinical trial results for all our phase three and four studies going forward, but also we will be listing online, and this was something that we had planned to do independently, all our ongoing trials, so that if we are performing a trial in phase three population or a phase four trial, people will know about it, and it will be identified and it can be tracked to its results later on.

In addition, we have gone even further. We have gone back to studies that go back to January 1, 2000 for all our marketed products, even before that for any of our promoted products in terms of any safety information.

Mr. BASS. One last question, Dr. Olanoff. Is there anything wrong with making available the complete trial, clinical trial, publishing the summary but making available the other information or the more complete or the thorough information if it is requested? Is anything wrong with doing that?

Mr. OLANOFF. Well, you are talking about the protocol itself when you say the clinical trial?

Mr. BASS. Yes.

Mr. OLANOFF. I don't see any major issues there. We actually plan to incorporate all the key entry and exit criteria or entry criteria for inclusion——

Mr. BASS. How about the study report?

Mr. OLANOFF. The study report, I think the issue with the study report we have no major objection in terms of the pediatric studies if that is requested. We provided it to the staffers. I think from the standpoint of putting it on a clinical trial web site, I am not sure that that serves a great deal of purpose because we are talking about in many cases thousands of pages of data. Whereas I think

the clinical trial summary I don't think we should confuse this with a short abstract. We are talking about 5 to 10 pages of very detailed information that hopefully can be navigated through and straightforward to the physician in terms of their understanding of the benefits and risks.

Mr. BASS. Very briefly, and if members of the panel don't want to comment, I don't want to force everybody to comment, what about my first question? Why would there be any hesitation on the part of any pharmaceutical company to publish information about the efficacy of a drug given the context of the potential issues that might be involved as a result of failure to publish information that you know might affect the outcome of treatment associated with a drug? Why aren't you willing just to publish everything if you are asked because it gets you off the hook, to some extent, passes the blame over to somebody else? Anybody have any comment about that? It is a general question. Why withhold anything? Does anybody have any objection to publishing—put it the other way so you don't have to say anything, does anybody have any objection to publishing everything associated with clinical trials of pharmaceuticals?

Mr. WHEADON. Well, I think what you have heard from everyone at the table is that certainly is the goal, and that is what we are working toward. We also have to ask the question, and I think Dr. Olanoff refers to that, in terms of to what purpose? So we always want to make sure we are serving the good, the right purpose, because, as you have heard before, if you inundate a single web site with 120,000 studies, the usefulness of that may be diluted in terms of what your intention might be. So you really need to make sure you are aiming for the right purpose and ultimately for the right reason in terms of helping physicians to treat their patients appropriately.

Mr. BASS. Anybody else? Yes.

Ms. CLARY. I would like to really second what Dr. Wheadon has said, which is that we all are committed to providing useful information which will improve prescribing and improve public health. I think, again, the concern—since a clinical study report with all the raw statistical analyses and data tables can really run thousands of pages, the concern is that flooding information out there may indeed cause confusion as opposed to really help inform people. But we are certainly at Pfizer committed to working to get the synopses, the rather lengthy synopses that have been described here that contain all the important primary and secondary efficacy and safety measures available.

Mr. BASS. My time has expired. I would only conclude by saying that agreeing to make information available, not publish it, but agreeing to make it available if it were requested would not flood anybody with anything unless they asked for it. The gentleman from California, Mr. Waxman, is recognized for 10 minutes.

Mr. WAXMAN. Thank you, Mr. Chairman. I agree with your point, and I think that we ought to recognize that we are not flooding people with information. They are going to look at a specific drug, they are going to look at a specific disease and try to find out what studies there are in that area, not everything that has ever been done. In theory, the legislation that gave the manufacturers this

pediatric exclusivity, which is a monopoly for an additional 6 months over their drugs, was supposed to remedy the problem of insufficient information on drug labels about how to prescribe for children. This was supposed to make sure that physicians finally had adequate information to know whether and how to use drugs in children. And in fact your companies gain literally billions of dollars from this extra monopoly, this pediatric exclusivity, for performing studies on Paxil, Zoloft, Effexor, Lovox and similar drugs. Can you tell us how much each of your companies spend on the pediatric trials on antidepressants that you submitted to the FBI—to the FDA? Wrong committee. Anyone have that information? Well, could we, Mr. Chairman, have the record open and I would like each of these witnesses to submit to us how much money they spent on those pediatric trials on antidepressants which they gave to the FDA.

Mr. BASS. Without objection.

Mr. WAXMAN. I am surprised that nobody here has that information. Do any of you know how much additional revenue your company gained as a result of the pediatric exclusivity? None of you seem to have a response to this, but, as I understand it, from Zoloft, it was over a billion dollars; for Paxil, which is Glaxo, there was over $800 million; for Forest, Celexa, it was a half a billion dollars; for Effexor, which is Wyeth, it was a half a billion dollars; and for Remeron, it was over $120 million, as I read it. But in other words, we are talking about huge sums of money. Somebody want to——

Mr. OSINSKY. Congressman?

Mr. WAXMAN. Yes.

Mr. OSINSKY. Remeron did not get pediatric exclusivity. FDA denied it for us.

Mr. WAXMAN. So you did not get pediatric exclusivity.

Mr. OSINSKY. We did not.

Mr. WAXMAN. So you got no benefit for the studies you did.

Mr. OSINSKY. No.

Mr. WAXMAN. Why is that? Why didn't you get exclusivity?

Mr. OSINSKY. There was some discussion with FDA about the scientific—if we completed all the requirements they wanted.

Mr. WAXMAN. I see. Now, the other companies got pediatric exclusivity without completing their studies to get any conclusive result, except perhaps Prozac might be an exception, but your company didn't even do the studies sufficient.

Mr. OSINSKY. Well, we thought we did the studies FDA wanted, but at the end they said that we didn't complete them all the way they wanted them.

Mr. WAXMAN. Well, I would like to have the record open for those of you who did get pediatric exclusivity to tell us how much money that was worth to you to get that additional 6-month monopoly. In exchange for the billions of dollars of profits that the manufacturers here today received for pediatric exclusivity on their antidepressants, did patients or physicians get any useful labeling information about how or how not to use antidepressants in children? Did any of you ask for label changes or get a label change? Yes, sir.

Mr. OLANOFF. We requested a labeling change. We were not able to get one.

Mr. WAXMAN. You were not. What was the label change you requested?

Mr. OLANOFF. We asked that the studies or the positive study that we did in the U.S. be included in the labeling.

Mr. WAXMAN. The positive study.

Mr. OLANOFF. That is correct. FDA considered—through our awareness, the FDA considered putting both the positive and the negative study in the labeling and then rejected that idea.

Mr. WAXMAN. So rather than have the positive and the negative, you—rather than have the positive with the negative, you decided not to have either.

Mr. OLANOFF. No, no. We——

Mr. WAXMAN. They decided.

Mr. OLANOFF. They decided.

Mr. WAXMAN. Okay.

Mr. MARCUS. We also requested a labeling change.

Mr. WAXMAN. And what was your request for?

Mr. MARCUS. Actually, we would indicate that both of our clinical studies were negative.

Mr. WAXMAN. So you wanted a label change that would say your clinical studies were negative?

Mr. MARCUS. Well, we wanted it to reflect the information from the clinical trials, including pharmacokinetic information as well as some safety information.

Mr. WAXMAN. This came up earlier with Dr. Woodcock. What was the reason FDA refused to give you that label change?

Mr. MARCUS. I am not clear but we can always provide you with the FDA correspondence.

Mr. WAXMAN. Anybody else ask for a label change?

Ms. CLARY. Yes.

Mr. WAXMAN. Go ahead.

Ms. CLARY. Pfizer did ask for a label change for Zoloft and indeed much valuable information was included in the label. As I had mentioned earlier in the hearing, we did do a pooled analysis of the studies. We asked for some efficacy labeling. We did not receive that. However, there was a significant amount of safety information that was included in the label, including adverse events, safety information about weight loss in children, and the label also clearly stated that efficacy had not been established in MDD in pediatric patients. So we do believe that even though there was not an efficacy statement, there was valuable information for prescribers that was included in the Zoloft label based on the studies that were performed.

Mr. WAXMAN. Okay. And did someone else want to respond?

Mr. CAMARDO. Yes, Mr. Waxman. Wyeth requested a label change to inform that in two studies efficacy was not demonstrated against placebo and to add some safety information.

Mr. WAXMAN. And what reason did FDA not go along with that label change?

Mr. CAMARDO. Well, we believe that one of the reasons is that the absence of the positive studies was not sufficiently definitive to declare the resulting labeling and——

Mr. WAXMAN. Well, wait. You said the label you wanted was that it was not effective for pediatric use.

Mr. CAMARDO. Yes.

Mr. WAXMAN. What studies did you need for that?

Mr. CAMARDO. What studies did we need——

Mr. WAXMAN. I mean you said that the positive studies—what positive studies, to show that it was not effective?

Mr. CAMARDO. Well, it is generally considered in depression studies that one or two negative studies may not be definitive proof that the product is not effective, and the FDA wanted to take a more balanced view of how to interpret those studies. And so they did not approve that request for us to put that information in the labeling. And I think partly, if I could just remind the committee what Dr. Wheadon said. Part of the reason I think was not to disseminate information that might actually have a negative effect on patients and parents who would seek treatment but rather to have that reviewed and advice taken from outside and then decide what would be best to put in labeling. But we had a specific request to add the results of the two studies and to add some safety information, and I believe that informed experts might disagree about what to do and the FDA had a review and we had a different point of view.

Mr. WAXMAN. Do any of you disagree with the idea that the medical community deserves to have a complete and accurate picture of the data on a drug?

Mr. CAMARDO. No. I would speak for everybody that none of us disagree with that.

Mr. WAXMAN. As I understand it, the companies assembled here today published only what they regarded as the positive studies on their drugs and failed to publish a single negative study. Antidepressants are certainly not an isolated case of this. Medical journals have repeatedly reported that studies published by drug companies are far more likely to favor the company's drug than studies published by independent sources. Do you think that physicians and patients are well served when pharmaceutical companies publish only those results that are favorable to their products and withhold the remaining data from the public? Does anybody think that physicians and the patients are well served when they only get part of the story?

Mr. HAYES. My answer to that, Mr. Waxman, is, no, I don't think they are well served, but I also wanted to point out that not only Lilly but the authors of studies about Prozac did in fact publish the one study in which efficacy was not demonstrated, and this was before there was any legislative pressure to do so.

Mr. WAXMAN. Now, for drugs Zoloft and Paxil, something even more troubling occurred than simple suppression of negative data. Your companies took studies that the FDA had concluded did not show effectiveness and published reports claiming that the studies did show effectiveness. So your companies, in effect, tried to convince doctors to prescribe Zoloft and Paxil to kids on the basis of studies that FDA said had failed. The medical journal reports acknowledged that FDA had found the studies to be negative, and do you think it is appropriate to publish studies that you claim show effectiveness and withhold from doctors the crucial information

that FDA disagreed with you? And if you are not responsible for telling the doctors this, should FDA do so? Anybody from those two companies?

Mr. WHEADON. Congressman Waxman, with all due respect, I must correct one statement that you have made, and that is in the case of GlaxoSmithKline we have not submitted any of the pediatric depression studies in an attempt to get an indication. So the FDA did not give that sort of statement that the studies were not acceptable or what have you. Those studies we have never submitted for a pediatric indication for depression.

However, I also want to point out that the study that was published, study——

Mr. WAXMAN. There was an FDA review that said that the studies were not published, not effective.

Mr. WHEADON. The FDA has looked at those studies in the context of other submissions. For example, we do have an outstanding submission for pediatric obsessive-compulsive disorder. The data from those studies were submitted as a part of the safety data base filed with that submission, but we have never submitted asking the FDA for approval for Paxil for pediatric depression.

Mr. WAXMAN. Did you get pediatric exclusivity for that report, for that research?

Mr. WHEADON. We have pediatric exclusivity for a host of studies that we have done, including depression, obsessive-compulsive disorder, social anxiety disorder.

Mr. WAXMAN. But not effectiveness. You never submitted studies for effectiveness to get——

Mr. WHEADON. We have not submitted the depression studies for an indication for depression.

Mr. WAXMAN. Dr. Clary, you testified that the letter you gave to physicians who ask about the use of Zoloft in kids contains a description of all published studies on Zoloft in kids, but we have heard today that companies routinely publish only positive studies and withhold negative data. So you have stacked the deck. A letter that lists all published studies will tend to promote your drug as safe and effective and will fail to give physicians a fair picture of the data on your drug. Is it your view that it is appropriate to withhold negative data from physicians in these letters you use to communicate to physicians?

Ms. CLARY. No, Mr. Waxman—Congressman Waxman, it is not, and, indeed, I wanted to sort of disagree with the characterization you had made before about Pfizer trying to convince doctors that Zoloft is effective for major depression. In the pooled analysis we performed, there was a small drug placebo difference, which is talked about in the article, put in context, and I also want us to sort of refocus on what Dr. Marcus, I think, alluded to.

Mr. WAXMAN. Do you dispute the statement I just made, that you only published the studies that were positive and did not publish the studies that were negative and therefore——

Ms. CLARY. Yes, I do dispute that.

Mr. WAXMAN. Okay.

Ms. CLARY. I do.

Mr. WAXMAN. And how do you dispute it?

Ms. CLARY. I dispute it in the fact that we have published all the pediatric data on Zoloft with the exception of the one small uncontrolled trial conducted back in 1994 that I characterized in my oral testimony.

Mr. WAXMAN. So it is not true that you pooled two negative studies and published them as positive.

Ms. CLARY. That is true, but that was a scientific decision that was made before we knew what the outcome could be. It could have gone against us. We didn't know. We didn't know whether Zoloft would be effective or not when we did this pooling.

Mr. WALDEN [presiding]. All right. The gentleman's time has expired. Before I turn it over to the gentleman from New Jersey, I understand we have some votes in a few minutes. We would like this panel to stay with us for probably a second round. And in addition, Dr. Marcus, if possible, if you could provide the committee with Bristol-Myers correspondence with the FDA regarding the changed label issue, that would be most helpful to us. And, Dr. Camardo, if you could provide us as well with communication you had with FDA.

Mr. CAMARDO. I think that may already be in documents we sent, but if it is not, we will be happy to.

Mr. WALDEN. Thank you, sir.

And now I recognize the gentleman from New Jersey, Mr. Ferguson.

Mr. FERGUSON. Thank you, Mr. Chairman. I had intended to ask Dr. Marcus some questions about the labeling issue as well, but I think Mr. Waxman has covered much of what I was going to ask about. So I will turn to Dr. Hayes. Thank you all for being here. I know many of the members have been in and out all day, but we have reviewed your testimony and appreciate the fact that you are here and appreciate some of the proactive steps that you are taking on some of these important issues.

Dr. Hayes, I just have some questions specifically about the registry and the various steps that the companies are taking proactively, and Lilly has done a number of things, and I wanted to probe that a little bit. Your company has the only approved antidepressant drug for use in kids and has published all of its studies on Prozac on kids in peer review journals; is that correct?

Mr. HAYES. That is correct.

Mr. FERGUSON. Would you turn on your microphone?

Mr. HAYES. That is correct.

Mr. FERGUSON. That is correct. Is the reason that these studies have been published all over because the journals will easily accept positive studies?

Mr. HAYES. As I stated before, one of them is a study which shows no separation from placebo, although both the placebo and the drug response were quite high, but that is still a failed study if you don't show a difference from placebo. I can't answer that. Of course it is possible that had we submitted negative studies the journals would not have accepted them.

Mr. FERGUSON. So they are not all positive studies.

Mr. HAYES. No, they are not.

Mr. FERGUSON. Yet you have submitted and they have all been published.

Mr. HAYES. Yes. Yes.

Mr. FERGUSON. That is important.

Mr. HAYES. Yes, it is.

Mr. FERGUSON. Particularly in the context of what we are talking about today. Can you discuss—we are going to have several bells here. I will just be patient. Can you discuss some of the specifics surrounding Lilly's clinical trial registry, and, specifically, how does that differ from what PhRMA is suggesting and doing?

Mr. HAYES. I think the major difference, as I understand the PhRMA proposal, probably lies in Lilly's intent to publish a list of all studies at their inception, the date that the study begins with a very brief descriptor. That list won't contain a lot of information, but it will say, "This study that has this title has begun," and we will attach an identifier to that so that people, if they wish, can then track what happened to all those studies. If one ends, if it ends before it was expected to, if it takes longer than it was expected to, you can always go back to that and say what happened to this study? And when we get to the end——

Mr. FERGUSON. This is what you are doing.

Mr. HAYES. This is what we are doing. And when we get to the end of that, we intend then to append the results of the study and the methodology, the primary and secondary outcomes to the identifier so that anyone who has had an interest of what became of that study will be able to see. So each study, I guess, will tell its own story. It will have a beginning, and it will have an end of some sort, whatever that is.

Mr. FERGUSON. How is that different from what PhRMA is doing?

Mr. HAYES. I don't believe that the PhRMA proposal calls for listing the inception of each study.

Mr. FERGUSON. Why are you enhancing your internal standards when it comes to sharing information and creating this, I think you could accurately describe it as a more comprehensive trial registry? What has prompted the change at Lilly? What has encouraged you to go that route?

Mr. HAYES. Well, we have been talking about this for some time and put together a task force that went across various levels and disciplines within the company, perhaps, I don't know, months ago to try to find a way to deal with transparency of our data and our results, and we believe that there is clearly, if you will, a societal crisis in terms of credibility for drug company results. We believe that we do a lot of good research, and we would like for people to have access to that in ways that they are comfortable with, which is why we have chosen to do the registry in the way that we have and also are choosing to have independent third party auditing of that, because I think we need to not only do that to be credible to you and everyone else who cares but also to assure our own compliance with our intent.

Mr. FERGUSON. Does your registry include summaries or is it more comprehensive data?

Mr. HAYES. Well, I have been confused as to what various members of the committee have meant by entire studies. I think we are having a communication gap between the two sides of us here about that. I mean if you talk about a complete study, it is hard

to describe what that means. And I am not trying to obfuscate; people have alluded to it. We recently had a new drug application that was 417,000 hard copy pages for a single indication. That is filled with lots of raw data, and if somebody wants to say, "Gee, I need to have access to all the raw data, each data point," each patient comes for a visit they have perhaps 100 things, their blood pressure is measured, they are asked various questions. All of those things are in those summary reports.

That is not what goes into a scientific article that is peer reviewed, which is usually considered enough information, which is what I meant when I answered Mr. Bass' question or perhaps it was Mr. Walden's question about do you mean the format in which a scientific article appears in a journal in which there should be an adequate explanation of the methods, including the statistical analysis plan, enough understanding of the results as well as the conclusions that someone reading the article can tell what you planned to do and how it came out. Now, that sort of summary in either the usual journal template fashion or some other fashion is I think probably what all of us intend, because I think anything much more than that in terms of posting it on our web site will not be of use either to doctors and certainly not to families.

Mr. FERGUSON. Is there any reason other than sheer volume of data not to share complete data? Is there any internal reason at the company that—is there some sort of competitive disadvantage?

Mr. HAYES. Well, I think people are hesitant to put raw data pools in the public because that allows not only the kind of transparency we would like to have but all sorts of shenanigans, if you will, that you wouldn't like to have.

Mr. FERGUSON. Obviously, you would protect people's privacy and what not but——

Mr. HAYES. Sure.

Mr. FERGUSON. [continuing] other than that.

Mr. HAYES. No. Other than that, I don't see good reasons for that. It is the volume, and it is the possibility that raw data could be used in ways which would be unintended and not useful to anyone.

Mr. FERGUSON. Does Lilly plan to participate in PhRMA's registry——

Mr. HAYES. Yes.

Mr. FERGUSON. [continuing] as well as your own?

Mr. HAYES. Yes.

Mr. FERGUSON. Why?

Mr. HAYES. As far as I know. Lilly people actually chaired the committee that came up with the principles that Congresswoman DeGette had a few minutes ago, as well as the questions and answers that were there. We have provided leadership, I think, within PhRMA to try and deal with this issue ever since about 2000. We will continue to cooperate with all of our colleagues in trying to deal with the issue, and also we will proceed with our web site that I think inculcates our own principles because we think it is important.

Mr. FERGUSON. I am just about out of time and I know we have a vote on, but I appreciate—I want to say again I appreciate the

witnesses for being here to testify and to talk about some of these issues today.

I will refer back to my opening statement when I said sharing of this information is crucial. Giving information to the decision-makers, to the parents and by extension the kids of potential red flags, of potential problems that could be coming down the pike for them is absolutely crucial, and I would urge you to continue to take steps, as you are doing at Lilly and others in the industry and with PhRMA, to continue to make as much information as possible available to those who can use it and who can benefit from it and frankly whose lives can be saved by it. And as we have said, a lot of people have said here today, if that type of cooperation isn't forthcoming and if we don't see that kind of benefit, we are going to end up taking legislative or regulatory action, which should be a last result, but if it means the lives of our kids, that is something that is clearly going to happen. So I appreciate your cooperation and hope that cooperation will continue in an even more enthusiastic way. Thank you, Mr. Chairman.

Mr. WALDEN. I want to thank the gentleman from New Jersey. We are going to recess now. We would like this panel to remain with us, but you will get about a 50-minute break it looks like. We have 5 votes and so probably 50 minutes to an hour. So a good time to catch your breath, and the committee will return as soon as the last vote is over.

[Brief recess.]

Mr. WALDEN. We're going to reconvene the committee. So if our panelists would return to their chairs. And I'll call the Subcommittee on Oversight and Investigations back to order. And I'll now recognize the ranking member, the gentleman from Florida for 10 minutes.

Mr. DEUTSCH. Thank you, Mr. Chairman. Thank you, panelists for your indulgence.

Dr. Wheadon, you have expressed considerable concern that patients and their physicians not be confused by whatever information is disclosed. This includes, as I understand it, concern that neither patients nor physicians be misled or overwhelmed by data. I find that to be a genuine concern, but I'm a bit confused about Glaxo's position on this matter.

If you turn to page 9 of Tab 11, the complaint that New York State filed against GlaxoSmithKline, item 38, in part states and I'm quoting, "in a cover memo that transmitted the published articles concerning Study 329 to all sales representatives selling Paxil, Zachary Hawkins, CSX, Paxil Product Management stated Paxil demonstrates remarkable efficacy and safety in the treatment of adolescent depression."

You notice in bold the word "remarkable." First, would you please provide a copy of this entire memo to the committee to be included in the record. Second, would you have this committee believe that Paxil demonstrates remarkable safety and efficacy in the treatment of adolescent depression?

Mr. WHEADON. Well, first of all, Congressman, we'd be happy to give you the entirety of that memo. Second of all, I think it's important that the committee be fully aware that this was an internal memo provided from the author of the memo to sales representa-

tives with a clear instruction of "for your information only" and not to be used for any sort of promotional purpose.

To go specifically to your question concerning the adjective, if you will of in terms of "remarkable", while I did not author this memo and I certainly would not have chosen to use the words that the author of the memo used, as you cite, I think it is important as we've discussed earlier in this particular panel, that we keep in mind that pediatric depression and the study of how one approaches in terms of treatment, pediatric depression, has been extraordinarily difficult.

The literature is just littered with all sorts of studies where we've not been able to show that medications that we know, based on personal experience of clinicians to be effective, we've not been able to show it in a controlled way in terms of separation from placebo.

So in the case of this particular study, Study 329, there were, while the primary efficacy parameters did not show the expected separation from placebo, there were findings within the study, most notable, for example, the Hamilton rating scale score, Hamilton is a rating scale for depression, looks at the many symptoms of depression. And one parameter was looking at the rating scale score of less than or equal to 8 which is usually and pretty traditionally in these types of studies viewed as response. And in that particular assessment, the response rate for Paxil was 63 percent versus 46 percent for placebo. That was to the minds of the individuals who were carrying out the study quite an important and interesting finding because it was one of the first times, particularly with Paxil, we've been able to see even a beginning of a hint of efficacy.

So while I would not have used the terms used by the author of this memo, I would encourage that we do take a step back and look at the fact that we are trying to do the best. Everyone at this table, everyone involved in treating depression in children, are trying to do the best we can to discern exactly how these agents can be effective in a safe and appropriate way.

Mr. DEUTSCH. Let me just follow up on two specific things you mentioned. I mean would your—I mean based on your the evidence you just cited, would you say that Paxil is effective in terms of treating adolescent depression? I mean is it an appropriate prescription?

Mr. WHEADON. Well, first of all, I have to be, Congressman, certainly very quick to say that Paxil is not approved by the FDA as a treatment for adolescent or pediatric depression. I then have to add that based on personal experience, not my own personal, but personal experience of individuals that practice child and adolescent psychiatry, there are those situations that have been reported where the drug has been effective in treating children. However, due to the very difficult circumstances of studying this particular disease, we, in the case of Paxil have not been able to discern a significant effect versus placebo, based on the protocols that have been carried out. Fortunately, other companies and other agents have been able to do so and we're very pleased that at least that advance has occurred.

Mr. DEUTSCH. Again, I understand what you're saying and your words are obviously well chosen. I mean wouldn't by inference what you just said, placebo would have the same effect?

Mr. WHEADON. Quite honestly, Congressman, I think everyone at this table who has ever treated someone with depression would not begin to even think of using placebo as a treatment for depression because while you may see a 40 to 50 to 60 percent placebo response rate, we know that that is short-lived. We know that due to the inherent fluctuation of the symptoms of depression within an individual, that individual may on 1 day actually score relatively low on the Hamilton rating scale or the MADRAS, which is another rating scale and then the next day, the full force of the symptoms are back.

So simply looking at placebo response is really not looking at the totality of the disease you're trying to study. You really do need to look at the whole host of parameters including the rating scales, the clinical global impression, activities of daily living. It's a very difficult study or area of study.

Mr. DEUTSCH. You know, I mean just to follow up also, as well, in terms of what you're saying, I just find it and I hate to use this word "remarkable", but remarkable to say that in a memo about remarkable efficacy for your eyes only to sales reps and having some experience with pharmaceutical sales reps, that they're not going to mention that. I just think it is not credible that the sales reps are not going to use that information in terms of making sales.

Mr. WHEADON. I certainly can tell you that that is not our corporate practice, that is not our standard operating procedure. Instructions are clearly, clearly delineated for the sales reps, that they are not to promote off-label which obviously this study would be off-label promotion.

Mr. DEUTSCH. If you turn to Tab 13 which also is a Paxil adolescent depression issue, the positive piece on the phase three clinical studies, first please note that this is a 1998 memo that's marked confidential for internal use only. If you turn to the last page of that document under proposals, the following statements are made and I'm quoting again: "based on the current data from studies 377 and 329 and following consultation with SB country regulatory and marketing groups, no regulatory submissions will be made to obtain either efficacy or safety statements related to adolescent depression at this time. Regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use. And finally, it would be commercially unacceptable to include a statement that efficacy had not been demonstrated as this would undermine the profile of Paroxetine."

Again, there seems to be a considerable discrepancy with the impression your company would like to lead with the committee regarding the nonpromotion of Paxil for off-label use in treating adolescent depression.

What exactly was Glaxo's position before Mr. Spitzer filed his suit and what does it now discourage or does it discourage off-label use of Paxil in adolescents at this point in time?

Mr. WHEADON. First of all, let me be very clear that this particular memo that you're referring to is authored by an individual based in the United Kingdom, not in the U.S. Second of all, while the reference to the negative studies as you cited in the memo, are as you've cited, the negative study 377 has indeed been published in abstract form by one of the investigators involved in that study, so that information was disseminated.

In terms of promoting off-label, we do not promote off-label. We do not allow our sales reps to promote off-label. We, however, cannot control the legal right of prescribing clinicians to prescribe a medication as they deem fit. We do not encourage it, we do not promote it, but also cannot control the legal right of that prescriber to prescribe a medication off-label.

Mr. DEUTSCH. Just as one last follow-up question, do you ever audit your sales force to see about off-label prescriptions, just to get a feel for how much is, in fact, done off-label? I know that sometimes companies send audit personnel to physicians' offices to make sure sales forces are staying on message.

Have you done that in the face of Paxil?

Mr. WHEADON. We do that in the case of all of our medications. We have an internal auditing program that, as you say, will go out, ask physicians to relate back what they've heard from their sales reps and we are very keen to ensure that there is not—as best we can, off-label promotion because that is not per our procedures and obviously is not acceptable from the regulations standpoint.

Mr. DEUTSCH. And in terms of Paxil, could you relate to us what your auditing has found out?

Mr. WHEADON. I unfortunately don't have that information in front of me.

Mr. DEUTSCH. Can you provide that to the committee?

Mr. WHEADON. Okay.

Mr. DEUTSCH. Thank you.

Mr. WHEADON. Thank you.

Mr. WALDEN. I thank the gentleman from Florida. The chair now recognizes the gentleman from Michigan, Mr. Stupak.

Mr. STUPAK. Thank you, Mr. Chairman. Dr. Clary, you mentioned adverse events. How many adverse events have been with your drug there, which one you have. You have Zoloft. How many adverse events have been reported to FDA with your drug?

Ms. CLARY. Congressman, all of the adverse events from the clinical trials, both in pediatric and adult, have been reported to the FDA. That's a routine matter.

Mr. STUPAK. I'm not asking about the clinical, I'm asking about the people who have been using your drug for some time here, Zoloft, you're the No. 1 seller. How many adverse events have been reported to the FDA?

Ms. CLARY. I think you may be asking me about spontaneous——

Mr. STUPAK. No, you got to do—yes, spontaneous adverse events. You're required as a manufacturer when it comes to your attention to report it to the FDA.

Ms. CLARY. Yes.

Mr. STUPAK. So how many do you have?

Ms. CLARY. I want to make sure that I'm answering the question correctly because——

Mr. STUPAK. I want to make sure you're not stalling.

Ms. CLARY. I'm really not. I'm wanting to clarify because there's adverse events in clinical trials and there's spontaneously reported adverse events which come from all different places, physicians, patients and they report these to Pfizer, to the pharmaceutical company or to the FDA MedWatch and we report them routinely to FDA. If they're serious, we report them to——

Mr. STUPAK. I'm asking for a number.

Ms. CLARY. I'm sorry, Congressman, I don't have the exact number.

Mr. STUPAK. Okay.

Ms. CLARY. We can get that to you, if you'd like.

Mr. STUPAK. Sure, I'd really like to know that. If Zoloft, in your testimony, has not been effective, no efficacy, and if there's some question about the safety, how is it you become the No. 1 seller of this drug?

Ms. CLARY. I'm not sure what you mean by the question about the safety. In adults, Zoloft is approved for six different indications, major depression——

Mr. STUPAK. I'm looking here for Zoloft, Pfizer, top sales was $258 billion.

Ms. CLARY. Yes.

Mr. STUPAK. And from the pediatric exclusivity, almost got another $1 billion. So if it's not effective, and actually may increase the danger of some people, especially pediatric patients, how is it you become the top seller in this area, I guess?

Ms. CLARY. Zoloft is approved in adults for six different indications and the vast majority of its use is in adults. A small portion of that is in children and adolescents and it's recognized by physicians. It's been recognized by the FDA as being efficacious, safe and well tolerated in multiple disorders in adults.

Mr. STUPAK. Okay, if you've got almost $1 billion, what do you sell Zoloft for say 30 tablets?

Ms. CLARY. I don't know the exact number, it's about $60 a month, that's the wholesale price, approximately.

Mr. STUPAK. Okay.

Ms. CLARY. I can get you that exact number, if you'd like it.

Mr. STUPAK. Sure, and I'd really like to know how much are sold to people under 18. Okay?

Ms. CLARY. Sure, we'd be happy to provide that.

Mr. STUPAK. You said that in response to an earlier question that all the stakeholders should come together. Would the public have a chance to come to your meetings on how we're going to do this reporting?

Ms. CLARY. We would welcome that. We would welcome organizations that deal with people who have depression and other mental health problems. They're certainly——

Mr. STUPAK. How about public citizen? Would you invite public citizen to the table?

Ms. CLARY. I certainly think they should have a voice and that they're a voice in this debate.

Mr. STUPAK. You know, there's this—Dr. Wheadon, when Mr. Deutsch, Congressman Deutsch was asking a question there on this remarkable efficacy and safety in the treatment of adolescent

depression, that was in an article on your study 329 to all sales representatives selling Paxil, by Zachary Hawkins the Paxil Products Management, right?

Mr. WHEADON. That was in a memo from the Products Management Sales Reps——

Mr. STUPAK. Is he head of all your Paxil Product Management, United States and Great Britain?

Mr. WHEADON. That is not correct, no.

Mr. STUPAK. Where is he?

Mr. WHEADON. I quite honestly don't know where Mr. Hawkins is now.

Mr. STUPAK. I thought you said that was a Great Britain study or something.

Mr. WHEADON. That was in reference to the second question from Congressman Deutsch which was, I think, tab 11, if I recall correctly.

Mr. STUPAK. If your company doesn't condone this, why would you even put this in writing to your sales representatives, that remarkable efficacy, when all the studies show it's not?

Mr. WHEADON. Well, again, Congressman, I go back to the statement I made earlier in response to Congressman Deutsch, and that is I would not have used those particular words. But also, as I mentioned earlier, we need to keep in mind the context in which those results were becoming known. The context was——

Mr. STUPAK. But your study was, it's right here. It's negative results, except for the positive on most secondary endpoints. Why would you tell a sales team you have a remarkable efficacy, when you don't have a study that shows any efficacy for depression?

Mr. WHEADON. Again, I would not use the word remarkable, however, the context is or was historically it was extraordinarily difficult to show effectiveness of these agents in pediatric patients. A number of the parameters, albeit not a priori defined primary parameters, but a number of the parameters did show some effect for drug——

Mr. STUPAK. Not for depression.

Mr. WHEADON. For depression.

Mr. STUPAK. No, no, it's the secondary endpoints.

Mr. WHEADON. Congressman, if I could finish?

Mr. STUPAK. Sure.

Mr. WHEADON. As I mentioned, one of the parameters of response is looking at the score on the Hamilton rating scale for depression. It's called the HamD. It's the number of items——

Mr. STUPAK. I'm familiar with it.

Mr. WHEADON. [continuing] that look at the degree of the symptoms. One of the analyses looked at what we call a responder analyses. That's HamD, total score less than or equal to 8. And in that analysis, 63 percent of patients on Paxil met that definition of response, i.e., they had——

Mr. STUPAK. But it's not enough to elevate to be an effective drug for depression by the FDA standards.

Mr. WHEADON. Paxil showed the 63 response. Placebo showed a 44 percent response. That was a significant finding. However——

Mr. STUPAK. My question is why would you use words like remarkable to your sales representatives, if you say they're not using

it to help sell the drug. I think you just had about $2.13 billion in sales in 2002 of this drug?

Mr. WHEADON. Again, I would not have used the term remarkable.

Mr. STUPAK. Right.

Mr. WHEADON. However, we do think it is important that sales reps are familiar with studies that are being reported in the literature.

Mr. STUPAK. And I think they should get accurate information to sales reps.

Mr. WHEADON. Absolutely, they should get accurate information and the accurate information would be in the actual article, not in the memo and the memo, unfortunately——

Mr. STUPAK. Do you give your sales reps the full study?

Mr. WHEADON. If it's a published article, yes.

Mr. STUPAK. If it's not published, they don't get them.

Doctor, I'm going to say your name wrong, I'm sorry, and I apologize. Camardo?

Mr. CAMARDO. That's right.

Mr. STUPAK. You said in earlier testimony high risk patients. Could you describe what the high risk patients are in this group of people we're trying to treat here?

Mr. CAMARDO. Actually, I would have to defer to practicing psychiatrists for more, really a more accurate definition of that, but in fact, we would leave it to the psychiatrists who identify children who might be—who might have demonstrated suicidal behavior in the past. That would be a high risk child. A child who might have had a reaction to a drug in the past, that might be a high risk child. Certainly, a child or an adult who had had a suicide attempt in the past. It really has to be up to the practicing physician to help identify some of the higher risk for possible suicide attempt when depression, anti-depression therapy is initiated.

In fact, the language in our label is pretty standard for psychiatric guidelines and for most of the antidepressants. It's been observed that occasionally initiating therapy can bring on a period where suicide might, suicide risk might increase.

Mr. STUPAK. A lot I've heard from this panel is a concern if we post these studies, we'd be flooding the marketplace with too much information. How about unless you can establish the effectiveness and safety and if you can't establish that, then how about if your company doesn't sell these drugs to anyone under the age of 18? Would you agree that's a good idea?

Mr. CAMARDO. Let me answer—I think that we have in the United States taken the position in terms of regulation that unless there is a clear consensus for contraindication or a clear consensus of an unacceptable side effect we have given doctors the latitude to make practice related decisions.

Mr. STUPAK. Right, but you control the drug and you could very well, as you're all telling me these profits are from people, adults, so why don't you just sell your drug, until you can prove effectiveness and safety, you don't sell it to anyone under age 18. You can put that right on the packaging, inform the doctors, why don't you go that way?

Mr. CAMARDO. Congressman Stupak, we actually do inform the doctors that it hasn't been approved——

Mr. STUPAK. No, no. How about if you accept the moral, legal and ethical responsibility, not to sell it if they're under 18 unless you can prove safety and effectiveness? Hell, you might as well give them placebo, right? That's just as effective as some of the studies I've seen up here.

Mr. CAMARDO. That's not——

Mr. STUPAK. And it isn't really—these kids really are depressed and you're giving them a drug that's shown to be ineffective and they actually increase their suicide behavior. Don't you share the responsibility here to say, I'm giving this pill that's marketed to help you out, but we know it really doesn't, but you'll get better if you take this.

Mr. CAMARDO. Our literature, our promotion, our practices, our training, which is all subject to very rigorous internal review, has never promoted or recommended effects are for children, but we have——

Mr. STUPAK. Well, how do these doctors know about your drugs if they're not promoted to that? Don't your sales reps promote them to the doctors?

Mr. CAMARDO. They promote under very rigorous guidelines for adults.

Mr. STUPAK. Right, with remarkable efficiency?

Mr. CAMARDO. Well, they promote with—under rigorous guidelines, very highly regulated to adults and in fact, we take very seriously precaution to make sure that they're aware that the product is not approved in children. But we have, in the United States, decided that the absence of data in a certain area would not restrict a practicing expert physician from using the product. I think that's a decision that was made somehow, but that's what we've accepted.

Mr. WALDEN. The gentleman's time has expired. I recognize the gentleman from Maine.

Mr. ALLEN. Thank you, Mr. Chairman. Dr. Marcus, FDA told Bristol-Myers that Serzone was not indicated for use in pediatric patients. But a Bristol-Myers sponsored study which is at tab 26 concludes that and I quote: "in this study, Serzone was shown to be safe and effective in the acute treatment of adolescents with major depressive disorder." So the question is if your studies conclude that this drug is safe and effective for adolescents with MDD, why would the FDA not approve your drug for pediatric patients?

And the second question is did the FDA disagree with the way your study was conducted or with your results?

Mr. MARCUS. Can I first ask you which tab was that?

Mr. ALLEN. Twenty-six.

Mr. MARCUS. Twenty-six.

Mr. ALLEN. And I'll repeat the question if it's helpful.

Mr. MARCUS. Twenty-six is a press release from Forest Labs. I'm sorry.

Mr. ALLEN. Just 1 minute. Let me put that question aside. We'll try to find the right citation and let me go back to some other questions. I'll come back to that one.

This is really for the whole panel and I guess Dr. Wheadon, we'll start with you. And just work down the row, if we can.

The PhRMA guidelines on publishing clinical trial data states there should be a timely publication of meaningful trial results. So my question to all of you is how would each of your companies interpret compliance with these guidelines? What would be considered timely and what would be considered meaningful? That's partly a question about if you accept the PhRMA proposal, is that really a proposal that each individual company decides what's timely and what's meaningful, in addition to being a voluntary proposal?

Let me ask the second part of the question too, and then you can deal with it one by one. Do you believe the voluntary nature of the proposal from PhRMA serves the public interest of having better access to clinical trial results both positive and negative? And the question I'm really interested in there is if you have a voluntary proposals, if individual companies, basically can choose whether or not to provide the clinical trial data, don't you have an unlevel playing field that essentially gives an advantage to those companies which don't perhaps provide the data? Wouldn't it be better to have a system, a regulatory system that treats all of the companies the same way?

So there are the two questions. If you could talk about timely publication, meaningful trial results, how you interpret those and also react to the voluntary nature of the proposal as opposed to a mandatory proposal.

Thank you.

Mr. WHEADON. Going down in that order, Congressman, timely, obviously, can have a variety of definitions applied to it, particularly in the context of publishing in peer-reviewed journals or even in presenting at medical conferences. You may want to publish within a month after the completion of the study. But due to the process that I think is appropriate, peer review, editors often sending manuscripts back for changes for further analyses, for answering questions, what you and I may view as timely may actually take the better part of a year, 2 years, actually actualize the appearance of the manuscript in a peer-reviewed journal, the acceptance of the poster or presentation for medical conference.

So within as much control as we can garner, I think it is appropriate for us to publish or make public in a timely fashion. Hence, the evolution of the websites. The websites obviously are things that we control 100 percent. So we have ultimate ability to post those data on the website within virtual complete control of our individual companies.

Mr. ALLEN. But is it your position that what is timely and what is meaningful should be decided by your company?

Mr. WHEADON. Well, let me get to meaningful. Meaningful, obviously, can also be subject to a variety of definitions, depending on the disease entity you're discussing. So for example, and I think this is a point we've not had a chance to really put on the table, a negative study in depression, quite honestly, until the present discussion has not been something that the scientific arena would necessarily view as inordinate. In adults, it is not unusual for there to be upwards of 30 to 40 percent placebo response rate and upwards of two or three studies that one needs to do for each, for one positive study because of the disease that we're studying.

In pediatrics, it's even worse, if you will. The placebo response rate—the hurdle of trying to establish efficacy in terms of how we do these studies. So a negative study would not necessarily have raised an eyebrow because of that fact. A positive study, as you've heard today, was in the timeframe in which these studies were done, quite—I don't want to use the word remarkable—quite interesting, because of that extant literature, that extant experience in terms of studying depression.

So meaningful can change. Now obviously, meaningful——

Mr. ALLEN. I'm going to have to—in order to give anyone else on the panel a chance to speak.

Mr. WHEADON. And then last voluntary. I think voluntary can work because we as a regulated industry, obviously, police ourselves and if GSK decides to voluntarily post a host of studies in a way that Forest may decide not to do and they're trying to take advance of that system, we obviously will self-police and say well, hold on, this isn't a level playing field.

Mr. ALLEN. I'd like to ask anyone on the panel who has a different opinion when Dr. Wheadon? A nuanced difference or——

Mr. HAYES. Nuanced difference perhaps. At Lilly, we've defined meaningful as all of our phase one, two, three and four results and we've defined timely as phase one, two and three results at the time of approval of the indication for which they were done; and phase four, when we have a marketed product as soon as possible, but no longer than 1 year. We picked 1 year because it may take 6 to 8 months to get all of the analyses done and be able to put something in an understandable format and rather than pick 6 or 8 months and perhaps make a promise that we might not keep once in a while, we chose 1 year. But we addressed those things, meaningful and timely in that way and tried to provide concrete answers for them.

As for voluntary, I think you have a point about the levelness of the playing field, but I think we're going to do this anyway, regardless of whether someone else chooses to play on a more favorable field.

Mr. ALLEN. When you say "we", you mean your company?

Mr. HAYES. I mean Lilly, yes.

Mr. ALLEN. You mean your company?

Mr. HAYES. Yes.

Mr. ALLEN. But you don't speak for all of the other companies?

Mr. HAYES. No, I don't.

Mr. ALLEN. Dr. Hayes, could you—I'm sorry, Dr. Camardo or whoever it was had their hand up there?

Mr. OLANOFF. If I could just make a comment, I think I agree in large part with what's been said. I would just also include, I think meaningful from a standpoint of content, I think a publication on a clinical trial registry should be to the same level of what would appear in a peer review publication in terms of the content and the explanatory value, perhaps less interpretation, if that wasn't necessary, but at least get the results out there so someone could review them. I think that's critical.

In our case, we have a binding agreement with the Attorney General's Office, so we will be putting out studies for some years ahead and it would be nice to have a level playing field.

Mr. ALLEN. Other comments?

Ms. CLARY. I just wanted to reiterate that Pfizer has worked with PhRMA on the proposal and it does include timely the definition is at most 1 year after the completion of the study for marketed products and that we are committed to getting those meaningful results out of all phase three and four studies of marketed products.

Mr. ALLEN. Are there any definitions of the word "meaningful" in the PhRMA proposal?

Ms. CLARY. I'm not sure in the PhRMA proposal. There is an issue which you may have seen. And again, I think it's one of these issues that perhaps we can all discuss together which has to do with exploratory or hypothesis-generating studies. There's some very early studies that are done early in drug development before there's any notion of efficacy which really are just to generate a hypothesis about what the drug might be used for. And there is some earnest discussion, I think, about whether those trials are really useful to patients and to physicians.

Mr. ALLEN. Any other comments? Mr. Chairman, if I might just ask for the record, if Dr. Marcus, if I could ask him to respond later to the question that I have, I have the correct tab number, it's tab 28. But if you could respond in writing afterwards to the question I asked you and we'll give it to you in writing, so it will be clear.

My time has expired which is why I'm suggesting that procedure.

Mr. WALDEN. We're going to do a second round here, very quick.

Mr. ALLEN. Thank you. I'll come back with it.

Mr. WALDEN. Thank you. I guess I want to make sure that people are clear on one thing when they leave here and correct me if I'm wrong, Dr. Wheadon to Dr. Clary, Glaxo did three studies on pediatric depression, MMD, MDD, sorry. And FDA said it showed no effectiveness, correct? Did your three studies show effectiveness as defined by the FDA for treatment of MDD in children and adolescents?

Mr. WHEADON. To be clear, Congressman, when you say FDA said it showed no effectiveness, again, we have not submitted for the indication of pediatric depression. If you are referring to——

Mr. WALDEN. Do your studies, do you believe your studies showed that your drug is effective or would pass the FDA effectiveness test for treating pediatric depression?

Mr. WHEADON. Certainly, obviously, since we have chosen not to submit for pediatric depression, we recognize that the studies do not meet the requirements as outlined by Dr. Woodcock earlier today in terms of showing the effectiveness for approval.

Mr. WALDEN. But in short, your studies were negative according to the FDA, right?

Mr. WHEADON. Again, when you say according to the FDA, I'm trying to understand what you're referencing in terms of the FDA.

Mr. WALDEN. Why didn't you submit your studies to the FDA to prove efficacy for your drug for treatment of pediatric depression?

Mr. WHEADON. We internally knew that we did not meet the standard that the FDA would set for approval.

Mr. WALDEN. Thank you. That's what I was trying to get at. Is you know your study showed that your drug would not pass an

FDA test to show effectiveness for treatment of pediatric depression?

Mr. WHEADON. For an approval for that indication, that is correct.

Mr. WALDEN. Right, so it should not be marketed for that use.

Mr. WHEADON. It is not marketed for that use.

Mr. WALDEN. And would you encourage doctors not to prescribe it for that use?

Mr. WHEADON. We obviously do not encourage doctors to prescribe it for that use.

Mr. WALDEN. Would you encourage doctors not to prescribe it for that use which is different than not encouraging doctors to prescribe it? Because I'm learning a lot about language up here and how we prescribe off-label and how in journals or articles or posters when studies show these various drugs are not effective, according to the FDA, but yet you'll see words about effectiveness. And then I'm told that effectiveness is different than efficacy as defined by the FDA and that's a word choice I'm just getting confused about. So that's why I'm asking.

Mr. WHEADON. We certainly have indicated that the drug has not been shown to be effective.

Mr. WALDEN. Okay. So you would not encourage doctors—well, you can't encourage doctors to prescribe, that would be illegal?

Mr. WHEADON. That's correct.

Mr. WALDEN. All right, and on Pfizer, your two studies, if they were to be published, stand alone, those two studies individually would show that Zoloft is not effective as the FDA would say effective is, right, in treatment of——

Ms. CLARY. Each individual study, taken by itself——

Mr. WALDEN. Taken by itself——

Ms. CLARY. Yes. But as you know, Pfizer made a determination that the most scientifically sound thing to do was to pull.

Mr. WALDEN. To pull.

Ms. CLARY. I wanted to clarify a point because you were asking Dr. Wheadon about what the intention was when Pfizer filed and indeed, as I've said, we did file all these studies with the FDA. We, as you know, in 1997, received an approval for use in children, in adolescents with OCD. And this approval was based on one placebo-controlled trial, not two, but one.

When we received the written request, it was clear in the written request that we were to perform two studies. What was not clear was that two studies needed to be positive in order to receive approval. It just wasn't clear, which is why we sought approval——

Mr. WALDEN. Approval for pediatric depression?

Ms. CLARY. For use in pediatric depression—approval for use in pediatric depression.

Mr. WALDEN. So the FDA letter to you didn't make it clear. You needed to replicate the study that showed that it was effective.

Ms. CLARY. Right, for efficacy approval. I don't want to sound like we're parsing words, but—based on our understanding of the OCD, we really didn't know whether we would need two positive studies, one positive study.

Mr. WALDEN. Isn't that fairly standard though in scientific research to do a study and then you prove the results of that study?

Ms. CLARY. I think the nuance here is that because the drug was already approved for depression in adults and the tests, these two studies were in a sub-population which were children and adolescents, just as was the same with OCD, it wasn't clear.

Mr. WALDEN. Can I refer you to tab 60 in the book? You'll see it's a sample written request from FDA, this is their sample letter which I assume they sent to you and it says on the second page, "study design, pediatric efficacy and safety studies. For the controlled efficacy studies—"

Ms. CLARY. Tab 60?

Mr. WALDEN. Tab 60. It starts out "pediatric program summary statistics".

Ms. CLARY. Yes, I have it.

Mr. WALDEN. You have it, good. Go to the second page and actually under the pediatric depression, about three quarters of the way down you'll see the word "consequently"?

It says "consequently, we believe that a pediatric depression claim for any anti-depressant already approved in adult depression would need to be supported by two independent, adequate and well-controlled clinical trials in pediatric depression."

So did they send you a letter different from this one then?

Ms. CLARY. I would have to check the exact letter, but I believe they did. My experience with other drugs is that the actual content of these letters has been changing and they've been becoming more specific.

Mr. WALDEN. Can you supply us with that letter?

Ms. CLARY. Sure, I'd be happy to.

Mr. WALDEN. This is what we've been given from the FDA as their sample which—you can understand why we——

Ms. CLARY. The letters have been changing and becoming more specific over time.

Mr. WALDEN. Dr. Camardo, turn to tab 42, if you would. This is a document you prepared in response to inquiries, to any inquiries from anyone in the public about effects or bids or only doctor inquiries. Is this one tab 42, sir?

Mr. CAMARDO. This is attachment D, use of vaccine in children or adolescents? Is that 42?

Mr. WALDEN. I'll double check. I'm sorry, it should be Tab 41.

Mr. CAMARDO. Right. This is the so-called "Dear Doctor" letter.

Mr. WALDEN. Okay, so this would go to doctors or to doctors or anyone who inquired?

Mr. CAMARDO. No, this one went without inquiry. This was mailed to 450,000 doctors.

Mr. WALDEN. So Wyeth was strengthening their warnings. Was this done at the request of the FDA or by the company itself?

Mr. CAMARDO. This was the company's decision.

Mr. WALDEN. At the time, Wyeth implemented these new warnings, did FDA raise any objections to Wyeth having that in its label?

Mr. CAMARDO. The FDA allowed us to proceed with the letter and with the change in the label. I think they had a somewhat different view of what should be done, but they allowed us to proceed with this.

Mr. WALDEN. Does the effect source still contain that warning?

Mr. CAMARDO. No, this warning was eliminated in favor of the class label warning that was added in April. So I guess——

Mr. WALDEN. Isn't it correct to say the FDA basically made you back off with more specific language?

Mr. CAMARDO. Well, the FDA had a different view and they essentially asked everyone to adopt similar labeling that would be a little broader. I believe that would be——

Mr. WALDEN. Didn't they make you take out the references to increased hostility?

Mr. CAMARDO. They did want us to take out the references from the pediatric——

Mr. WALDEN. Are you comfortable in doing that?

Mr. CAMARDO. Well, we thought it was reasonable to keep it in the labeling, but when we compared what we were saying with what was in the class labeling about suicide warning, I thought at the time it would be a reasonable compromise and we also knew that there would be additional advisory committee discussion about what actually should be done here.

Mr. WALDEN. Did you ask FDA to tell you to do that in writing?

Mr. CAMARDO. I think that they—we have a record of telephone calls and teleconferences. I think we may have asked them to specifically request it in writing, but there is——

Mr. WALDEN. You might want to turn to tab 40 in the book.

Mr. CAMARDO. Okay.

Mr. WALDEN. And you'll see this is from—to you from Dr. Katz.

Mr. CAMARDO. Right, I see this.

Mr. WALDEN. "We note your agreement to our request to remove your proposed position of hostility and suicide-related adverse events from the precautions usage in children's section. As discussed during that April 28, 2004 meeting, we continue to feel it not would be helpful to include the language regarding reports of hostility and suicidality that you have proposed for the pediatric use section."

Why did you think it was important to include that language?

Mr. CAMARDO. Actually, we were taking a pretty simplistic view which is we observed it in the trials. We couldn't explain it completely. We wanted to provide doctors with the information we had, even though it wasn't fully interpretable and that's why we thought——

Mr. WALDEN. Basically, it's a directive and I assume you wanted to flag it as something physicians should watch for, if indeed, they were prescribing a drug that's not supposed to be prescribed to children?

Mr. CAMARDO. I would say it's fair, a fair way to characterize what we wanted to do, yes, that we wanted them to be aware of it, yes.

Mr. WALDEN. Thank you. My time has expired. The gentleman from Maine?

Mr. ALLEN. Thank you, Mr. Chairman.

Dr. Marcus, we'll come back to you. Let me restate the question, just so the record is clearer than it would be if people have to go back and look at it.

FDA told Bristol-Myers that Serzone was not indicated for use in pediatric patients, but Bristol-Myers' sponsored study, tab 28, con-

cludes that "in this study, Serzone was shown to be safe and effective in the acute treatment of adolescents with major depressive disorder."

So the question was if your studies conclude that this drug is safe and effective for adolescents with MDD, why would the FDA not approve your drug for pediatric patients? Did the FDA disagree with the way your study was conducted or with its results?

Mr. MARCUS. It's really very simple and the primary outcome measure, if you go to the last slide on this tab, it gives the conclusions of the study and essentially on the primary efficacy measure which is sort of the one you have to be positive on for it to be, from a regulatory perspective, a positive study, we just missed statistical significance. We need .05 and we had .055. On every other measure in the study for efficacy, we were actually robustly positive.

Mr. ALLEN. Did you go back and do another study or follow-up studies on this particular——

Mr. MARCUS. We did a second study which essentially was absolutely no difference between Serzone and placebo. So we did a second study. That was—this was just in adolescents, but we did a study that was in both children and adolescents and that study was absolutely no difference between Serzone and placebo.

Mr. ALLEN. So that's why you didn't pursue it any further, I take it?

Mr. MARCUS. That's correct.

Mr. ALLEN. I would like to go through—I'd like to get the reaction of the panel to the AMA proposal. After you are finished, I understand that a representative from the AMA will testify about their support for a new Federal level comprehensive clinical trials registry.

Two questions. Do you believe that the creation of this type of registry would benefit physicians and patients? And two, would your companies be willing to fully participate in the Federal clinical trials registry?

Dr. Clary, why don't we start from your end this time?

Ms. CLARY. Yes, so the AMA proposal just has come out and we have looked at it. We haven't had time to fully digest it, but we are certainly open to considering it. We, as I've said repeatedly today, we really would like to convene a group to speak with multiple stakeholders to decide. But we're certainly very open to considering that.

Mr. ALLEN. Mr. Osinsky?

Mr. OSINSKY. Organon is open to considering it. We don't know the details. We haven't studied it yet.

Mr. HAYES. I'm going to provide pretty much the same answer. I have not spoken to people within senior management to have a sense of what their response to it is. I think we'll also consider it.

Mr. OLANOFF. As I indicated in my testimony, we are open to participating in centralized registries.

Mr. CAMARDO. We're open to participating in centralized registries as well. I think it would help physicians if it could be managed appropriately, so that they can actually use it.

Mr. ALLEN. Could you punch the button?

Mr. HAYES. Same answer. We'd be open to it, but we'd have to see the details and discuss and I think take a position on whether it met the goals we've been speaking about today.

Mr. WHEADON. We, as well, would be willing to consider it and further discuss it with the AMA.

Mr. ALLEN. Thank you all. Dr. Wheadon, in a lawsuit brought against GlaxoSmithKline, Elliott Spitzer, the Attorney General of the State of New York, alleges that Glaxo misrepresented the full details of their studies regarding Paxil. The lawsuit alleges that an additional study, extensions to studies 329 and 701 were misleading.

First, can you please explain what an extension study is?

Mr. WHEADON. Typically, studies have what we call an acute phase and an extension. The acute phase may run anywhere from 8 weeks to 12 weeks. And an extension may go out through a year or longer.

Typically, patients that are showing some level of response go into the extension, so it's a longer term treatment for those who are responding.

The primary parameters for assessing efficacy are typically carried out in the acute phase, but then you do obviously some follow-on assessments to see how the efficacy or the response is maintained over the course of longer term treatment.

Mr. ALLEN. Thank you. The lawsuit states that the extension of study 329 was not randomized and was designed to evaluate relapse rate and longer-term safety and not efficacy.

Can you respond to that accusation, that charge?

Mr. WHEADON. I wouldn't say it was necessarily an accusation or charge, as I mentioned, those patients that respond go into an extension and you then, in that frame of study, look at relapse rate. So what is the reoccurrence of the depressive symptoms, active drug versus placebo, so that's relapse.

Mr. ALLEN. And that's why you would say it was not randomized, because it's a follow on for those people who are responding?

Mr. WHEADON. Exactly.

Mr. ALLEN. I understand that. The lawsuit further alleges that study 716 was not randomized, placebo-controlled or blind and included participants from completed studies of pediatric patients with MDD or OCD.

Can you respond to that as well, same kind of answer?

Mr. WHEADON. If I recall 716 was just sort of an ability for patients to have continued treatment, but it was no intended to test an a priori hypothesis per se.

Mr. ALLEN. And finally, Dr. Wheadon, the lawsuit also asserts that Glaxo is allowed positive information about the pediatric use of Paxil to be disclosed publicly, but has withheld and concealed negative information concerning its safety and efficacy.

Can you respond to those allegations about whether or not Glaxo has misrepresented information concerning the safety and efficacy of Paxil for treating major depressive disorder in children and adolescents?

Mr. WHEADON. With all due respect to the New York State Attorney General, I think as we've disclosed to this committee, we have indeed published 329, 377 which is the negative studies, 701. So

those studies have been published in various venues, be it peer-reviewed journals, abstracts, presentations.

Mr. ALLEN. Thank you. Mr. Chairman, I yield back.

Mr. WALDEN. Thank you. I just wanted to get a couple of things quickly here on the record, Dr. Wheadon. I note that this summer Glaxo posted all of its study reports for pediatric clinical antidepressant trials on its website for public access and this does go beyond simply post summaries. I also note that Glaxo posted study 511 which was a non-industry—I'm sorry, non-IND study on its website. Did Glaxo submit the 511 study to the FDA since it was a non-IND study? And is Glaxo required to do so?

Mr. WHEADON. Well, the study, since it's non-IND, it's not required to be filed to the FDA, however, I think as we've discussed with the committee staff members before and as Dr. Woodcock pointed out, any data that's garnered in any studies that are ongoing or included in annual reports in terms of safety information.

Mr. WALDEN. And that's safety, not efficacy.

Mr. WHEADON. That's safety, exactly.

Mr. WALDEN. So if a non-IND study showed no efficacy, there's no requirement for the company to inform FDA of that result, correct?

Mr. WHEADON. In the context of updating, you can, for example, report to FDA the outcome of the study or the progress of the study, but there's no regulatory requirement that that study report be filed to the FDA if it's not done an IND.

Mr. WALDEN. So you do provide safety information in an annual report, but are not required to report efficacy results?

Mr. WHEADON. That's correct.

Mr. WALDEN. Is Glaxo going to post efficacy results of non-IND studies on its clinical trial registry?

Mr. WHEADON. We are doing that.

Mr. WALDEN. So the Paxil registry has IND and non-IND studies posted to the website. Okay.

One other question, just perhaps for all of you, do your companies engage in marketing studies or analysis for sales of products that are off-label? Do you look at that? Do you do marketing analysis out there to see who's prescribing what drugs that are off-label and to whom? Does anybody do that first of all?

Mr. HAYES. I think the major way in which sales are analyzed is through national data bases of prescriptions. You can get a rough idea of the reasons why your products was prescribed over some certain period of time in the same way you can have some sense of how many units were sold in a particular period.

Mr. WALDEN. Do you look at age groups?

Mr. HAYES. I don't—age groups can be looked at. I am trying to think whether I've really seen that.

Mr. WALDEN. I don't know about you specifically, but in the companies, are you doing market analysis?

Mr. HAYES. Certainly to some extent.

Mr. WALDEN. Obviously, this is big dollar stuff.

Mr. HAYES. To some extent you could, but I think people are—again, I can't speak for other companies, but I think when we do a market analysis or a market research about something that's not on label, it's by way of exploring the possibility that patients and

doctors need some indication and if we find such a need, we may well pursue the appropriate research and the appropriate interactions with the FDA to see if we can develop a drug for that indication.

And I understand what you're getting at. I'm not aware of——

Mr. WALDEN. I guess in the final analysis what I hear and what I've come to understand and correct me if I'm wrong, is that you do clinical trials that may not show efficacy and so some companies don't turn those trial results into the FDA because you don't pursue the label. I've heard that today. And yet, in some of the posters and in some of the publications, a novice like myself in reading the words would be left with the opinion that these drugs are indeed effective and we see those words used in treatment of young people for a very serious disease. Even when the FDA, and some of you know the FDA wouldn't certify these drugs for that use, and I think I've heard nobody is out there telling docs not to prescribe. You're not encouraging them to prescribe, but nobody is saying don't prescribe, other than maybe raising a flag or two about the hostility or suicide, being told by the FDA don't raise that flag the way you did it. And it's a big industry.

Am I missing something here?

Ms. CLARY. If I could make one comment, and that is I would really like us not to forget the patients. I think you know that I practiced psychiatry for quite a long time.

Mr. WALDEN. They are the ones who are most concerned about it.

Ms. CLARY. Yes, exactly. I think we all are. I know we share that and there are not a lot of treatments that have been proven effective for pediatric depression, but physicians are struggling to try to figure out the best way to treat this disease. They're faced with a patient in their office who has very significant symptoms. They can't prescribe the older drugs, the tricyclics because they were not shown to be helpful and they had safety problems, so it's really a dilemma, I think, for all of us.

Mr. WALDEN. I appreciate the time you've taken to be here today and your comments and we may have, obviously, some questions. I think you've heard we'll submit for the record. We'll have another hearing on the 23rd. So thank you for your participation.

We have a third panel that we'd like to—oh yes, you're dismissed, I guess I'm supposed to say. Excused, whichever.

And our third panel is Dr. Ronald M. Davis, M.D., Member, AMA, Board of Trustees from the American Medical Association; Dr. Caroline Loew, Vice President of Scientific and Regulatory Affairs with PhRMA; and Dr. Richard Gorman, M.D., American Academy of Pediatrics.

Okay, as you're aware the committee is hold an investigative hearing and when doing so it has had the practice of taking testimony under oath. Do you have any objection to your testimony being taken under oath? Let the record show they do not.

The chair then advises you that under the rules of the House and the rules of the committee, you are entitled to be advised by counsel. Do any of you desire to be advised by counsel? The record shows they do not.

In that case, I would rise, since you already are, raise your right hand and I will swear you in. Do you swear the testimony you're about to give is the truth, the whole truth and nothing but the truth?

[Witnesses sworn.]

Mr. WALDEN. They answered in the affirmative. Please be seated and we'll begin with the testimony of Dr. Davis.

TESTIMONY OF RONALD M. DAVIS, MEMBER, AMA, BOARD OF TRUSTEES; CAROLINE LOEW, VICE PRESIDENT, SCIENTIFIC AND REGULATORY AFFAIRS, PhRMA; AND RICHARD GORMAN, AMERICAN ACADEMY OF PEDIATRICS

Mr. DAVIS. Good evening. My name is Ron Davis. I'm a member of the American Medical Association's Board of Trustees and a preventive medicine physician in Detroit. On behalf of the AMA, thank you for the opportunity to share our views on the need for more clinical trial information pertaining to children and adolescents.

The AMA has long supported congressional efforts on this front and we're pleased to be here today to offer a broader solution to further address this problem. Quite simply, physicians need complete and unbiased information about the safety and effectiveness of the treatments they prescribe for their patients. A centralized clinical trials registry would improve physician and researcher access to this information and would facilitate patient enrollment in clinical trials.

The bottom line is that physicians and researchers who formulate treatment guidelines for patients must be able to trust the information they use. To this end, the AMA this past June called on the Department of Health and Human Services to establish a centralized registry for clinical trials conducted in the United States. How such a registry would be constructed and maintained requires further discussion with key stakeholders including Congress, HHS, the research community and the pharmaceutical manufacturers.

As initial guidance, we recommend the following. The registry should include phase 2 and phase 3 clinical trials that evaluate a new drug, biologic or medical device, post-marketing studies and other trials designed to test the therapeutic intervention. Identifying information should be included such as the name of the trial sponsor, sources of funding, a unique identifier and contact information for the persons responsible for the clinical trial.

Details such as the trial purpose and objective, the methodology, the population and diseases being studied and the dates the trial began and ended should all be included in a simple, easy to understand format.

To ensure that clinical trials are reported to the registry, Institutional Review Boards or IRBs should require registration as a condition for approval of the clinical trial. It is important to remember that the basic conduct and operation of IRBs are already federally regulated.

And finally, clinical trial results should be made publicly available. Centralized clinical trial registry should offer links to published journal articles or clinical trial reports. And if a trial was terminated early, the reason for such termination should be explained.

The AMA is encouraged by the individual efforts of a number of pharmaceutical companies, as well as the recent PhRMA proposals intended to promote voluntary disclosure of clinical trial information for currently marketed drugs.

As we move forward, we hope to work closely with these organizations, as well as Congress, the Administration, and the research community to develop a centralized clinical trials registry that benefits physicians, researchers and especially our patients.

Thank you.

[The prepared statement of Ronald M. Davis follows:]

PREPARED STATEMENT OF RONALD M. DAVIS, MD, MEMBER, AMA BOARD OF TRUSTEES ON BEHALF OF THE AMERICAN MEDICAL ASSOCIATION

The American Medical Association (AMA) appreciates the opportunity to present its views on the need for broader public information about clinical trials. We commend the Chairman and members of this Subcommittee for holding this important hearing. In particular, the AMA shares your commitment to improving the value of clinical research for the pediatric population.

The AMA has long-standing policy that supports the development and testing of drugs in the pediatric age groups in which they are used. Specifically, AMA policy states,

> Our AMA urges pharmaceutical manufacturers and the FDA to work with the American Academy of Pediatrics and experts in pediatric medicine to identify those investigational drugs that would have pediatric indications and set up a mechanism to ensure that necessary pediatric clinical studies are completed prior to submission of [New Drug Applications] (NDAs) for approval of these drug products.

Fortunately, through the leadership of the American Academy of Pediatrics with support from the AMA, Congress has passed and we have seen legislation enacted to address this problem. The Better Pharmaceuticals for Children Act (P.L. 107-109), which re-authorized and improved upon Section 111 of the Food and Drug Administration (FDA) Modernization Act of 1997 (P.L. 105-115), provides additional patent exclusivity as an incentive to pharmaceutical manufacturers to do clinical trials of their drugs in the pediatric population. In addition, in 2003 Congress passed the Pediatric Research Equity Act (P.L. 108-155), which provides the FDA with the authority to require pharmaceutical companies to evaluate the clinical effectiveness and safety of their products in children when appropriate. Recent evidence suggests these laws are proving successful in increasing the number of clinical trials conducted in children and in improving the pediatric information in FDA-approved drug product labeling. The AMA supported passage of these laws and is hopeful that we will continue to see necessary pediatric clinical trials conducted so that children will no longer bear the label of "therapeutic orphans."

Against this backdrop of concern for continued and enhanced pediatric clinical trials, in today's testimony, the AMA will focus on the broader issue of clinical trials registries. The issue, which is not limited to pediatrics, involves the lack of disclosure or publication of the results, either positive or negative, of clinical trials involving a therapeutic intervention, such as a drug product. Such information is invaluable to researchers, scientists and physicians, who conduct or evaluate clinical research, formulate treatment guidelines and provide advice on best practices which ultimately benefits patients, both young and old.

Therefore, more needs to be done to address the issues that are keeping physicians and researchers from having access to information about what clinical research is currently being conducted, as well as the results of such research, regardless of whether the clinical trials are done on adult or pediatric populations.

At the AMA's 2004 Annual Meeting, our House of Delegates adopted a report by the Council on Scientific Affairs (CSA) which recommended, among other things, that "the Department of Health and Human Services establish a comprehensive registry for all clinical trials conducted in the United States." Additionally it recommended that "every clinical trial should have a unique identifier," and that "all results from registered clinical trials be made publicly available through either publication or an electronic data-repository." A longstanding concern about the impact of pharmaceutical industry sponsorship on publication bias in pharmaceutical research was a major factor in adopting this policy.

Publication bias is the selective publication of studies based on the direction (positive), magnitude, and statistical significance of the treatment effect. When an inves-

tigator has a financial interest in or funding from a company with activities related to his or her research, the research is more likely to favor the sponsor's product, less likely is to be published, and more likely to have delayed publication. Publication bias is often attributed to decisions made by authors/investigators and journal editors, but in fact can intrude into the entire process of planning and conducting the clinical trial and publishing the results, leading to outcome bias.

In its review, the CSA found, among other things, that industry-funded studies with positive results were more likely to be published than studies with negative or neutral results. Factors that contribute to such bias include: trial designs that make favorable results more likely; clinical trial agreements that may restrict publication of some results; and even the simple human factor that researchers may be more excited by and interested in pursuing publication of positive results. In addition, journal editors and reviewers may give preference to publishing positive results because they are more likely to impact medical practice and, therefore, be of more immediate interest to their audience. The consequences of these shortcomings are obvious. The evidence-based practice of medicine depends on the analysis of current research, and medical practice guidelines are often based on systematic reviews or meta-analyses of available data. If negative and neutral trial results are not published or lost, for whatever reasons, the interpretation of this data is incomplete and faulty, inevitably skewed, and presents a more positive picture than may be warranted.

There is general agreement that the two most powerful remedies to publication bias are to register all clinical trials, and to make results publicly available. Clinical trials should be registered when they are begun so that essential details are made public from a trial's inception, rather than from publication many years later. Openness about trials in progress reduces the impact of publication bias, prevents duplication of effort, promotes collaboration, and may improve evidence-based medical practice.

Recently, the International Committee of Medical Journal Editors (ICMJE), of which the Journal of the American Medical Association (JAMA) is a member, announced that it is considering a proposal to require registration of a clinical trial as a prerequisite for publication. The AMA applauds ICMJE's proposal and believes that such an effort will significantly increase the number of clinical trials that are registered. However, there are currently not enough peer reviewed medical journals in existence to accommodate and publish the results of every clinical trial, even with the increasing number of online journals. Additionally, hundreds of clinical trial registries currently exist, ranging from individual hospitals or practice groups to meta-registries that attempt to collate information from disparate sources. Yet, information in these registries is not standardized and many contain only a subset of trials, often in high profile areas such as cancer or AIDS. Many are hard to use, none are comprehensive, and many trials are not registered anywhere. It is for this reason, as well as for the reasons mentioned above, that the AMA has recommended a comprehensive clinical trials registry at the Federal level.

The infrastructure for such a registry is already in place. ClinicalTrials.gov, established by Section 113, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases," of the Food and Drug Administration Modernization Act of 1997 (P. L. 105-115), currently provides information about federally and privately supported clinical research involving drugs for "serious or life-threatening diseases and conditions." This registry includes information about the purpose of a trial and a brief description, inclusion and exclusion criteria, locations, and phone numbers for additional information and is required to be "integrated and coordinated with related activities of other agencies of the Department of Health and Human Services, and to the extent practicable, coordinated with other data banks containing similar information." Currently, this registry contains references to roughly 7885 NIH-sponsored trials, 2382 industry-sponsored trials, 4566 university-sponsored trials, and 379 trials sponsored by other Federal agencies.

ClinicalTrials.gov is not a comprehensive registry. For example, trials do not have to be registered if the sponsor has provided a detailed certification to the Secretary that disclosure of such information would substantially interfere with the timely enrollment of subjects in the investigation, and the Secretary agrees. Also, ClinicalTrials.gov does not require the results of clinical trials to be included although the law allows the registry to include information pertaining to the results of clinical trials, with the consent of the sponsor. Finally, a recent analysis by FDA staff showed that many industry-sponsored trials have not been submitted to the registry at all.

While it is still too early in the process to say definitively what a comprehensive Federal clinical trial registry should include or precisely how it should be imple-

mented, the AMA recommends that such a comprehensive clinical trials registry should meet the following criteria:

1. To the extent possible, the registry should be comprehensive. For example, Phase 2, 3 and 4 clinical trials conducted in support of new drug, biologic, or device applications, other randomized controlled trials (e.g., investigator-initiated and federally-funded studies involving therapeutic interventions), and pharmacoepidemiologic studies designed to test a hypothesis should be included. At the same time, however, access to information to more effectively translate clinical research into medical practice must be balanced with the need to protect pharmaceutical manufacturers' proprietary information in order to preserve the incentive to conduct clinical trials that will result in innovative new therapies. How to achieve this balance requires further discussion among key stakeholders.
2. Identifying information should be included such as, the name of the trial sponsor(s), protocol number and contact information for the lead principal investigator or person with overall responsibility for the trial. Additionally, a unique alpha-numeric identifier should be assigned by a database administrator. For example, trials registered through ClinicalTrials.gov are assigned a unique NLM identifier (e.g., NCT00037952).
3. Sources of funding for the clinical trials should be revealed, complete with reference numbers given to the trials by each funding agency.
4. Trial details should be included while also ensuring that the information is not overly burdensome for either patients or researchers who wish to access the information. Such details should include:
   - Trial purpose and/or Objectives;
   - Type of trial, for trials conducted as part of an NDA, the phase of the trial;
   - Methodology (Interventions and duration of treatment for trial groups);
   - Title of the trial and acronym (if relevant);
   - Disease or condition;
   - Participants (eligibility criteria);
   - Trial locations and Principal Investigator(s);
   - Recruitment status;
   - Date trial started; and
   - Date completed or terminated.
5. The results of all clinical trials should be publicly available. If the trial was terminated, the reason for the termination should be explained. Conceptually, the registry could include a link to another site where the published results could be found (i.e., PubMed citation), or for studies that were conducted in support of a New Drug Application (NDA), a link to the Medical Review of the NDA. We recognize that there are inherent risks in publishing data that has not been validated or peer-reviewed in one way or another. The question of what would comprise validated results (other than the raw data) for studies that have not been published in the peer-reviewed literature or as part of an NDA needs broader discussion. The synopsis of the guideline approved by the International Conference on Harmonization for the structure and content of clinical study reports may be a useful template for standardized reporting of such results. This guideline and synopsis are available electronically on the FDA website www.fda.gov/cder/guidance/iche3.pdf.
6. In order to create an efficient enforcement mechanism, approval of clinical trial protocols by Institutional Review Boards (IRBs) should include the additional criteria of clinical trial registration and assignment of a unique alpha-numeric identifier. The basic conduct and operation of IRBs is already federally-regulated.

The AMA recognizes that there are other proposals currently that attempt to address the issues of publication bias, and we applaud the independent efforts of organizations such as ICMJE and the Pharmaceutical Research and Manufacturers Association (PhRMA) who, on June 30, 2004, released an update of its voluntary guidance on "Principles for Conduct of Clinical Trials and Communication of Clinical Trial Results." PhRMA's "principles" cover (1) commitment to protecting research participants; (2) conduct of clinical trials; (3) ensuring objectivity in research; and (4) public disclosure of clinical trials results. While these principles do not necessarily address all of the AMA's concerns, particularly with regard to registration of clinical trials, they contain much we could support. It is the AMA's hope that as we move forward in our efforts to establish a comprehensive clinical trials registry, we are able to work closely with all interested parties, including both the Congress and the Department of Health and Human Services, to make sure that our nation's patients have access to complete information, either directly or through their physi-

cians or other researchers, to allow them to make informed decisions about their health care treatment options.

Once again, the AMA commends the committee for holding today's hearing, and we thank the chairman for the opportunity to present our views. We look forward to working together on this important issue.

Mr. WALDEN. Thank you, Dr. Davis.

Dr. Loew.

TESTIMONY OF CAROLINE LOEW

Ms. LOEW. Mr. Chairman and members of the subcommittee, thank you for the opportunity to testify today on issues surrounding the publication and disclosure of clinical trial information.

My name is Dr. Caroline Loew and I'm the Vice President of Scientific and Regulatory Affairs at PhRMA, Pharmaceutical Research and Manufacturers of America. PhRMA shares the subcommittee's view that clinical trial information should be made available to physicians and patients and we have taken concrete steps to ensure that the clinical trial process is transparent and accessible.

At the outset, it is important to distinguish between a clinical trial registry and a clinical study results data base. The two are often confused. A registry, such as clinicaltrials.gov, created by Section 113 of FDAMA, lists clinical trials into open and recruiting patients. A clinical study results data base, by contrast, has results of completed studies. PhRMA believes it is important to keep these concepts separate when discussing publication and disclosure issues to clinical trials.

Regarding the clinical trials registry, PhRMA strongly supports the National Library of Medicine's clinical trial registry as an important resource for physicians and patients seeking information about on-going clinical trials.

Following passage of FDAMA, it took several years to implement the registry. PhRMA worked closely with the National Library and the FDA to ensure that the registry was successfully implemented and that it educated its members about the registry and the statutory requirements.

Further details on our efforts in these regards have been provided in our written testimony, but in short, we believe the registry is a critical resource for patients and physicians and PhRMA and its member companies are committed to ensuring that it is complete and effective.

I would now like to turn to the disclosure of clinical study results. PhRMA's commitment to transparency in this area is not new. It was 2 years ago that the PhRMA Board approved a set of principles on the conduct of clinical trials and communication of clinical trial results. These principles expressed the commitment of PhRMA member companies to communicate the results of all hypothesis testing clinical trials, both positive and negative, for drugs that are on the market.

Given the publication in a peer-reviewed journal, as we've heard today, is not always possible, other publication means are necessary. PhRMA has sought to address this problem and I am pleased to inform this subcommittee that the PhRMA Board recently approved the establishment of a clinical study results data base. This data base is a central, widely accessible, web-based repository for clinical study results in a user-friendly, standardized

format. This data base will make clinical study results more transparent and accessible and be a valuable resource for physicians and patients.

The data base will contain results from all hypothesis testing clinical studies completed since the first of October 2002 for drug products approved in the United States. It will have a bibliography of published articles, summaries of unpublished clinical studies, as well as a link or reference to the FDA approved drug label. Study summaries are in a standard, nonpromotional format, accepted by regulators in the United States, Europe and Japan.

It is important that the information presented not be considered a substitute for the FDA-approved prescribing information. The website will thus include a notice stressing that the data base is being made available for informational purposes only and that the full prescribing information approved by the FDA should be the physicians primary source of information about the use of every medicine.

We have consulted with several physician groups, including the American Medical Association, and the American Psychiatric Association. While we do not want to speak for any of these groups, we are optimistic that we're heading in the right direction. We realize it will be critical to obtain on-going feedback from physicians and patients once the site is up and running. There is a form on the site for this purpose and we look forward to receiving feedback over the coming months.

Finally, PhRMA believes the data base will be most useful if it is administered in partnership with, or by, an independent third party. We plan to explore this possibility. However, as we are committed to establishing the data base as quickly as possible, we will be launching it initially as a PhRMA project. A data base will be operational and available for public use on the first of October of this year, with information being added on an on-going basis.

In sum, PhRMA and its member companies are firmly committed to transparency of clinical trial information. We are excited about our data base initiative, and we will be pleased to keep the subcommittee updated.

Thank you for the opportunity to inform the subcommittee about PhRMA's activities in this critical public health area.

[The prepared statement of Caroline Loew follows:]

PREPARED STATEMENT OF CAROLINE LOEW, VICE PRESIDENT, SCIENTIFIC AND REGULATORY AFFAIRS, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

INTRODUCTION

Mr. Chairman and members of the subcommittee, thank you for the opportunity to testify today on issues surrounding the publication and disclosure of clinical trial information. My name is Dr. Caroline Loew, and I am Vice President of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America, also known as PhRMA. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Our member companies invested more than $32 billion last year in discovering and developing new medicines for American patients. It is thus no overstatement to say that PhRMA companies are leading the way in the search for cures.

While I cannot provide any information specific to anti-depressant clinical trials conducted by our member companies, I can address generally PhRMA's efforts to facilitate the accessibility of information about clinical trials. PhRMA and its member companies are committed to ensuring that physicians and patients have access to

all relevant information from the clinical studies our companies conduct—consistent with applicable regulatory requirements—so that our products can be used in a manner that is as safe and effective as possible. This commitment is reflected in the PhRMA *Principles on Conduct of Clinical Trials and Communication of Clinical Trials Results* (the *Principles*), which I will discuss later in more detail, and in our strong support for Section 113 of the Food and Drug Administration Modernization Act (FDAMA). In short, PhRMA shares this subcommittee's view that clinical study information, including both positive and negative data, should be made available to physicians and patients, and we have taken concrete steps to ensure that the clinical trial process is transparent and accessible.

Before discussing the steps we have taken to improve transparency, it is important to distinguish between two different concepts: the clinical trial registry and the clinical study results database. A clinical trial registry, of which there are many, is designed to inform patients and health care providers about clinical trials that are open and recruiting patients. An example of a clinical trial registry is the website clinicaltrials.gov created by Section 113 of FDAMA. A clinical study results database, by contrast, is designed to provide access to the results of clinical studies that have already been completed. These two concepts often are confused, but they are fundamentally different and are intended for different audiences. PhRMA thus believes it is important to keep these concepts separate when discussing publication and disclosure issues for clinical trials.

CLINICAL TRIALS REGISTRY

The first issue I would like to address today is PhRMA-member participation in the clinical trial registry established by Section 113 of FDAMA. In particular, I would like to discuss the steps taken by PhRMA and its member companies to ensure compliance with the requirements of Section 113.

PhRMA strongly supports the National Library of Medicine's Clinical Trials Registry as an important resource for physicians and patients seeking information about ongoing clinical trials for serious or life-threatening diseases and conditions. While a clinical trial should not be viewed as a treatment option, such trials nevertheless can provide access to promising new therapies for seriously ill patients with few other options. Ultimately, a successful and robust clinical trial enterprise in the U.S. leads to new cures for all patients. PhRMA thus supports full participation in the Clinical Trials Registry by all sponsors of eligible clinical trials.

Following passage of FDAMA, the National Library of Medicine and the Food and Drug Administration (FDA) took several years to establish and implement the registry. During that time, PhRMA worked closely with both government organizations to ensure that the registry was successfully implemented. For instance, PhRMA established a task force on Section 113 that provided significant comments and feedback to FDA and NLM during the implementation period on a number of issues associated with the registry, including technical issues regarding the web-based interface for posting clinical trial information. PhRMA's efforts have been directed at ensuring that the registry functions as seamlessly as possible so that patients and physicians have access to all relevant information about ongoing clinical trials.

PhRMA also has made significant efforts to educate its members about the registry and the statutory requirement to submit information about ongoing clinical trials regarding serious or life-threatening diseases and conditions. On March 21, 2002, for instance, PhRMA notified its member companies (through its list of regulatory contacts) that as of March 18, 2002, the registry had begun accepting clinical trial information from industry sponsors and thus that the Section 113 reporting requirement had finally been implemented. PhRMA specifically informed its members in that memorandum that "there is an obligation on the part of all sponsors to submit descriptive information on the drug trial, recruitment information and trial location and contact information." Likewise, on November 7, 2003, PhRMA sent another memorandum reminding its members of the Section 113 reporting requirements and requesting that they "review [their] ongoing trials to see if they meet the criteria [for submission] as outlined in the FDA guidance."

PhRMA and its member companies are strongly committed to full implementation of the Clinical Trials Registry. This issue, in fact, was discussed at a recent meeting of the PhRMA board of directors, during which we reiterated PhRMA's history of strong support for the registry and the need to ensure that all PhRMA members are and continue to be in full compliance with the reporting requirements. The commitment to transparency thus is being addressed at the highest levels of our member companies.

Although there have been some reports of industry non-compliance, we are not aware of any reliable information demonstrating that the pharmaceutical industry

is not meeting its commitment to comply with Section 113 with respect to clinical trials for serious and life-threatening diseases. Information from the FDA appears based on submission rates for the first nine months of 2002. We do not believe these data should be construed as representative of the situation that exists today since the registry did not even begin accepting industry-sponsored clinical trial information on a routine basis until March 2002, three months into the evaluation period selected by the FDA.

PhRMA understands that the FDA is undertaking a more comprehensive study of compliance with the requirements of Section 113 and looks forward to reviewing that study when it is completed. As such, we believe that conclusions about industry compliance should be deferred until the FDA's report has been completed and fully reviewed. If the FDA study identifies current problems with the system, we will work closely with the FDA and our member companies to identify the source of those problems and to make any necessary improvements as quickly as possible to ensure that there is full compliance with the statutory reporting requirements.

The registry clinicaltrials.gov is a critical resource for patients and physicians, and PhRMA and its member companies are committed to ensuring that it is complete and effective.

CLINICAL STUDY RESULTS DATABASE

I would now like to turn to the second issue before the subcommittee this morning: the communication and disclosure of clinical study (clinical trial) results. PhRMA member companies are firmly committed to communicating meaningful results of all controlled clinical trials of marketed drugs—regardless of outcome. This means that results will be communicated if they are positive, negative, or anywhere in between. While these disclosures of negative results may not make splashy headlines or conform to the current negative view of the pharmaceutical industry, they are made everyday by this industry. One recent example is the disclosure of the results of a multi-year head-to-head trial involving two well-known cholesterol-lowering agents, even though the results did not support the marketing position of the sponsor of the trial.

And this commitment to transparency is not new. Two years ago, the PhRMA board of directors approved a set of voluntary *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results* (the *Principles*). These *Principles,* which have been in effect since October 1, 2002, express in straightforward language the commitment of PhRMA-member companies to communicate the results of clinical trials, both positive and negative:

> "We commit to timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing, regardless of outcome." (*PhRMA Principles, Section 4(a)*).

To strengthen this commitment even further, the PhRMA executive committee approved at its June 2004 meeting additional "Questions and Answers" to clarify some of the concepts in the *Principles.* In particular, the *Principles* now state that PhRMA member companies commit to publish the results of "all hypothesis-testing clinical trials [they] conduct, regardless of outcome, for marketed products or investigational products that are approved for marketing." (*PhRMA Principles, page 30*). Significantly, the *Principles* clearly state that results should be communicated regardless of whether they are positive or negative. Copies of the updated *Principles* have been provided to this subcommittee and staff.

The *Principles* encourage sponsors to communicate clinical trial results by means of publication in a peer-reviewed medical journal, such as the *New England Journal of Medicine,* but recognize that manufacturers do not control which studies get published and that not all studies will merit publication in a peer-reviewed journal. The *Principles* thus provide for alternate methods of communication, such as through presentation at a public scientific meeting or posting the results on a website.

One difficulty with these alternative methods of communication is they often only reach a limited audience, such as the physicians who attend a particular meeting. PhRMA believes an appropriately designed internet database could solve this problem. By providing a central, widely accessible repository for clinical study results and a standardized format for the reporting of such results, a clinical study results database could serve the valuable function of making clinical trial results more transparent and accessible. More importantly, in our opinion, this could be a valuable resource to support practicing physicians and their patients.

Consequently, I am pleased to inform this subcommittee that the PhRMA board of directors recently approved the establishment of a Clinical Study Results Database. The database is a central, widely accessible, web-based repository for clinical study results in a user-friendly, standardized format. This database will serve the

valuable function of making clinical study results for U.S.-marketed pharmaceuticals more transparent.

The database will contain the results from all "hypothesis-testing" clinical studies completed since October 1, 2002—the implementation date of the PhRMA *Principles*—for drug products that are approved in the United States. This will include both positive and negative results by providing a bibliography of published articles and unpublished clinical study summaries. In short, the database will contain information that is consistent with the PhRMA Principles, i.e., the results of all hypothesis-testing clinical trials, regardless of outcome, for marketed drugs or investigational drugs that are approved for marketing.

The information on the database will be presented in a standard format that is easily searchable and includes the sponsoring company's name, the proprietary and generic names of the drug, a link or reference to the FDA-approved drug label, the studied indication(s), a bibliography of published studies together with a link (where available) to the printed articles, and a summary of the results of clinical studies that have not been published.

The summaries of unpublished results will be presented in a standard format accepted by regulators in the United States, Europe and Japan—the International Conference on Harmonization's (ICH) E-3 guidance on the structure and content of clinical study reports. This will provide scientific information about the results of a study in a standard, non-promotional manner that doctors can understand. It will include basic information about the study and its results, such as the design of the trial, the number of patients studied, the dose and mode of administration, and a summary of conclusions and outcomes on the safety and efficacy of the drug.

As we implement the database, we are addressing several important regulatory and policy issues. For example, while PhRMA supports both the free flow of scientific information and the practice of medicine, PhRMA wants to ensure that the information in the database is not considered a substitute for the FDA-approved prescribing information. Thus, while it is important that the information in a results database be comprehensive and presented in a manner that is useful to physicians seeking additional information about a drug product, we think it is equally important that users understand the limitations of the database. The website thus will include a notice stressing that the database is being made available for informational purposes only and that the full prescribing information approved by the FDA should be the physician's primary source of information about the use of every medicine. In addition, the database will provide a link to the drug's full prescribing information.

We also want to ensure that the database is useful for practicing physicians. During the past few months, we have consulted with several physician groups, including the American Medical Association (AMA), the American Psychiatric Association, and others. While we do not want to speak for any of these groups, we are optimistic that we are heading in the right direction. We realize, however, that it will be critical to obtain ongoing feedback from these groups and from individual physicians and patients once the site is up and running. For that reason, the site will have a web-based form so users can comment on the utility of the database. We look forward to using this feedback to improve the site over the coming months.

Finally, PhRMA believes a database will be most useful if it is administered in partnership with or by an independent third-party. We thus plan to explore the possibility of partnering with an independent group to actually administer the database. Because we are committed to establishing a database as quickly as possible, however, we do not intend to wait for a third party before initiating the program. On the contrary, we plan to establish the database, at least initially, as a PhRMA project to ensure it is up and running and available to practicing physicians in a timely manner. We will then seek to transition the program once an appropriate partner or independent third party has been identified.

PhRMA also believes that the need for rapid deployment of a database counsels against government involvement at this time. For instance, the registry authorized by Section 113 of FDAMA was not fully implemented by the National Library of Medicine until nearly five years after passage of the authorizing legislation. We do not believe it is in anybody's interest to delay implementation of a results database in a similar fashion.

PhRMA is taking a leadership role on this issue and plans to have its Clinical Study Results Database operational and available for public use on October 1, 2004. However, we realize that this is no small undertaking and expect that it may take up to a year before all relevant information is incorporated, especially clinical study information from complex multi-national phase IV studies.

In sum, PhRMA and its member companies are firmly committed to the value of transparency of clinical trial information. We are excited about our initiative to es-

tablish the Clinical Study Results Database and anticipate rapid progress in the coming weeks. We would also be pleased to keep this subcommittee updated on its progress.

Thank you for this opportunity to inform the subcommittee about PhRMA's activities in this critical public health area.

Mr. WALDEN. Thank you, Dr. Loew.

Dr. Gorman.

While that buzzer is going off, what we're going to do is take your testimony, recess, and then we're going to go vote and come back for at least one round of questions before heading to the airports.

Thank you.

TESTIMONY OF RICHARD GORMAN

Mr. GORMAN. Mr. Chairman, members of the committee, I am Richard Gorman, a practicing pediatrician for over 20 years. I am pleased to be here on behalf of the American Academy of Pediatrics which represents 60,000 pediatricians nationwide. My testimony has also been endorsed by several pediatric academic societies.

I want to thank all the members of the Energy and Commerce Committee on behalf of the Academy and especially Representatives Jim Greenwood, Henry Waxman and Mike Bilirakis for their exceptional efforts, leadership and support of legislation that has advanced children's health.

In my practice, I am able to better care for my young patients because of the passage of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

The American Academy of Pediatrics is pleased to testify today about the publication and disclosure of clinical trial findings. Over the last several years, the Academy has been a champion for disseminating information gained through pediatric clinical drug trials and has strongly supported these efforts as they relate to all medications, not just anti-depressants.

This important issue is neither simple, nor easy to navigate and we want to thank you for beginning now to engage the medical community, pharmaceutical manufacturers, researchers, scientific journal editors, policymakers and other stakeholders in this open, thoughtful discussion with a goal of constructing constructive solutions.

I'd like to focus my remarks on three major points. First, there are models for disseminating clinical trial information already in use. In 2002, the Best Pharmaceuticals for Children law established a mechanism to provide a public summary of clinical and medical information gathered through the clinical trial medications. An example of one of these summaries is attached to my written testimony.

This information is intended to complement the label information by providing pediatricians and other health professionals with clinically significant findings from trials. This information is available for physicians to review, but is not necessarily included in the label. For an example, if Effexor is approved in adults for the treatment of major depressive disorders and generalized anxiety disorder, the pediatric section for Effexor reads simply that safety and effectiveness in individuals under 18 has not been established. Pediatric studies were conducted and the FDA clinical review of

Effexor is available on the FDA website. The clinical summary states that Effexor failed to demonstrate effectiveness for the treatment of major depressive disorder and generalized anxiety disorder for 6 to 17-year-olds.

Under the present legal and regulatory structure, the Food and Drug Administration recommended not including this demonstrated lack of pediatric efficacy in a positive way on the label, despite the accuracy of the label statement, not demonstrates safe and effective. The availability of important information for both clinicians and parents was not widely appreciated. The availability of this critical clinical information is a new phenomena which is only available in a limited way for clinical trials conducted under BPCA.

These clinical summaries provided as a result of BPCA may be used as a model for the development of a dissemination tool for all clinical trial data that are determined to have important clinical findings.

Second, we need to determine the scope of clinical trial reporting. While there presently seems to be compelling reasons to focus on medications related to the treatment of mental illness, there is limited scientific rationale as to why medications for this class of conditions should be highlighted over other medications in developing a national response to prevent subsequent miscommunication about clinical drug trial results.

The need to publish and disclose findings from clinical trials is not limited to a particular drug, a particular age group or any specific medical therapy.

Last, solutions require thoughtful and thorough review of both the needs and barriers to this dissemination. It is critical that we give careful consideration to the developments of a means to review and summarize in an impartial and accurate way, the extensive clinical trial data. We need to develop a system of dissemination of this information in a format that can be readily understood by the average U.S. citizen as well as the medical community.

Let me conclude by saying it is not an issue of if there is a need to provide health care professionals and patients appropriate information about clinical findings. Rather, it is a matter of how and when this information is to be provided. Existing models such as pediatric clinical trial summaries within the Best Pharmaceuticals for Children Act may help shape this process. The AAP and pediatric societies stand ready too and expect to be called upon to provide their expertise and to participate in this process.

Thank you, Mr. Chairman.

[The prepared statement of Richard Gorman follows:]

PREPARED STATEMENT OF RICHARD GORMAN FOR THE AMERICAN ACADEMY OF PEDIATRICS

Mr. Chairman, members of the Committee, I am Richard Gorman, MD, FAAP, a practicing pediatrician who has taken care of infants, children and adolescents for over 26 years. I am pleased to be here on behalf of the American Academy of Pediatrics (AAP), which represents 60,000 pediatricians nationwide.

Though I am a Clinical Associate Professor of Pediatrics at the University of Maryland School of Medicine, and chair of the AAP Committee on Drugs, it is in my practice, Pediatric Partners in Ellicott City, Maryland, that I see first-hand the need for appropriately studied and approved medicines for children. I can also say with a sense of pride that through the efforts of the Congress, the Administration, and the Academy and pediatric societies, I am able to provide better care to my

young patients because of the passage of important pediatric-focused legislation such as the Best Pharmaceuticals for Children Act (BPCA-Pub. Law 105-155) and most recently the Pediatric Research Equity Act (PREA-Pub. Law 108-155). With over 80,000 pediatric visits annually in the five clinical sites in four counties in Maryland, my partners and I can attest to the importance of having information available regarding safe and effective pediatric drug dosing.

This testimony is also endorsed by the pediatric academic research community that includes the Ambulatory Pediatric Association, American Pediatric Society, Association of Medical School Pediatric Department Chairs and the Society for Pediatric Research also supports and endorses the Academy's testimony. These societies comprise academic general pediatricians, pediatric researchers, and full time academic and clinical faculty responsible for the delivery of health care services to children, the education and training of pediatricians, and the leadership of medical school pediatric departments.

Before I begin my formal testimony, I want to thank the Energy and Commerce Committee on behalf of the American Academy of Pediatrics and the pediatric academic societies for its leadership and support of legislation that advances children's health—particularly pediatric therapeutic issues. This hearing is yet another example of the Committee's strong desire to ensure that infants, children and adolescents are not an afterthought when it comes to clinical studies that may affect the health and wellbeing of our citizens. I would be remiss if I didn't also thank Representatives Jim Greenwood, Henry Waxman, Mike Bilirakis and the other members of the Subcommittee for their efforts on behalf of children.

The issue of today's hearing "Publication and Disclosure Issues in Anti-Depressant Pediatric Clinical Trials," is both timely and complex. Over the last several years, the AAP has been a champion for disseminating information gained through pediatric clinical drug trials and has strongly supported these efforts as they relate to all medications, not only anti-depressants.

The recent media attention regarding allegedly suppressed negative study results related to antidepressant use in children is just the latest volley on the issue of pediatric use of psychotropic medications. While the New York Attorney General's lawsuit against GlaxoSmithKline, the makers of Paxil, may be an appropriate trigger to action, the AAP and pediatric societies urge that the response by policymakers, whether in the public or private sectors, not be simply reactive but rather thoughtful and comprehensive.

This committee should be commended for their efforts to explore the publication and disclosure of pediatric clinical trial findings. However, the AAP and pediatric societies respectfully caution that this important issue is neither simple nor easy to navigate. Acknowledging the degree of difficulty must not be interpreted as a desire to avoid or delay addressing this issue. Rather, it is a plea that efforts begin NOW to engage the medical community, pharmaceutical manufacturers, researchers, scientific journals, policymakers and other stakeholders in an open, thoughtful, thorough discussion with the goal of developing constructive solutions to this vexing problem.

Let me propose an analogy: publication and disclosure of anti-depressant pediatric clinical trails is a small tip of an iceberg visible above the water line, giving warning to great danger lurking nearby—if we responded by simply addressing drug trials of antidepressants it would be comparable to removing only the tip of the iceberg—thereby obscuring the rest of the iceberg and increasing the overall danger.

I would like to address several issues during my testimony.

- The need to disseminate pediatric findings of information is one of great importance to the pediatric community. Some progress has begun through the dissemination of information provision within the Best Pharmaceuticals for Children Act, but more is needed;
- The need to publish and disclose findings from clinical trials is not limited to a particular class of drugs or to just infants, children and adolescents. In fact, it is not limited to drugs, as the same concerns apply to clinical trials focused on other non-pharmacological therapies—but for practical reasons the AAP suggests that the initial efforts to create a clinical trial registry center on medication trials;
- The issues surrounding the need to publish and disclose all sentinel clinical trial findings are compelling and complex. Solutions require thoughtful and thorough review of the needs and barriers. It is critical that we give careful thought to the development of the means to summarize and review with accuracy the extensive trial data and results, and develop a system for dissemination of this information in a format that can be readily understood by the average U.S. citizen as well as the medical community.

Disseminating Pediatric Clinical Trial Information:

There currently exists a mechanism to provide a public summary of clinical and medical information gathered through pediatric clinical trials of medications—the "Dissemination of Information" provision within the Best Pharmaceuticals for Children law (Pub Law 105-115). The AAP was a catalyst for inclusion of this provision in BPCA.

Congress acknowledged that timely dissemination of information to pediatricians, health care practitioners, and the public about findings in the pediatric studies is critical to ensuring that infants, children, adolescents and their caregivers have appropriate information about the medications available for their use. Dissemination of information is intended to not only complement the label information by providing pediatricians and other health professionals with significant clinical findings that are necessary for pediatricians and physicians to review but which may not be included in the label.

The intention of the law is to make important information available to pediatricians and other health professionals within 6 months of submission of a report on a pediatric study, while ensuring that confidential and commercial trade secrets are not revealed through the summary process. These clinical and medical summaries are available on the pediatric page of the Food and Drug Administration web site. As an attachment to my testimony, I have included a copy of the pediatric Clinical Review of Effexor (venlafaxine) used for major depressive disorders (MDD) to illustrate the concise and useful information included in the summaries.

These pediatric clinical summaries are an important starting point. They currently focus on a narrow but important segment of pediatric clinical studies and may be used as a model for the development of a dissemination tool for all clinical trial data that is determined to have important clinical findings.

Determining the Scope of Clinical Trial Reporting:

Science must drive the process to define clinical trial reporting. Media attention, legal filings or isolated incidents should not dictate the availability or dissemination of the results of clinical trials. While there are compelling reasons to focus on medications related to the treatment of mental illness at this particular moment, given recent events, there is limited scientific rationale as to why medications for this class of conditions

should be highlighted over other medications in developing a national response to prevent subsequent miscommunication about clinical drug trial results. Unfortunately, limited access to clinical drug trial data has long had an impact on the choice and use of all classes of drugs—antidepressant use in children is only one recent example. We therefore strongly encourage the inclusion of ALL classes of medications within any registry or monitoring system that is developed as a result of this effort.

In addition, there is a need to define the kind of clinical trials that will be considered. Thus far, the discussions have focused on drug/medication trials; however, clinical trials include a great deal more than just drug/medication trials. Including all clinical trials (e.g., research related to human subjects; surgical, pharmacological, and non-pharmacological interventions; devices, etc.) may prove to be unwieldy to track in one database.

We anticipate that the effort required to develop a safe and effective clinical drug trial registry will be extensive and therefore recommend that the focus, at least initially, be on clinical drug trials. Clinical drug approvals are already overseen by one federal agency—the Food and Drug Administration (FDA)—and this may help facilitate the development of a single, centralized drug trial registry. The success (and challenges) of this registry can inform the later development of comparable efforts to promote broader access to clinical trials of non-pharmacological interventions.

Publication and Disclosure of Clinical Trial Data: Understanding the Challenges/Identifying Possible Solutions:

There is a need to define the scope of the challenges related to publishing and disclosing clinical trial data in order to best address them. A series of questions helps illustrate the information necessary in order to determine the best course of action: How are clinical trials being defined (e.g., just for medications or for non-pharmacological interventions as well)? Will the information released be peer reviewed (if not, who will review the data and at what time during the clinical trial)? How will the information be distilled and updated (e.g., summaries, full release of unfiltered trial results, etc.)? How are "negative studies" being defined? Who is the audience for these trial results (e.g., physicians, patients, researchers, etc.)? What is the intended outcome for releasing the clinical trials data (e.g., improved patient

care, legal pursuits, etc)? What might be the unintended consequences of well-intentioned policies?

A number of proposals have been raised. Each comes with potential benefits but must be carefully examined within the context of potential issues. Proposals include:

Review of Clinical Trial Findings: There are considerable concerns that non-published studies which have not undergone peer review (or for that matter, any review) may be included in a database that will be easily accessible by the general population and will contain insufficient information by which to judge a study's validity. Examples include:

- Medications have the FDA for oversight, but there is little to prevent a company or individual from posting "results" of their independent research that demonstrates the benefit of a completely non-efficacious or potentially harmful intervention (with claims based on seriously flawed research).
- Through the media and advertising industry there are many claims of product or intervention efficacy that are likely based on research that would not be judged as supported if subjected to the peer review process of professional journals (e.g., dietary supplements, some non-evidence-based mental health interventions, non-pharmacological diet or pain "treatments" to name just a few).
- Inclusion of a disclaimer that a study did not undergo "peer-review" will not likely have sufficient impact, especially if the study is posted on a government website along with the best of scientific studies. The general population may likely view the study as having more credibility, irrespective of any disclaimers.

Clinical Trial Registries and Databases: A central clinical trial registry or database for clinical trial information would go a long way towards addressing concerns about a lack of awareness outside the scientific community of the full nature, scope, and results of clinical trials.

One of the most frequently-cited rationales for registries is that such a database would lead to a decrease in reporting bias—the tendency of scientists to publish only those studies yielding positive results. However, this may not necessarily be the case. If all results, including negative ones, are available in a registry, then it is quite possible that the prevalence of positive studies reported in peer-reviewed journals might actually increase, since the negative studies will have already been disclosed elsewhere (and possibly in a relatively cursory manner).

There are many other concerns that must be addressed on this issue of a registry, including what entity will administer it and how compliance will be enforced, how the raw data will be filtered and presented in a way to allow those outside the scientific community to interpret it, concerns of industry over the disclosure of proprietary information, etc.

Clearly it is imperative that any effort to establish or expand clinical trial registries be well considered and thoughtful, as well as taken at a reasonable pace.

Conclusion and Recommendations

It is not an issue of IF there is a need to provide health care professionals and patients appropriate information about clinical trials findings. Rather it is a matter of HOW the information is provided. It is no simple task to develop an appropriate mechanism but there are existing models such as the pediatric clinical trials summaries within the Best Pharmaceuticals for Children Act that may help shape the process.

The AAP and pediatric academic societies propose the following initial recommendations:

- We urge Congress to broaden their investigation to include all medications, rather than simply anti-depressants. In addition, it is necessary to include all populations and ages in order to best improve patient care.
- While concerns related to publication and disclosure of clinical trial findings are not limited to medications, it may be necessary to begin with that therapy as an incremental step.
- Thoughtful and deliberative assessment of how data collection and registries are developed is essential.— The role of peer-review of studies must be thoroughly explored. The AAP urges the medical community, pharmaceutical manufacturers, scientific journals, policy makers, researchers and other stakeholders to work together to identify the scope of the problems and develop appropriate solutions. We must work with deliberate speed but must also ensure that the solutions adequately address the problem and do not, in fact, cause even more problems.

On behalf of the American Academy of Pediatrics and the pediatric academic societies, thank you for the opportunity to testify on this important issue. We offer our assistance and expertise to the Congress and other stakeholders as this important discussion continues.

CLINICAL REVIEW

Executive Summary Section

Clinical Review for NDA 20-151 Supplement SE5-024

Non-Approval Action for Pediatric Supplement for Effexor XR; negative results for Effexor XR in the treatment of Major Depressive Disorder (MDD and negative trial in Effexor XR in the treatment of Generalized Anxiety Disorder) in pediatric patients

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The original supplement for the expanded indications of the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in children and adolescents was submitted September 25, 2002 as Supplement SE5-024 to NDA 20-151. Two of two studies of MDD failed to provide evidence of efficacy over placebo. Only one of two studies provided convincing evidence of efficacy over placebo in the treatment of GAD. It is my view that none of the efficacy results of this negative program for venlafaxine in pediatric MDD and GAD should be noted in labeling. However, there are safety findings of decreased weight gain and growth with venlafaxine use in this pediatric sample and I recommend that they should be added to labeling.

I recommend that the sponsor pool the four, 8-week, placebo controlled studies of MDD and GAD combined and look at the mean changes in weight and height in the venlafaxine treated patients versus the placebo treated patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Effexor and Effexor XR are combination serotonin and norepinephrine reuptake inhibitors that are approved for the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in adults. This supplement was submitted in support of pediatric labeling for Effexor XR in the treatment of MDD and GAD. This supplement presents the results of four studies: two studies in support of a claim for GAD and two in support of a claim for MDD. The MDD studies individually fail to provide evidence that Effexor XR is effective in the treatment of MDD in pediatric patients. Although one of two clinical trials did not individually support the efficacy of Effexor XR in the treatment of GAD, the sponsor proposed that the indication might be approved on the basis of one study.

It should also be noted that the sponsor had sought pediatric exclusivity for this program under FDAMA, and they are given 6 months of additional exclusivity based on the fact that they conducted the studies required under the Written Request. The Written Request stipulated that two positive studies were required to support a claim for MDD and GAD.

Since the proposal was to use the currently approved Effexor XR formulations for this expanded population, there was no need for chemistry or pharmacology reviews. Glenn Mannheim, MD did the primary review of the clinical efficacy and safety data from the clinical group. Fanhui Kong, PhD, from biometrics, also reviewed the efficacy data. Ron Kavanagh, PhD, reviewed the pediatric pharmacokinetic data.

There are two pharmacokinetic studies of venlafaxine in the pediatric population; one is done with the IR formulation (126-US) and one is done with the ER formulation (169-US). 126-US was a multiple dose study and 169-US was a single dose PK study. Dr Kavanagh pointed out that dose normalized AUCs are lower in adolescents than in adults and even lower in preadolescents and younger children. Therefore, Dr. Kavanagh concluded that children, depending on age, might need a 2-4 fold higher dose on a mg/kg/basis as compared to adults. Adolescents needed only a slightly higher mg/kg/dose as compared to adults to achieve equivalent exposures (with the caveat that the exposures to the active metabolites, NDV and NODV, were not considered). However, because effectiveness has not been demonstrated, we will not add pharmacokinetic data for pediatric patients to labeling.

B. Efficacy

Summary of Studies of MDD

Two, 8-week, multi-center parallel group randomized, double blind, placebo controlled flexible dose studies did not provide any evidence of venlafaxine's efficacy in the treatment of MDD in children. These studies employed doses ranging from 37.5 to 225-mg/day. They were adequately powered studies with 161 (103 completing) patients in study 382 and 193 patients (143 completing) in study 394. There were no differences between placebo and drug treatment groups at week eight (8) via the last-observation-carried-forward (LOCF) on-therapy evaluation (382: P=0.338; 394: P=0.386).

Summary of Studies of GAD

The sponsor submitted the results of two 8-week, double blind, placebo controlled, parallel group, flexible dose studies of children aged 6-17 years. Effexor XR demonstrated efficacy in only one of two studies (397-US).

Study 396-US did not separate Effexor XR treatment from placebo at any time point. The following table (Table 9.4.1A) from the sponsor's report shows that there was no time point at which the two treatment groups were significantly different. This difference from study 397-US is difficult to explain. Potential explanations for study failure such as differences in mean ages, placebo responses, drop-out rates, and mean daily doses, were nearly identical across the studies. In the end, drug effect was markedly different between the two studies with a mean adjusted venlafaxine change from baseline in 396-US of -15.5 and in 397-US of -18.7. Treatment separation from placebo was statistically significant starting at week 2 in study 397-US and generally speaking became stronger over the duration of the study. This was not the case in Study 396-US.

Study 396-US Primary Efficacy Variable Analysis Summary

TABLE 9.4.1A. COMPARISON BETWEEN TREATMENT GROUPS FOR C-KIDDIE-SADS GAD 9 DELINEATED ITEMS (INTENT-TO-TREAT PATIENTS) - LOCF ANALYSIS

Week on-therapy	Therapy Group	Number of Patients	Mean Score	Change From Baseline	Adj Change From Baseline	Standard Error	Adj Means (95% CI)	Placebo Minus Ven ER Adj Means (95% CI)	p-Values F-test
Baseline	Placebo	82	39.7				39.5 (39.5,39.5)		
	Venlafaxine ER	78	39.3				39.5 (39.5,39.5)		
Week 1	Placebo	81	35.2	-4.4	-4	0.8	35.5 (34.0,37.0)		0.276
	Venlafaxine ER	74	34.6	-4.7	-5	0.8	34.5 (33.0,36.0)	1.0 (-0.8,2.9)	
Week 2	Placebo	82	31.2	-8.4	-7.9	1.01	31.6 (29.6,33.6)		0.486
	Venlafaxine ER	77	30.4	-8.9	-8.8	1	30.7 (28.8,32.7)	0.9 (-1.6,3.3)	
Week 3	Placebo	82	29.9	-9.8	-9.1	1.06	30.3 (28.1,32.5)		0.257
	Venlafaxine ER	78	28.1	-11.2	-10.7	1.04	28.8 (26.7,30.9)	1.5 (-1.1,4.2)	
Week 4	Placebo	82	29.6	-10.1	-9.6	1.03	29.9 (27.7,32.1)		0.088
	Venlafaxine ER	78	27.2	-12.1	-11.9	1.04	27.6 (25.5,29.7)	2.3 (-0.3,5.0)	
Week 5	Placebo	82	28.6	-11.1	-11.8	1.11	27.7 (25.3,30.1)		0.180
	Venlafaxine ER	78	25.6	-13.6	-13.8	1.18	25.7 (23.4,28.0)	2.0 (-0.9,4.9)	
Week 7	Placebo	82	26	-13.7	-13.9	1.2	25.6 (23.1,28.1)		0.342
	Venlafaxine ER	78	23.7	-15.6	-15.3	1.16	24.2 (21.8,26.6)	1.5 (-1.5,4.5)	
Week 8	Placebo	82	25.7	-13	-12.6	1.17	26.9 (24.4,29.4)		0.050
	Venlafaxine ER	78	23.5	-15.8	-15.5	1.12	24.0 (21.6,26.4)	2.9 (-0.1,5.9)	
Final	Placebo	82	26.8	-12.9	-12.7	1.17	26.8 (24.3,29.3)		0.075
	Venlafaxine ER	78	23.6	-15.7	-15.5	1.12	24.0 (21.6,26.4)	2.8 (-0.2,5.8)	

Study 397-US Primary Efficacy Variable Analysis Summary

TABLE 9.4.1A COMPARISON BETWEEN TREATMENT GROUPS FOR C-KIDDIE-SADS GAD TOTAL (9 DELINEATED ITEMS)
LOCF ANALYSIS

Time on Therapy	Therapy Group	Number of Patients	Mean Score	Adj. Change From Baseline	Standard Error	Adj Means (95% CI)		Placebo Minus Ven ER Adj. Means	p-Value F-test
Baseline	Placebo	77	40.3			40.4	(40.4 - 40.4)		
	Ven-ER	76	40.4			40.4	(40.4 - 40.4)		
Week 1	Placebo	74	36.1	-6.8	0.86	33.5	(31.8 - 35.1)		.683
	Ven-ER	76	35.7	-7.2	0.87	33.1	(31.6 - 34.6)	0.4 (-1.4 - 2.1)	
Week 2	Placebo	77	34.9	-7.1	0.91	33.3	(31.3 - 35.3)		.021
	Ven-ER	76	32.7	-9.8	1.02	30.6	(28.6 - 32.5)	2.7 (0.4 - 5.0)	
Week 3	Placebo	77	32.8	-10.3	1.02	30.1	(27.8 - 32.3)		.005
	Ven-ER	76	29.9	-13.9	1.08	26.4	(24.2 - 28.6)	3.7 (1.1 - 6.2)	
Week 4	Placebo	77	31.7	-12.0	0.93	28.4	(25.9 - 30.8)		.009
	Ven-ER	76	28.3	-15.7	1.19	24.7	(22.3 - 27.0)	3.7 (1.0 - 6.4)	
Week 5	Placebo	77	30.3	-13.0	1.12	27.3	(24.8 - 29.8)		.007
	Ven-ER	76	27.1	-17.0	1.15	23.4	(20.9 - 25.8)	4.0 (1.1 - 6.8)	
Week 7	Placebo	77	30.0	-12.7	1.02	27.7	(25.0 - 30.4)		.002
	Ven-ER	76	25.7	-17.5	1.12	22.8	(20.2 - 25.4)	4.8 (1.8 - 7.9)	
Week 8	Placebo	77	30.2	-12.4	1.18	28.0	(25.1 - 30.8)		< 001
	Ven-ER	76	24.8	-18.6	1.16	21.7	(19.0 - 24.3)	6.2 (3.0 - 9.5)	
Final	Placebo	77	30.2	-12.5	1.19	27.9	(25.1 - 30.7)		< 001
	Ven-ER	76	24.8	-18.7	1.16	21.7	(18.9 - 24.4)	6.2 (3.0 - 9.4)	

Abbreviations: C-KIDDIE-SADS GAD = Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia; LOCF = last observation carried forward; Ven ER = venlafaxine extended release.
EFF397.lst 26 Mar 2002

Conclusions Regarding Efficacy Data

Given the pediatric PK data, under dosing is a tempting hypothesis to entertain for the reason of the failure of study 396-US in GAD; however, the mean age and mean mg/kg dose across studies 396-US and 397-US are nearly identical. This therefore argues against under dosing alone as an explanation for this inconsistency.

Under dosing likewise is probably not the most likely explanation for the failure of the MDD pediatric studies with Effexor XR. Development programs for MDD in children with the exception of fluoxetine are failing even with adequate dosing. This is not the case with OCD. This is even more mysterious given that in adults only about half the doses of SSRIs that are required to treat Panic, OCD and Social Phobia are necessary to treat MDD.

There are no drugs approved for the treatment of GAD in children. Therefore, it is difficult to say whether or not the treatment response of pediatric patients with GAD will behave more like OCD or MDD. In the tricyclic antidepressant (TCA) era, off-label use of TCAs in the treatment of panic disorder was common but there did not seem to be much utility in using these drugs for GAD. OCD did not respond to TCAs in general with the one exception being clomipramine.

Most people would not have predicted the lack of efficacy of SSRI (and now venlafaxine) antidepressant treatments in children given the experience in adults. This lack of predictability and the historical lack of uniformity in treatment response across the anxiety disorders as a group leads me not to endorse the approval of a pediatric indication for GAD based on one positive study and positive results in adults. Though ultimately with experience it may prove to be sufficient evidence for efficacy, there is not enough experience at this point with GAD for me to come to that conclusion.

C. Safety

The pediatric safety of venlafaxine was explored in four placebo controlled 8-week studies (two in MDD and Two in GAD) and one open label extension study of MDD. One other 6-week phase I-II study of Conduct disorder (Study 126) was included in the sponsor's review of the safety. Thus 339 patients were exposed to Effexor XR in the four 8-week placebo controlled studies and 86 MDD patients received Effexor XR for up to 6-months. This represents 52.2 patient-years of exposure in patients with MDD and GAD.

The safety profile of venlafaxine ER in children and adolescents appears to be generally comparable to the safety profile in adults with some differences. The mean increase from baseline in the total serum cholesterol was higher than adults in the pooled GAD, but, not in the pooled MDD trials. A slightly higher mean pulse rate and ECG heart rate in children and adolescents than in adults was seen. Increases in blood pressure in children were of similar magnitude with adults.

In the pediatric population, a smaller increase in height in children in the pooled GAD studies versus placebo was noted. This was not noted in the MDD group; however, it is surprising that this was noted at all in an 8-week study period. Though height was significantly increased from baseline after 8 weeks of treatment for both venlafaxine ER- treated and placebo- treated patients, the adjusted mean increase at month 2 in the placebo group (1.3 cm) was significantly greater than the venlafaxine ER group (0.4 cm). Mean height in the long term open label treated patients only increased 1.2-cm over 6-months.

Both MDD and GAD patients treated with venlafaxine had mean decreases in weight. The mean weight losses were 0.5 kg (MDD) and 0.6 kg (GAD) over an 8-week period while there was a mean weight gain in the placebo treated MDD and GAD patients. Weight changes in both MDD and GAD patients were statistically significant.

SUPPLEMENTAL NEW DRUG APPLICATION – PEDIATRIC INDICATIONS *BPCA SUMMARY REVIEW* *OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS*			
NDAs:	20-151	20-699	
SLRs:	024	030	
Drug: **[Brand / Generic]**	Effexor Tablets (Venlafaxine HCl)	Effexor XR Extended Release Capsules (Venlafaxine HCl)	
Sponsor:	Wyeth-Ayerst Philadelphia, PA	**Correspondence Date:**	September 25, 2002

1 EXECUTIVE SUMMARY

1.1 RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-1) has reviewed NDA 20-699 S-029 submitted September 25, 2002, and finds the sponsor's submission acceptable.

1.2 PHASE IV COMMITMENTS

No phase IV commitments are requested.

2 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The sponsor has applied for approval of the indication of General Anxiety Disorder in pediatric patients (GAD).

The efficacy studies for GAD were conducted with the ER formulation, whereas the initial pediatric pharmacokinetic studies were performed using the IR tablet formulation. Upon review of materials in a pre-NDA package OCPB requested a pediatric pharmacokinetic study with the ER formulation to assess if absorption of venlafaxine from an extended release formulation would be truncated before the end of the dosage interval. Collection of both of urine and feces was suggested to determine the fraction of the dose absorbed. In addition, since the youngest patients are most at risk for truncated absorption, and since the weight range in the protocols effectively excluded subjects less than 8 years old, the sponsor was requested to modify the weight range. In addition, and the sponsor was requested to study a minimum of 4 subjects in each of the following age brackets: 6 - 7 years old, 8 - 11 years old, and 12 - 17 years old.

The data submitted was sufficient to answer the most pertinent clinical pharmacology questions and the submission is therefore acceptable.

Results of the pharmacokinetic studies suggest that exposure to venlafaxine is slightly lower in adolescents as compared to adults when dosed at the same mg/kg dose. Whereas when children are given the same mg/kg dose, exposures drop sharply as age declines in preadolescents. The data with the ER formulation suggests that preadolescent children may need a much higher mg/kg dose as compared to adults. Inspection of the pharmacokinetic data suggests that pediatric patients may have been under-dosed in the pivotal efficacy studies.

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/s/

Russell Katz
3/21/03 02:02:43 PM

Mr. WALDEN. Thank you, Doctor, for your testimony. I'm going to recess the committee at this point. We'll go over and cast the two votes that we have. We should be back here no later than 6:30. And we'll reconvene for some questions and then we'll wrap it up for a really long day. Thank you. We're in recess.

[Off the record.]

Mr. WALDEN. I'm going to call the subcommittee back to order. Again, I want to thank our witnesses for putting in a pretty long day.

There are several questions I'd like to ask for the record and Mr. Allen who will not be able to rejoin us, apparently, did want to make sure we kept the record open for written questions for committee members who obviously aren't able to be with us any longer tonight.

My first question really gets at an issue that has troubled me a bit and maybe this is standard practice and I'm just learning about it, but Dr. Davis, can you talk to me about doctors prescribing drugs for children that have not been approved on the label for the uses by the FDA? I mean the top four anti-depressant drugs given to children all have not been approved for use as an anti-depressants. You can see tab 69, I'm at page 13.

And I figured that things weren't prescribed that weren't—didn't go through clinical trials and weren't designed for that use and yet, when you look at the data, I mean in some respects, poor old Prozac is out there, the one that has gone through clinical trials and been approved for this use and it's not even one of the top, what, two or three—it's No. 4 in line. It's No. 5 behind four drugs and I'm not picking favorites here at all, but it just seems peculiar to me that you have one that actually has been through clinical trials and shows some effectiveness in anti-depressant treatment for youth and yet, members of your profession or perhaps yours, Dr. Gorman, are prescribing four others in greater quantities.

How does that happen? Is it a problem, something we need to be concerned about?

Mr. DAVIS. This gets at the whole issue of off-label indications for medications and our position at the American Medical Association is that physicians should have the right to prescribe an FDA-approved drug or a medical device for an unlabeled indication when such use is based on sound, scientific evidence and sound medical opinion. In many cases, a physician is faced with a patient with a serious or even life-threatening condition. Other treatments may have already been tried and perhaps are no longer working, but this physician may have reason to believe that this medication, even though we're talking about an off-label indication may help in this patient who is in my office today. That reason may be based on the mechanism of action of that drug. Maybe it is known to be effective in a similar illness, but it has not get been proven to be effective in this particular illness. Or maybe it works in one population group. We have not proven that it is effective in another population group.

So when you have to make the decision facing an individual patient with a dearth of information for reasons that we've discussed, when no other treatments are available, that's a situation when off-label prescribing may be done.

Mr. WALDEN. So let's go to this issue a bit more because when you talk about, when it's backed up by sound science and yet the sound scientific evidence that may be out there isn't necessarily required to be out there or you can—professionals can access it. We found that out. Some of that sound, scientific evidence that has been done shows sugar pills may be almost as effective or more so. And most troubling, I think, is apparent, is when you look at the data put together by Dr. Mosholder, backed up by Columbia University just in this specific category of drugs, anti-depressants used to treat pediatric depression. There may be a fairly significant increase in suicidal tendencies or thought or ideas. All that science is out there and yet we're seeing fairly substantial rise in pediatric prescriptions for anti-depressants, SSRIs. Show me the evidence that says (a) it's effective; (b) it's not dangerous.

Mr. DAVIS. Dr. Gorman may want to speak to this in a minute, but we were talking about this during the recess, but let me just make this point. You might ask why is a physician prescribing Zoloft for depression in a teenager instead of Prozac. And it may be that a patient was prescribed Prozac and the depression is getting worse and so the physician wants to try another medication and there is no other labeled medication for that usage. Or it may be, and Dr. Gorman may speak to this, it may be that a physician, say a family physician who treats depression in adults and children is used to prescribing Zoloft, is familiar with that medication, treats many adults with that medication and then he sees a 17-year-old with depression and he's asking himself is there any reason why this medication should be good for an 18-year-old and not good for a 17-year-old? Is depression different in a 17-year-old versus an 18-year-old?

Mr. WALDEN. But the drug interaction may be different, right, according to the clinical trials?

Mr. DAVIS. That's possible, although you could have a patient who is not on another medication. I'm just saying as a hypothetical.

Mr. WALDEN. No, I know, but when you get into it that's possible. In fact, the data we have before us shows that is indeed the case. The FDA has said these aren't clinically——

Mr. DAVIS. But just a hypothetical situation might be an 18-year-old with no other medication, a 17-year-old, no other medication. Biologically, if it works for an 18-year-old, it should work for a 17-year-old.

Mr. WALDEN. Right. Dr. Gorman?

Mr. GORMAN. If I can follow up on that just a little, pediatricians are trained to use drugs off-label because that's the situation we've been in since the beginning of pediatrics.

Until recently, and including today, 75 percent of all drugs that come through the Food and Drug Administration, are not studied in or approved for use in children.

Mr. WALDEN. What percentage?

Mr. GORMAN. Seventy-five percent.

Mr. WALDEN. Wow.

Mr. GORMAN. Now, so in our training we're told to look at mechanisms of action and whether or not we believe that the pathophysiology of the disease, the cause of the disease is the same in adults and children and then we're asked to extrapolate.

Mr. WALDEN. So I guess for both of you then, it seems pretty obvious to me, but do you think your members would want more information on anti-depressants beyond what's on the label?

Mr. GORMAN. Now only do we want more information, we're thankful that this group and the American Congress has enacted legislation recently that makes the data that we're discussing today available not only to the pediatricians, the practitioners, but also to the American public.

Mr. WALDEN. You know, as we've kind of looked into this, it appears there are publications that describe clinical trial results in ways that are perhaps more flattering than the FDA would. There are references on posters at your conventions that describe some of these drugs in more flattering ways than perhaps the clinical trials on close peer review might describe them. Do you find that or am I missing something here?

Mr. GORMAN. Everyone gets excited about positive results because it gives you a possible way to treat people you have very few options for. There's an old saying in medicine, that you should always use the miracle drugs before they become less miraculous. So——

Mr. WALDEN. I thought it was "first do no harm."

Mr. GORMAN. Well, no, that's part of the oath we take.

Mr. WALDEN. Oh, okay.

Mr. GORMAN. But what happens is is that positive results are spread more rapidly by the pharmaceutical companies and they're more interesting to clinicians to listen to than negative results.

Mr. WALDEN. And I guess, at least me, I won't speak for the committee, but what I'm trying to get at is to make sure that the information you get is both sides and if there is information out there that shows there may be no effect, that people aren't being asked to waste their money on drugs that show no effect or if there's potentially a downside in the sense of some of these disturbing studies that would indicate that perhaps additional suicidal thoughts or actions, that your folks are made aware of that rapidly.

Mr. GORMAN. The research that was performed because of the Best Pharmaceuticals for Children Act resulted in exclusivity for these, gave us the information that there's perhaps no efficacy and perhaps a strong safety signal that these drugs are dangerous to use in children. This is exactly the information that we wanted to be made available.

Mr. WALDEN. But yet, I want to go back because I'm trying to remember which company it was that had the label, is that Glaxo? Wyeth. Wyeth tried to put on additional information saying watch for hostility in kids and potential suicide issues. I assume you were here for that testimony as well.

Does that bother you that they were basically told by the FDA to back off that direct comment?

Mr. DAVIS. I agree with your question a few moments ago, do physicians want more information about possible side effects and I would say absolutely yes.

Mr. WALDEN. I would think so. It's your nature.

Mr. DAVIS. We have long-standing policy at the AMA, this is again, getting into the issue of off-label use of drugs. We have a long-standing policy pointing out the important need for physicians

to have access to accurate and unbiased information about unlabeled uses of drugs and devices, while ensuring that manufacturer-sponsored promotions remain under FDA regulation.

So physicians want and need this information and this gets to our proposal that we've been testifying on today, the need for a single comprehensive registry where information on all clinical trials would be tracked from the very beginning, even before patients would be enrolled in these studies so that we would know which clinical trials have been done. We're talking phase 2 and phase 3 trials, track them all in a publicly accessible data base from before patients were even enrolled, follow up and add the results and then we would have the information we need.

Mr. WALDEN. And that goes beyond what PhRMA is proposing?

Mr. DAVIS. That's right. We're talking about not waiting until results are available, but registering the clinical trials before they begin, before patients are even enrolled and our proposal has an enforcement mechanism saying if you want your IRB approval to start the trial, to enroll patients, you need to be registered in a publicly accessible data base with a unique identifier. That would do three things. It would get around this problem of distorting the scientific literature because we'd know about all the studies that are out there. It would let patients know early on what trials are out there, so that they could get enrolled in one, if they would like, if they have that disease and three, it would allow researchers to know what studies are being done now or are about to be launched so that they could collaborate and avoid duplicating what somebody else might be doing.

Mr. WALDEN. Dr. Gorman, does your organization support that same set of protocols?

Mr. GORMAN. The organization supports them in principle in the sense that that is the goal to which we hope to get to.

Mr. WALDEN. Okay. I guess the question is if the prescribing community is seeking that level of protocols and evaluation of data and availability of data to Dr. Loew then, do you think your proposal at PhRMA goes far enough?

Ms. LOEW. A lot of the discussion that we've heard today, in fact, I would say it would be the majority of the discussion that we've heard has focused on access to information on completed clinical studies for products that are marketed in the United States.

Mr. WALDEN. Although they both said before the completion of the studies, right?

Mr. DAVIS. Before the initiation of the studies, before the enrollment of patients.

Mr. WALDEN. Okay.

Ms. LOEW. What we have established is a data base for companies to post information on completed clinical studies for products that are marketed. Many of the points that have been raised today focus around a lack of centralized access to this information. The fact that it's extremely difficult to publish negative clinical studies, that they often are disclosed at medical meetings, these types of venues which aren't widely open to practicing physicians. Recognizing this problem, this is why we have taken the unprecedented step of establishing this data base.

There are companies that will be posting three different types of information about their products that are on the market in the U.S. The first is they will be publishing a full bibliography of all peer-reviewed clinical studies. So it's a centralized point where physicians can access this information. The second thing is we mustn't lose sight of this. It will provide access to the FDA-approved drug label which should be the primary source of information for prescribing physicians. The third piece of information it will provide is a summary of unpublished clinical study results, something that's been a central point of concern——

Mr. WALDEN. What would you say the objections are to going to the level, Dr. Davis, and I don't want to speak for you, Dr. Gorman, but similarly, I think, agrees. Why wouldn't you go to that level? What's the reason?

Ms. LOEW. In assessment of the situation, we were trying to primarily address, to establish a data base that we thought would be useful to practicing physicians and it would give them access on products that they can, sorry, to give them information to products that they are in a position to prescribe. So we have focused on information on products that are marketed in the United States. As I said in my testimony, the issue of information on on-going clinical trials is a separate problem that I think should be addressed, distinct from this issue. And in fact, there are a large, there are a number of resources already available publicly for information on on-going clinical studies. There are a number of commercial data bases and there is, of course, clinicaltrials.gov and we already know that there are some companies that publish more than the legislated requirement for posting serious and life-threatening trials.

Mr. WALDEN. I'm sorry, Lilly, that's Lilly that goes beyond?

Ms. LOEW. Lilly, I believe there are other companies as well that are posting more than the——

Mr. WALDEN. What about this issue of publishing the stand-alone studies? Is that something PhRMA can support?

Ms. LOEW. I think there's been a lot of confusion around today is what does the study mean, what do the results mean.

Mr. WALDEN. Right.

Ms. LOEW. When we present data to FDA as part of a new drug application, the full study information is presented to the agency. On a study-by-study basis, that amounts to many thousands of pages——

Mr. WALDEN. But that's when you're trying to get a new drug approved, right?

Ms. LOEW. Correct, but any study that is completed, that is written up, will amount to many thousands of pages of data.

Mr. WALDEN. Right, but we can do the Congressional Record overnight and put it on line.

Ms. LOEW. The question is utility though. It's about——

Mr. WALDEN. Well, the Congressional Record, that's a question, can we share this?

Ms. LOEW. I don't know anything about the Congressional Record, but I would like to—what I would like to say is that we have tried to provide an information resource that is of use to busy, practicing physicians.

Mr. WALDEN. Sure, but there would be nothing that would stop you from publishing the summary data that you do now or want to or seek to, but it would seem to me for a researcher or a scientist or a physician who really wants to dig into it, what's the harm in allowing them access to more of the data, if they so choose? I mean you don't have to have one report that's so complicated and nobody understands it. You're going to have a summary of the findings, especially if they're good. It's going to get down to like one word, you know, well two, buy it.

It works. You know what I'm saying.

Ms. LOEW. Exactly.

Mr. WALDEN. I come from the belief that in a free and open, I think it's John Stuart Mill, in a free and open marketplace, the truth will win out and what you need is that information out there, so that these gentlemen to each side of you and others can, and parents, can know everything that's out there and make more important decisions.

Ms. LOEW. Understood. And what we have focused on in our data bases is a summary, as you rightly point out, something that we believe gives a brief, accessible amount of information that a physician can review relatively quickly. There's nothing to stop a practicing physician who is interested in gaining more information from approaching the particular company, asking them for more information, but that's not something that we have discussed as a policy within PhRMA. We took the position that we wanted to make this data base as useful as possible for practicing physicians and went for a summary format.

Mr. WALDEN. Okay, I long overshot my time and in fact, I'm going to defer to the chairman now of the full committee who I know has very strong opinions on this issue.

Chairman BARTON. Thank you, Mr. Chairman. I want to commend you and console you for having to chair most of this hearing. It started at 11 this morning. If we were a casino, you know when you go out to Las Vegas and you play poker or black jack, after so many hours, you get a meal voucher.

Mr. WALDEN. Well, Mr. Chairman, if I may——

Chairman BARTON. Not only would you get a meal voucher, the audience would get a meal voucher and probably a free room for the night.

Mr. WALDEN. Some time after midnight I think I'm in Las Vegas tonight because I get to Portland, Oregon at 2 a.m.

Chairman BARTON. Oh wow.

Mr. WALDEN. I'll look for that meal voucher.

Chairman BARTON. I want to thank this panel for persevering and being willing to still answer questions coherently at 7 in the evening and the audience that stayed with us.

I don't have too many questions. I've got one generic question that's probably been asked about a thousand times today, but I'm going to try to ask it one more time because this is our medical panel.

Why would the medical community prescribe off-label for children as young as six or seven drugs that to the extent the clinical trials have been made public, seem to indicate that there's no efficacy in the treatment? Why would a doctor do that?

And I'm sure you all have been asked that in some way, but I mean that's kind of the heart of this debate.

Mr. GORMAN. And we've tried to answer that, so we'll try again. The pediatricians as a group have been in that position since the inception of pediatrics. Seventy-five percent of all approved medicines in the United States are not approved for children. So any time we treat your children, your step children and your grandchildren, we are using——

Chairman BARTON. You listened. You listened to me. Children, stepchildren and grandchildren.

Mr. GORMAN. And remember, 75 percent of the time we're doing things off-label. This information dissemination that came through Best Pharmaceuticals for Children Act is new to the medical community and has not been widely disseminated that this information about drugs that have been tested and shown not to be effective, this is new stuff for us. We've heard from PhRMA that the data base will be for drugs that are approved. The information we've been discussing today is information about drugs that have been studied and not approved. This is the first time these kinds of information are widely available to physicians and the public. And it's due to the Best Pharmaceuticals for Children Act.

Chairman BARTON. So when some of my friends on the Democrat side, Mr. Markey, Mr. Waxman and others, talk about a registry where everything is put up as soon as possible on these websites and open for public display, that's something that the pediatric community would be very supportive of?

Mr. GORMAN. We'd be supportive of that as a goal, yes.

Chairman BARTON. What about our AMA rep and our PhRMA rep? Would you all support that?

Mr. DAVIS. Well, that's actually the crux of the American Medical Association's proposal. We want all phase 2 and phase 3 clinical trials to be registered, ideally in one central data base. We also have proposed an enforcement mechanism to make that happen which would involve IRBs, Institutional Review Boards, requiring a clinical trial to be registered in a publicly accessible data base in order for the IRB to approve that clinical trial.

So we believe that's the mechanism to allow physicians, other clinicians, researchers, policymakers and the public to know about all these phase 2 and phase 3 clinical trials that are underway or those that have been completed.

Chairman BARTON. Dr. Loew, do you want to comment?

Ms. LOEW. Just to—particularly to Dr. Gorman's point, but also a recurring theme today. The data base that we have established and that will be live from the first of October will contain both summaries of the positive and negative studies for products that are marketed in the United States. So to Dr. Gorman's point, if a product is marketed and approved for an adult population, what studies in the pediatric population did not result in an indication, that study, if it was a hypothesis testing clinical study will be published on the site. I think this is an unprecedented and major step forward for the industry. We're very committed to disclosing this information. We'll have this data base available in less than a month and physicians, practicing physicians will be able to start accessing this information.

Chairman BARTON. I have one more generic question and then I'm going to ask a staff question. And this again is to Dr. Gorman. Is there universal consensus on treating young children, like six and seven, with anti-depressant medications? Is that universally accepted, that that's acceptable practice? I mean I would think it might be hard to determine somebody that young whether they're actually clinically depressed or not.

Mr. GORMAN. I think that there is a growing belief and data to support that that children as young as six can be depressed. The treatment for any mental health condition is not just medication, but also the support of cognitive therapy and behavioral therapy as well. So I would hope that pharmaceutical intervention would be last on the list for potential interventions.

Talking about off-label use, these drugs are probably also being used for other conditions besides depression in children six and younger.

Chairman BARTON. Okay, well, I don't want to be facetious, but about that age when I felt like I was depressed, my father just paddled my bottom five or six times and gave me something to do and somehow I became undepressed, you know. But I don't want to be—I know this is a very serious issue, so my staff question is to Dr. Loew. And this was in your testimony, the PhRMA testimony referred to timely communication of meaningful study results. Exactly what is a timely communication?

Ms. LOEW. The data base that we announced earlier this week defines timely communication for marketed products of publication of the clinical study results within 1 year of completion of the clinical study. The 1 year timeframe comes from the FDA regulations for annual reporting of clinical study results and the definition of completion of a study is defined as lost patient, lost visit. It's very clearly defined.

We do have to exhibit some flexibility around that timeframe to allow for peer review publication of clinical studies. The peer review process can often take longer than 1 year and so we have a mechanism whereby companies can designate on the website that they have competed the clinical study, but it is undergoing peer review, so there will be no data published there. As soon as the study is either published, the bibliography, the bibliographic reference will be posted on the site or if it's rejected for publication, the company does not believe it can be published, they will put a summary of that study on the site. We have very clearly defined that and have also allowed for the slightly extended peer-review process.

Chairman BARTON. The timely is basically within a year?

Ms. LOEW. Correct.

Chairman BARTON. What about meaningful study results?

Ms. LOEW. Meaningful is something that we have defined in the Q&A that we published in June of this year, our principles. It's basically defined as hypothesis testing clinical trials. Hypothesis testing is again something that's defined in regulation.

Chairman BARTON. Try to talk in Texas.

Ms. LOEW. Being British, I'm not sure whether I could attain that, but I will do my best. I wouldn't even try to cross the Atlantic, but broadly hypothesis testing clinical trial is one that's defined to statistically answer a pre-defined question or set of questions.

There's typically phase 3 clinical studies and phase 4 clinical studies, but there can sometimes be phase 1 and phase 2 studies, but it's principally phase 3 and phase 4. These are the studies that are basically designed to inform how a physician could prescribe a product, if it were approved and in the marketplace.

Chairman BARTON. Does that mean it has to help 10 percent of the study group, 15 percent, 20 percent, to help somebody that's in dire straits?

Ms. LOEW. FDA has specific statistical criteria that they apply to efficacy standards. I don't have that information at my fingertips, but we can certainly get that to you in writing.

Chairman BARTON. Well, I listened carefully and I still don't understand meaningful study results. I mean I heard phase 3 and phase 4, but I didn't—what's the difference between a meaningful study result and an unmeaningful study result?

Ms. LOEW. We defined meaningful as hypothesis testing. Hypothesis testing is principally phase 3 and phase 4.

Chairman BARTON. I don't understand that. I'm not being dense. I have no clue what that means. Give me an example.

Ms. LOEW. Clinical development, up to new drug approval, occurs in three distinct stages. Phase 1 is done in a very small study population using healthy volunteers and it's simply to assess the safety of the drug. It's basically to tell whether something very significant and bad happens when this drug is put in humans.

When that study phase is completed, the drug moves to phase 2 which is principally aimed at, it's typically done using people who have the disease condition that the drug is being studied for. And it's in an effort to understand what dose the drug should be prescribed at. That's the principle aim of phase 2 clinical studies. Sometimes a little bit of extra data comes from it, but that's the main aim. .

In phase 3, you're using many, many more people who have the disease, to try and assess whether the drug is actually effective in treating that disease. So to take an example, if you have asthma, whether the drug improves your asthma, whether it gets your asthma under control. You would aim at the end of that study to have an answer to that question, yes, it does improve my asthma; no, it doesn't improve my asthma.

Chairman BARTON. But doesn't the FDA to be approved have a requirement that between the control group and the group that gets the new drug, that there be a significant, like a certain percentage it has to help at least a certain percentage?

Ms. LOEW. Correct. There are statistical criteria that they apply. As I said, I don't have that——

Chairman BARTON. Is that what meaningful means, that it——

Ms. LOEW. Correct.

Chairman BARTON. At that stage, it actually has to help some minimal percentage?

Ms. LOEW. Yes, you have to be able to show demonstrated efficacy and safety, that the drug is safe and that it treats what you're trying to indicate it for.

Chairman BARTON. Now I have one more question and I hesitate to ask it, but it wants me to ask you to define significant medical importance. Do you want to take a crack at that?

Ms. LOEW. I think in the earlier panel, this issue came up as well, the definition of significant medical importance. That definition will vary by therapeutic area, but essentially where the result of a clinical study provides information that it is believed to be important to practicing physicians, we believe that information should be disclosed.

Chairman BARTON. Does it have anything to do with the number of people?

Ms. LOEW. No.

Chairman BARTON. So it's not——

Ms. LOEW. It's independent of that.

Chairman BARTON. Okay. It's the efficacy on people that need that drug. Is that fair?

Ms. LOEW. That could be the reason, yes. But that could be one of many reasons.

Chairman BARTON. What would be another one? I'm just trying to get—I know it's late. I'm not trying to be argumentative. I'm trying to understand this and I'm not a medical major.

Ms. LOEW. An example could be and I should also say I'm not a physician either. An example could be that you are studying for one disease condition and that's the focus of your study, but you find out during the study that the disease—sorry, the drug has a significant impact in another disease area. That could be an example. You could, for instance, find a safety problem that you believe should be communicated. There are a number of different reasons, as I said.

Chairman BARTON. But it all revolves the result that occurs when you take that specific drug?

Ms. LOEW. Correct.

Chairman BARTON. Thank you, Mr. Chairman, and again, I appreciate you chairing this hearing and I want to thank our last panel again for being with us this late in the evening.

Mr. WALDEN. Thank you. Thank you, Mr. Chairman. And I, too, want to thank our panel for your endurance and your participation.

The committee record will remain open for members who have questions that we may want to ask and we would ask that all our witnesses today be able to respond before our September 23 hearing which will take up this issue in further detail. We do appreciate your enlightenment on this subject and thank you for your participation and you are excused. And we are adjourned.

[Whereupon, at 7:08 p.m., the hearing was concluded.]

[Additional material submitted for the record follows:]

GUIDE - 2610.11

ADMINISTRATIVE RESPONSIBILITES AND PROCEDURES TRANSMITTAL #98-11 DATE 01/26/98

FOOD AND DRUG ADMINISTRATION

PROCUREMENT MANAGEMENT

NONCOMPETIVTIVE ACQUISITIONS - CONTRACTING WITHOUT PROVIDING FOR FULL AND OPEN COMPETITION

1. **PURPOSE.** This guide sets forth the FDA policies and procedures applicable to all noncompetitive acquisitions; i.e. without providing for full and open competition. It describes the criteria for determining whether an acquisition may be made noncompetitively, describes the required justification for other than full and open competition (JOFOC), and prescribes review and approval requirements.

2. **POLICY.** Title VII of Pub. L. 98-369 entitled, the "Competition in Contracting Act of 1984 and Pub. L. 98-577 entitled, the "Small Business and Federal Procurement Competition Enhancement Act of 1984, authorize contracting without providing for full and open competition under certain conditions. Unless permitted by one of the circumstances provided in Part 3, below, contracting without providing for full and open competition is a violation of these statutes.

3. **CIRCUMSTANCES PERMITTING OTHER THAN FULL AND OPEN COMPETITION**

Items a through f, below, list the statutory authorities for contracting without providing for full and open competition. Select the authority which best describes the situation and fully explain the circumstances and rationale which support a noncompetitive acquisition. The more facts that are offered, the greater the conclusion that a noncompetitive acquisition is justified.

a. Only One Responsible Source and No Other Supplies or Services Will Satisfy Agency Requirements.

(1) Authority: 41 U.S.C. 253 (c)(1).

(2) This authority may be used in situations such as the following (these examples are not intended to be all-inclusive):

- (a) When there is a reasonable basis to conclude that the Agency's minimum needs can only be satisfied by unique supplies or services available from only one source or only one supplier with unique capabilities.
- (b) Follow-on contracts for the continuation of major research and development studies on long-term social and health programs, major research studies, or clinical trials may be deemed to be available only from the original source when it is likely that award to any other source would result in unacceptable delays in fulfilling the Agency's requirements.

- (c) Contracts for supplies or services that result from acceptance of an unsolicited research proposal shall be considered to be available from only one source if the source has submitted an unsolicited research proposal that demonstrates a unique and innovative concept, the substance of which (1) is not otherwise available to the Government and (2) does not resemble the substance of a pending competitive acquisition.
- (d) The existence of limited rights in data, patent rights, copyrights, or secret processes; the control of basic raw material; or similar circumstances, make the supplies and services available from only one source (however, the mere existence of such rights or circumstances does not in and of itself justify the use of these authorities).
- (e) When the Agency Head has determined that: (1) a specific item of technical equipment or parts must be obtained to meet an activity's program responsibility to test and evaluate certain kinds and types of products, and only one source is available, (this criterion is limited to testing and evaluating purposes only and may not be used for initial outfitting or repetitive acquisitions. Project Officers should support the use of this criterion with citations from the Agency's legislation and the technical rationale for the item of equipment required); or (2) there is existing equipment which, for reasons of compatibility and interchangeability, requires an item which is manufactured only by one source, (this criterion is for use in acquisitions where a particular brand name is required, and when an "or equal will not meet the Government's requirements. This criterion may not be used when there are other manufacturers available which may be able to produce acceptable items even though their products might require some adjustments and modifications. The other manufacturers must be given the opportunity to compete.)

(3) Limitations: For contracts using this authority, all proposed contract actions exceeding $25,000, unless otherwise excepted, shall be published in the Commerce Business Daily (CBD) and any bids and proposals must be considered.

b. Unusual and Compelling Urgency

- (1) Authority: 41 U.S.C. 253 (c) (2).
- (2) This authority applies in those situations where (a) an unusual and compelling urgency precludes full and open competition, and (b) delay in award of a contract would result in serious injury, financial or other, to the Government.
- (3) Limitations: This statutory authority requires that offers be requested from as many potential sources as is practicable under the circumstances.

c. Industrial Mobilization: Engineering or Development Work; or Research Capability

(1) Authority: 41 U.S.C. 253 (c) (3).

(2) Use of the authority may be appropriate when it is necessary to:

- (a) keep vital facilities or suppliers in business or make them available in the event of a national emergency;
- (b) train a selected supplier in the furnishing of critical supplies or services, prevent the loss of a supplier's ability and employees' skills, or maintain active engineering, research, or development work;
- (c) maintain properly balanced sources of supply for meeting the requirements of acquisition programs in the interest of industrial mobilization (when the quantity required is substantially larger than the quantity that must be awarded in order to meet the objectives of this authority, that portion not required to meet such objectives will be acquired by providing for full and open competition);
- (d) establish or maintain an essential capability for theoretical analyses, exploratory studies, or experiments in any field of science or technology;
- (e) establish or maintain an essential capability for engineering or developmental work calling for the practical application of investigative findings and theories of a scientific or technical nature; or
- (f) contract for supplies or services as are necessary incident to (d) or (e) above.

d. International Agreement

(1) Authority: 41 U.S.C. 253 (c) (4).

(2) This authority may be used in circumstances such as:

- (a) When a contemplated acquisition is to be reimbursed by a foreign country that requires

that the product be obtained from a particular firm as specified in official written direction such as a Letter of Offer and Acceptance; or

- (b) When a contemplated acquisition is for services to be performed, or supplies to be used, in the sovereign territory of another country and the terms of a treaty or agreement specify or limit the sources to be solicited.

e. Authorized or Required by Statute

(1) Authority: 41 U.S.C. 253 (c) (5).

(2) This authority may be used when statutes, such as the following, expressly authorize or require that acquisition be made from a specified source or through another agency;

- (a) Federal Prison Industries (UNICOR) - 18 U.S.C. 4124.
- (b) Qualified Nonprofit Agencies for the Blind or Other Severely Handicapped-41 U.S.C. 46-48c.
- (c) Government Printing and Binding-44 U.S.C. 501-504,1121.
- (d) 8 (a) Program - 15 U.S.C. 637.
- (e) Robert T. Stafford Emergency Relief and Emergency Assistance Act - 42 U.S.C. 637 (FAR Subpart 26.2).

f. Public interest

(1) Authority: 41 U.S.C. 253 (c) (7).

(2) Full and open competition need not be provided for when it is determined that it is not in the public interest in the particular acquisition concerned. This authority may be used when none of the other authorities apply. An "approval package must be prepared and staffed through Departmental acquisition channels to the Secretary. The package shall include:

- (a) a determination and findings, prepared by the contracting officer, for the Secretary to sign.
- (b) a letter for the Secretary to sign notifying Congress of the determination to award a contract under the authority of 41 U.S.C. 253(c) (7). This letter must be received by Congress at least 30 days before contract award.
- (c) a "Justification for Other Than Full and Open Competition (JOFOC).
- (d) a briefing paper presenting background, and need, etc.

- (e) any other pertinent papers or documents required by the Department.

g. Limitations:

Contracts awarded using these authorities shall be supported by the written justification and approvals as described in Parts 4, 5, and 6, below, except:

(1) when those contracts are awarded under paragraph 3e. (2) (b) and (d) above, and

(2) when a statute expressly requires that an acquisition be made from a specified source.

Justifications required as specified above may be made on an individual or class basis, except those for contracts awarded under the authority of Public Interest - 41 U.S.C. 253 (c) (7), which can only be made on an individual basis.

4. **REQUIREMENTS**

a. The program office should discuss prospective noncompetitive acquisition requests with the contracting officer as early as possible during acquisition planning, and before submitting the Memorandum of Need (MON) and/or HHS-393, "Purchase/Service/Stock Requisition. The discussions may resolve uncertainties, provide program offices with names of other sources, allow proper scheduling of the acquisition, and avoid delays which might otherwise occur should it be determined that the request for other than full and open competition is not justified.

b. When a program office desires to contract for goods or services without full and open competition, it shall, at the time of forwarding the MON and/or HHS 393, also forward a JOFOC. All justifications shall be submitted initially to the cognizant Contracting Officer.

c. All required justifications and approvals

- (1) must be obtained prior to issuance of a solicitation, except
- (2) in the case of Unusual or Compelling Urgency, authority 41 U.S.C. 253(c) (2), which may be made and approved after contract award.

  Preliminary arrangements or agreements with the proposed contractor will have no effect or influence on the rationale to support a noncompetitive acquisition.

d. It is the responsibility of the cognizant Contracting Officer and/or the Competition Advocate to determine whether a contract may properly be awarded without competition. Program offices and Project Officers are responsible for furnishing the cognizant Contracting Officer and other approving officials with pertinent factual information necessary to make such determination.

e. JOFOCs are required for all noncompetitive acquisitions greater than $2,500. Above $100,000, they must be separate self-contained documents submitted with the Memorandum of Need. For acquisitions between $25,001 and $100,000, the necessary documentation may vary by

acquisition from a paragraph or two on the HHS-393 to a full JOFOC depending on the nature of the supplies or services and whether or not simplified acquisition procedures can be used. Project Officers should consult with Contracting Officers prior to JOFOC preparation to preclude unnecessary paperwork.

f. ALL JOFOCs shall fully state what is to be acquired and the reasons why the requirement will not be competed. Justification must provide reasons which go beyond inconvenience and must explain why it is not reasonable to obtain competition. The justification will be documented with information based on facts, rather than untested, unsubstantiated conclusions or opinions. The JOFOC should be sufficient to permit an individual with technical competence in the area to follow the rationale for using other than full and open competition.

5. **CONTENT**

a. Each JOFOC shall contain sufficient facts and rationale to justify the use of the specific authority cited. As a minimum, each JOFOC must include the following information:

- (1) Identification of the Agency and the contracting activity, and specific identification of the document as a "Justification for Other than Full and Open Competition.
- (2) The program office and name, address, and telephone number of the project officer.
- (3) Project identification such as the authorizing program legislation, including citations or other internal program identification data such as title, and contract number;
- (4) Both a full description of the requirement and the dollar amount are to be included. This may be in the form of a statement of work, purchase description, or specification. A statement is to be included to explain whether the acquisition is an entity in itself, whether it is one in a series, or part of a related group of acquisitions.
- (5) An identification of the statutory authority permitting other than full and open competition.
- (6) A demonstration that the proposed contractor's unique qualifications or the nature of the acquisition requires use of the authority cited.
- (7) A description of efforts made to ensure that offers are solicited from as many potential sources as is practicable, including whether a CBD notice was or will be publicized, and, if not, which exception under FAR 5.202 applies.

- (8) A description of the market survey conducted and the results or a statement of the reasons a market survey was not conducted.

- (9) Any other facts supporting the use of other than full and open competition, such as:
- (a) Explanation of why technical data packages, specifications, engineering descriptions, statements of work, or purchase descriptions suitable for full and open competition have not been developed or are not available;
- (b) When the authority of 41 U.S.C. 253 (c) (1) is cited, for a follow-on acquisition and is based on award to any other source resulting in substantial duplication of cost to the Government, an estimate of the duplicate cost and how it was derived;
- (c) When the authority of 41 U.S.C. 253 (c) (2) is cited, provide some rationale as to the extent and nature of the harm to the Government.
- (10) A listing of the sources, if any, that express, in writing, an interest in the acquisition.
- (11) A statement of the actions, if any, the Agency may take to remove or overcome any barriers to competition before any subsequent acquisition for the supplies or services is required.
- (12) A determination by the Contracting Officer that the anticipated cost to the Government will be fair and reasonable.
- (13) A Contracting Officer certification that the justification is accurate and complete to the best of the Contracting Officer's knowledge and belief.

b. The JOFOC shall include signatory lines for the Project Officer, the Project Officer's immediate supervisor, the Contract Specialist, the Contracting Officer, and the Approving Official. A signatory line shall also be included, as shown below, for the Associate Commissioner for Information Resources Management for all acquisitions for Information Technology.

Recommended:

This is to certify that, to the best of my knowledge and belief, the justification for other than full and open competition, submitted in writing, as required by FAR 6.303 meets the minimum needs or scheduled requirements of the Agency, and is accurate and complete.

_____ _____

Project Officer Date

_____ _____

Project Officer's Supervisor Date

_____ _____

Associate Commissioner for IRM Date

(IT Acquisitions only)

Concur:

This is to certify that, to the best of my knowledge and belief, the justification for other than full and open competition, submitted in writing, as required by FAR 6.303 and the supporting documentation thereto, is accurate and complete and that the anticipated cost is fair and reasonable.

_____ _____

Contract Specialist Date

_____ _____

Reviewing Official/Title Date

Approved:

_____ _____

Approving Official/Title Date

6. **APPROVAL OF THE JUSTIFICATION**

a. The required approval levels for noncompetitive acquisitions are as follows:

NONCOMPETITIVE CONTRACT ACTION		
DOLLAR THRESHOLDS	**REVIEW MEMBERS**	**APPROVING OFFICIALS**
$2,501 - $300,000	Contract Specialist	Contracting Officer
$300,000 - $500,000	Contract Officer	Principal Official Resp. for Acquistion (PORA)
$500,001 - $50,000,000	PORO	Competition Advocate (Director, OFACS)
	Competition	

$50,000,001 and above	Advocate	Ass't Sec. for Mgmt. and Budget

b. The estimated dollar value of all options shall be included in determining the approval level of a justification.

c. A justification that applies to a class of contract actions shall be processed as an individual justification.

ATTACHMENT A

FORMAT OF JUSTIFICATION FOR OTHER THAN FULL AND OPEN COMPETITION

The following format should be used to provide the minimum necessary justification:

JUSTIFICATION FOR OTHER THAN FULL AND OPEN COMPETITION

1. Agency: Food and Drug Administration (FDA), Department of Health and Human Services

- a. Program Office/Center/Mail Code:
- b. Project Officer/Address/Telephone Number:
- c. Contracting Activity: Office of Facilities, Acquisitions and Central Services, FDA

2. Nature of Action Being Proposed for Approvals:

Restriction of full and open competition. The acquisition should be from the following source:

3. Title and Description of Supplies or Services and Estimated Value:

- a. Project Title/Contract No.
- b. Description of Supplier or services to be acquired:
- c. Estimated value:

4. Statutory Authority Cited for Other Than Full and Open Competition:

Enter the authority specified in Items 3(a) through (f), i.e.; 41 U.S.C. 253 (c) (1) for "Only one responsible source..."

5. Statement of Contractor's Unique Qualifications to Provide the Services or Supplies and/or a Statement of Why The Authority Cited Applies to This Acquisition.

6. Description of Efforts Made to Ensure Offers Are Solicited from As Many Potential Sources As

Practicable.

7. Description of the Market Survey Conducted and the Results, or Statement of the Reasons a Market Survey was not conducted.

8. Other Relevant Facts Supporting the Use of Other Than Full and Open Competition.

9. Sources that have Expressed Interest in the Acquisition in Writing.

10. Statement of Plans to Remove or Overcome Barrier to Competition Before Future Actions to Acquire the Supplies or Services are Initiated.

Certification and Signatures: See page 11 of this Staff Manual Guide.

ATTACHMENT B

SPECIAL CONSIDERATION FOR THE NATIONAL ACADEMY OF SCIENCES

Effective Date: Immediately

Expiration Date: January 24, 1998

Given the nature of the National Academy of Sciences (NAS) and considering those acquisitions for which NAS can be the only source that can provide the expertise, independence, objectivity, and audience acceptance necessary to meet the program requirements, a synopsis in the Commerce Business Daily, as required by FAR 5.201, would not accomplish the goal of enhancing competition or increasing small business participation normally attendant with such acquisitions. As a result, the Assistant Secretary for Management and Budget signed a Determination and Findings (D&F) in accordance with FAR 5.202(b) after obtaining the concurrence of the Administrator of the Office of Federal Procurement Policy and the Administrator of the Small Business Administration. This D&F exempts noncompetitive acquisitions above $10,000 with NAS from the synopsis requirements set forth in FAR 5.201. The D&F was signed January 25, 1995, and is effective for a 3 year period.

Instructions:

The following certification must be used as a substitute for the Contracting Officer's certification provided in Staff Manual Guide 2610.11, page 11. The Competition Advocate must certify all noncompetitive acquisitions with NAS regardless of the dollar value of the acquisition.

Certification:

This is to certify that, to the best of my knowledge and belief, the justification for other than full and open competition, submitted in writing, as required per FAR 6.303 and the supporting documentation thereto, is accurate and complete and that the anticipated cost is fair and reasonable. In addition, this is to certify that this requirement has not been synopsized pursuant to the determination and findings executed by the Assistant Secretary for Management and Budget, effective 1/25/95, and that only the

National Academy of Sciences can provide the measure of expertise, independence, objectivity, and audience acceptance necessary to meet the program requirements.

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Staff Manual Guide Numerical Table of Contents

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SEP-22-2004 13:12 P.02

ORDER FOR SUPPLIES OR SERVICES

PAGE 1 OF PAGES 3

IMPORTANT: Mark all packages and papers with contract and/or order numbers

1. DATE OF ORDER: 12/09/2003	2. CONTRACT NO. (If any):
3ER NO.: D1800204	4. REQUISITION/REFERENCE NO.:

5. ISSUING OFFICE (Address correspondence to):
DHHS/FDA/OAGS/DCGM
ATTN: Lauren Waller
5630 FISHERS LANE
ROOM 2129, HFA-531
ROCKVILLE MD 20857

6. SHIP TO:
a. NAME OF CONSIGNEE: DHHS/FDA/CDER
b. STREET ADDRESS: 5515 SECURITY LANE ROOM 7201
c. CITY: ROCKVILLE | d. STATE: MD | e. ZIP CODE: 20852

7. TO:
a. NAME OF CONTRACTOR: COLUMBIA UNIVERSITY
b. COMPANY NAME:
c. STREET ADDRESS: 722 W. 168TH STREET 4TH FLOOR
d. CITY: NEW YORK | e. STATE: NY | f. ZIP CODE: 10032-3702

f. SHIP VIA:

8. TYPE OF ORDER
[X] a. PURCHASE REFERENCE YOUR:
Please furnish the following on the terms and conditions specified on both sides of this order and on the attached sheets, if any, including delivery as indicated.
[ ] b. DELIVERY
Except for billing instructions on the reverse, this delivery order is subject to instructions contained on this side only of this form and is issued subject to the terms and conditions of the above-numbered contract.

9. ACCOUNTING AND APPROPRIATIONS DATA: D 18002 00 6992762 252Z 22320Q10

10. REQUISITIONING OFFICE: DHHS/FDA/CDER

11. BUSINESS CLASSIFICATION (Check appropriate box(es))
[ ] a. SMALL [X] b. OTHER THAN SMALL [ ] c. DISADVANTAGED [ ] d. WOMEN-OWNED

12. F.O.B. POINT	14. GOVERNMENT B/L NO.	15. DELIVER TO F.O.B. POINT ON OR BEFORE (Date)	16. DISCOUNT TERMS
Destination			Net 30

13. PLACE OF

a. INSPECTION	b. ACCEPTANCE
Destination	Destination

17. SCHEDULE (See reverse for Rejections)

ITEM NO. (a)	SUPPLIES OR SERVICES (b)	QUANTITY ORDERED (c)	UNIT (d)	UNIT PRICE (e)	AMOUNT (f)	QUANTITY ACCEPTED (g)
	Period of Performance: 01/01/2004 to 07/31/2004					
1	"Suicide Panel of Experts" to perform suicide research in the areas of biology, genetic transmission, and treatment Continued ...	250.00	EA	53.00	13,250.00	

18. SHIPPING POINT | 19. GROSS SHIPPING WEIGHT | 20. INVOICE NO. | 17(h). TOTAL (Cont. pages) $0.00

21. MAIL INVOICE TO:
a. NAME: DHHS/FDA/Accounting Operations Br.
b. STREET ADDRESS (or P.O. Box): ATTN: 5600 FISHERS LANE HFA-122 301-827-ERIC (3742)
c. CITY: ROCKVILLE | d. STATE: MD | e. ZIP CODE: 20857

SEE BILLING INSTRUCTIONS ON REVERSE

17(i). GRAND TOTAL $13,250.00

UNITED STATES OF AMERICA
BY (Signature): Hamilton Brown
23. NAME (Typed): HAMILTON BROWN
TITLE: CONTRACTING/ORDERING OFFICER

NSN 7540-01-152-8067
PREVIOUS EDITION NOT USABLE
OPTIONAL FORM 347 (Rev. 6/95)
Prescribed by GSA/FAR (48 CFR) 53.213(f)(2)

ORDER FOR SUPPLIES OR SERVICES
SCHEDULE - CONTINUATION

PAGE OF PAGES: 2 | 3

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

DATE OF ORDER	CONTRACT NO.	ORDER NO.
)9/2003		D1800204

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY ORDERED (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)	QUANTITY ACCEPTED (G)
	trials. The panel includes the following members of Columbia University: - Kelly Posner, PhD (Supervisor/Coordinator) - Maria Oquendo, MD - Ainsley Burke, PhD - Jill Harkevy-Freedman, PhD - Mike Grunbaum, MD 52.212-4 CONTRACT TERMS AND CONDITIONS-COMMERCIAL ITEMS (OCT 2003) RECEIPT AND ACCEPTANCE OF SUPPLIES/SERVICES: THE SUPPLIES AND/OR SERVICES DELIVERED HEREUNDER SHALL BE INSPECTED AND ACCEPTED AT DESTINATION BY THE CONTRACTING OFFICER'S REPRESENTATIVE (COR) SPECIFIED BELOW. IF THE SUPPLIES OR SERVICES ARE ACCEPTABLE, THE COR SHALL PROMPTLY FORWARD A REPORT OF INSPECTION AND ACCEPTANCE TO THE PAYING OFFICE. IF THE SUPPLIES OR SERVICES ARE NOT ACCEPTABLE, THE COR SHALL DOCUMENT THE NONCONFORMING ITEMS/SERVICES AND IMMEDIATELY NOTIFY THE CONTRACTING OFFICER. THE COR FOR THIS ORDER IS: Tom Laughren @ 301/594-2850 POINTS OF CONTACT: QUESTIONS CONCERNING THE PRICING OR TERMS OF THIS ORDER SHOULD BE DIRECTED TO: Lauren Waller @ 301/827-7163 QUESTIONS RELATING TO WHEN PAYMENT WILL BE RECEIVED SHOULD BE DIRECTED TO THE FDA PAYMENT OFFICE AT (301) 827-5007. Continued ...					

TOTAL CARRIED FORWARD TO 1ST PAGE (ITEM 17(H))

NSN 7540-01-152-8082 | OPTIONAL FORM 348 (Rev. 6/95) Prescribed by GSA FAR (48 CFR) 53.213(c)

SEP-22-2004 13:13 P.04

ORDER FOR SUPPLIES OR SERVICES
SCHEDULE - CONTINUATION

PAGE OF PAGES: 3 | 3

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

DATE OF ORDER	CONTRACT NO.	ORDER NO.
'09/2003		D1800204

..EM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY ORDERED (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)	QUANTITY ACCEPTED (G)
	52.232-33 PAYMENT BY ELECTRONIC FUNDS TRANSFER-CENTRAL CONTRACTOR REGISTRATION (OCT 2003) Total amount of award: $13,250.00. The obligation for this award is shown in box 17(i).					

TOTAL CARRIED FORWARD TO 1ST PAGE (ITEM 17(H))

NSN 7540-01-152-8082 — OPTIONAL FORM 348 (Rev. 6/95)

SEP-22-2004 13:13 P.05

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PURCHASE/SERVICE/STOCK REQUISITION

RFA and Call No. _____

Requisition Number: Req. #D18002
Office Code/Symbol: HFD-101

To: Office of Acquisitions & Grants, HFA-531	Reason For: ☐ Purchase ☒ Service ☐ Stock Issue ☐ Rental/Lease			
Requisitioning Individual and Phone: CDER/OND/Office of Drug Evaluation I/Immediate Office	Fiscal Year: 0730	Date: 11/12/03	Object Class: 25.2Z	
For Information Call: Tammy Russell	Extension: 443-5392	Appropriation: 7540600 22320Q10		
Deliver To: Columbia University Department of Psychiatry 1051 Riverside Drive, Box 42 New York, New York 10032		CAN: 6992762 D-18002 Date Required: ASAP		

Item No.	Description (Include Stock Number, Model, Part No., Etc.)	Quantity Requested	Unit of Issue	Cost Unit	Cost Total
	Professional Service Contract for "Suicide Panel of Experts" See attached for sole source justification DUNS # 621889815 Federal ID # 135598093-A7 Contact Information: Columbia University Department of Psychiatry Div. of Child Psychiatry & NeuroScience 1051 Riverside Drive, Box 74 New York, NY 10032 Attn: Kelly Posner, M.D. Phone: 212-543-5504 Fax: 212-543-6660 Email address: PosnerK@child.cpmc.columbia.edu Period of Performance. Six months from initial start of Contract Anticipated Start Date: January 5, 2004				13,250.00

I certify that the property/services requested are required for Government business, and are not available from excess or current stocks."

Funds Available (Signature/Title): Tammy Russell, Management Officer, ODE1
Date: 11/12/03
Total: $13,250.0

Requisitioning Official (Signature/Title): Russell Katz, M.D. Director, Div of Neuropharm	Date: 11/8/03	Receiving Official - I certify that the quantities indicated in the "Quantity Received" column above have been received in good order or as contracted.	
Reviewing Official (Signature/Title): Rae Ann Behrman, M.D. Dep Director, ODE1	Date: 11/9/03	Receiving Official (Signature/Title)	Date
Approving Official (Signature/Title): Robert Temple, Director, ODE1	Date	Name of Carrier (Air, Van, Courier, Etc.)	Carrier Date
Property Management Officer (Signature)*	Date	Received By	Received Date

*GSA Optional (GPO)

Sole Source Justification:

The Columbia Expert Suicidality Classification Board is a joint collaboration between the Depts. of Child Psychiatry and Neuroscience. The Columbia group has been conducting suicide research (including biological, genetic transmission, and treatment trials across the life-span)for approximately 20 years, includes a federally-funded suicide research center, and is responsible for approximately 40 federal and non-federal currently funded investigations over the past 5 years alone, with approximately 150-200 resultant suicide-related publications. Adequate measurement and classification of suicide variables has been an integral component of this extensive body of work and as a result the Columbia expert group has developed measures, manuals, and methodology based on and fostering a conceptual clarity for evaluation of suicidality, with associated scientific rigor and systematic methodology and training, and corresponding reliability and validity. Consequently and based on this experience utilizing this methodology to determine suicide-related variables, the Columbia group has unparalleled experience and expertise in assessment and classification of such events, both behavioral and ideation-related. Columbia has also collaborated with other national sites in a multi-center NIMH-funded treatment study for adolescent suicide attempters, and Columbia has been nationally responsible for directing the suicide evaluation process. Specifically, Columbia has guided the choice, implementation and running of the evaluation process that will determine all outcome variables (a particularly comprehensive system to assess and classify suicidal events in these high-risk adolescents). In addition, members of the Columbia group (those that are not investigators in this trial) have been designated as the Suicide Evaluation Board, responsible for the independent review and classification of suicidal events.

Thus, the work of the Columbia Expert Suicide Classification Board will be based on its experience with the standardized and systematic classification of suicidal events. The reclassification of the data that the FDA will provide to the expert board will initially involve determination of appropriate event classifications, based on reliable and valid constructs. The expert panel will then convene and partake in an extensive and rigorous consensus procedure in which each case will be reviewed to determine the appropriate classification and each classification will be then consensed by the board. Methodology for especially challenging cases, either because of missing data or the difficult nature of the data, will involve a two-tier process, with a second round of review and consensus (with additional expert board members).

Panel of Experts:

Kelly Posner, Ph.D. Supervisor/Coordinator
Maria Oquendo, M.D.
Ainsley Burke Ph.D.
Jill Harkevy-Freedman, Ph.D.
Mike Grunbaum, M.D.

Price Calculations:

5 Expert Panel Members @ $53 per hour (current SGE rate)
Estimated 50 hours of review/work per person

5 X $53 X 50 = $13,250

SMG 2610.7 - ATTACHMENT C

Special Program Clearances & Approval Checklist

Introduction: The following checklist must be attached to each Requisition submitted to the Contracting Officer. The applicability of these clearances is discussed in the DHHS Project Officers' Contracting Handbook, or see reference noted by each clearance. The Project Officer must indicate which of the clearances apply, if any.

MON No. _____

Applicable	Not Applicable	Part A - Special Clearances/Approvals Required Prior to Approval of the Requisition
	✓	1. ADP Systems Security - Handbook
	✓	2. Approval for Providing Government Property - SMG 2620.2
	✓	3. Approval of Contracts with Present or Former Federal Employees - See A&AS in Handbook
	✓	4. Approval of Contracts with State Governments - ORA for clearance
	✓	5. Approval of Studies on Fraud, Abuse, and Waste in FDA Programs - notify FDA, Mgt. Policy & Analyses II Br.
	✓	6. Audiovisual (videotape, television and motion picture) Production Approval - Handbook & SMG 2480.2
	✓	7. Classified Contracts Clearance - HHS Security Manual, FDA, DELMAR, (301) 827-5511
✓		8. Clearance for Release of Privileged Information to Contractors - SMG 2280.6
	✓	9. Commercial or Industrial Products or Services Clearance (A contract vs. In-house performance review and determination pursuant to OMB Circular A-76) - Handbook
	✓	10. Environmental Impact Determination - GAM 30-20-20
	✓	11. Evaluation Contracts - Handbook
	✓	12. Good Laboratory Practices - 21 CFR Part 58
	✓	13. Information Technology (IT) - SMG 2730.1
	✓	14. Micrographics Approval - SMG 2490.1
	✓	15. Paid Advertising Approval - Handbook

	✓
	✓
	✓
	✓
✓	✓
	✓
	✓
	✓
✓	
	✓

16. Paperwork Reduction Act - Handbook and SMG 2470.2
17. Printing Services Clearance - Handbook
18. Privacy Act (P.O. 93-579) Systems of Records Determination - Handbook and SMG 2460.6
19. Public Advisory Committee Approval - OMB A-63, SMG 2111.1
20. Public Affairs Services - Handbook
21. Publications Approval - Handbook
22. Safety and Health Approval for Contracts Involving Hazardous Substance - FDA Safety Officer
23. Senior Management Review - SMG 2610.1
24. Scientific Review - SMG 2113.2
25. Training Contracts Clearance - Section 410.501 of Title 5, CFR - require Commissioner's approval

Part B - Clearances/Approvals Required Prior to Contract Award

Applicable	Not Applicable
	✓
	✓
	✓

1. Animal Welfare Approval - PHSAR 380.2 - NIH, Office of Protection from Res. Risk (OPRR) (301) 496-7041
2. Approval for Projects Involving Human Subjects - PHSAR 380.1 NIH/OPRR (301) 496-7041
3. Foreign Research Contract Clearance - GAM 20-60, Notify Office of Int'l Affairs, (301) 827-4480

The above indicated clearances apply to the acquisition and the appropriate clearance documents are attached or action has been initiated to obtain them.

Division Contact most knowledgeable about contract:

Project Officer Thomas P. Laughren, MD 11-19-03

Thomas P. Laughren. M.D.
Medical Officer, Div. of Neuropharm Drug Products, CDER
301-594-2850

SEP-22-2004 13:14 P.10

ORDER FOR SUPPLIES OR SERVICES

PAGE OF PAGES 1 4

IMPORTANT: Mark all packages and papers with contract and/or order numbers

1. DATE OF ORDER: 06/07/2004	2. CONTRACT NO. (If any):
3. ORDER NO.: 800204 01	4. REQUISITION/REFERENCE NO.: D1800204
5. ISSUING OFFICE (Address correspondence to): DHHS/FDA/OAGS/DCGM ATTN: Lauren Waller 5630 FISHERS LANE ROOM 2129, HFA-531 ROCKVILLE MD 20857	6. SHIP TO: a. NAME OF CONSIGNEE: DHHS/FDA/CDER b. STREET ADDRESS: 5515 SECURITY LANE ROOM 7201 c. CITY: ROCKVILLE d. STATE: MD e. ZIP CODE: 20852 f. SHIP VIA:
7. TO: a. NAME OF CONTRACTOR: COLUMBIA UNIVERSITY b. COMPANY NAME: c. STREET ADDRESS: 722 W. 168TH STREET 4TH FLOOR d. CITY: NEW YORK e. STATE: NY f. ZIP CODE: 10032-3702	8. TYPE OF ORDER [X] a. PURCHASE REFERENCE YOUR: Please furnish the following on the terms and conditions specified on both sides of this order and on the attached sheets, if any, including delivery as indicated. [ ] b. DELIVERY Except for billing instructions on the reverse, this delivery order is subject to instructions contained on this side only of this form and is issued subject to the terms and conditions of the above-numbered contract.
9. ACCOUNTING AND APPROPRIATIONS DATA: D 18002 00 6992762 252Z 22320Q10	10. REQUISITIONING OFFICE: DHHS/FDA/CDER

11. BUSINESS CLASSIFICATION (Check appropriate box(es)): [ ] a. SMALL [ ] b. OTHER THAN SMALL [ ] c. DISADVANTAGED [ ] d. WOMEN-OWNED

12. F.O.B. POINT	13. PLACE OF		14. GOVERNMENT B/L NO.	15. DELIVER TO F.O.B. POINT ON OR BEFORE (Date)	16. DISCOUNT TERMS
	a. INSPECTION: stination	b. ACCEPTANCE: Destination			Net 30

17. SCHEDULE (See reverse for Rejections)

ITEM NO. (a)	SUPPLIES OR SERVICES (b)	QUANTITY ORDERED (c)	UNIT (d)	UNIT PRICE (e)	AMOUNT (f)	QUANTITY ACCEPTED (g)
	Tax ID Number: 135598093 The Purpose of this modification is to extend the Period of Performance from 7/31/2004 to 12/31/2004, and to increase Continued ...					

	18. SHIPPING POINT	19. GROSS SHIPPING WEIGHT	20. INVOICE NO.	17(h). TOTAL (Cont. pages)
	21. MAIL INVOICE TO:			
SEE BILLING INSTRUCTIONS ON REVERSE	a. NAME: DHHS/FDA/Accounting Operations Br.		$10,600.00	
	b. STREET ADDRESS (or P.O. Box): ATTN: 5600 FISHERS LANE HFA-122 301-827-ERIC (3742)			17(i). GRAND TOTAL
	c. CITY: ROCKVILLE	d. STATE: MD	e. ZIP CODE: 20857	$10,600.00

22. UNITED STATES OF AMERICA
BY (Signature): Hamilton Brown

23. NAME (Typed): HAMILTON BROWN
TITLE: CONTRACTING/ORDERING OFFICER

JM 7540-01-152-8083 PREVIOUS EDITION NOT USABLE

OPTIONAL FORM 347 (Rev. 6/95) Prescribed by GSA/FAR (48 CFR) 53.212(a)

SEP-22-2004 13:14 P.11

ORDER FOR SUPPLIES OR SERVICES
SCHEDULE - CONTINUATION

2 6

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

DATE OF ORDER	CONTRACT NO.	ORDER NO.
06/07/2004		D1800204 01

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY ORDERED (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)	QUANTITY ACCEPTED (G)
	funds obligated from $13,250.00 by $10,600.00 to $23,850.00. The following duties shall be added to the scope of work: - Careful review of adverse event dictionaries for these trials to ensure that important events were not missed. - Review of a sample of CRFs to check on the completeness of the narratives. - Classification of additional narratives from a large NIMH-sponsored adolescent depression study that would give more data to include in the FDA's analysis. -Work on developing a guidance document for better ascertainment of suicidality in future studies. All other terms and conditions remain unchanged as a result of this modification. LIST OF CHANGES: Period Of Performance End Date changed from 07/31/2004 to 12/31/2004 Total Amount for this Modification: $10,600.00 New Total Amount for this Award: $23,850.00 Obligated Amount for this Modification: $10,600.00 New Total Obligated Amount for this Award: $23,850.00 CHANGES FOR LINE ITEM NUMBER: 1 Quantity changed from 250 to 450 Total Amount changed from $13,250.00 to $23,850.00 Obligated Amount for this modification: $10,600.00 End Date changed from 07/31/2004 to 12/31/2004 Continued ...					

TOTAL CARRIED FORWARD TO 1ST PAGE (ITEM 17(h))

NSN 7540-01-152-8082 OPTIONAL FORM 348 (Rev. 6/95)

SEP-22-2004 13:15 P.12

ORDER FOR SUPPLIES OR SERVICES
SCHEDULE - CONTINUATION

PAGE OF PAGES 3 4

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

DATE OF ORDER	CONTRACT NO.	ORDER NO.
06/07/2004		D1800204 01

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY ORDERED (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)	QUANTITY ACCEPTED (G)
	CHANGES FOR DELIVERY LOCATION: 50 Quantity changed from 250 to 450 Amount changed from $13,250.00 to $23,850.00 CHANGES FOR ACCOUNTING CODE: D 18002 00 6992762 252Z 22320Q10 Quantity changed from 250 to 450 Amount changed from $13,250.00 to $23,850.00 Period of Performance: 01/01/2004 to 12/31/2004 52.212-4 CONTRACT TERMS AND CONDITIONS-COMMERCIAL ITEMS (OCT 2003) RECEIPT AND ACCEPTANCE OF SUPPLIES/SERVICES: THE SUPPLIES AND/OR SERVICES DELIVERED HEREUNDER SHALL BE INSPECTED AND ACCEPTED AT DESTINATION BY THE CONTRACTING OFFICER?S REPRESENTATIVE (COR) SPECIFIED BELOW. IF THE SUPPLIES OR SERVICES ARE ACCEPTABLE, THE COR SHALL PROMPTLY FORWARD A REPORT OF INSPECTION AND ACCEPTANCE TO THE PAYING OFFICE. IF THE SUPPLIES OR SERVICES ARE NOT ACCEPTABLE, THE COR SHALL DOCUMENT THE NONCONFORMING ITEMS/SERVICES AND IMMEDIATELY NOTIFY THE CONTRACTING OFFICER. THE COR FOR THIS ORDER IS: Tom Laughren @ 301/594-2850 POINTS OF CONTACT: QUESTIONS CONCERNING THE PRICING OR TERMS OF THIS ORDER SHOULD BE DIRECTED TO: Lauren Waller @ 301/827-7163 QUESTIONS RELATING TO WHEN PAYMENT WILL BE RECEIVED SHOULD BE DIRECTED TO THE FDA PAYMENT OFFICE AT (301) 827-5007. Continued ...					

TOTAL CARRIED FORWARD TO 1ST PAGE (ITEM 17(h))

NSN 7540-01-152-8067 OPTIONAL FORM 348 (Rev. 6/94)

SEP-22-2004 13:15 P.13

ORDER FOR SUPPLIES OR SERVICES
SCHEDULE - CONTINUATION

PAGE OF PAGES 4 4

IMPORTANT: Mark all packages and papers with contract and/or order numbers.

DATE OF ORDER	CONTRACT NO.	ORDER NO.
06/07/2004		D1800204 01

ITEM NO. (A)	SUPPLIES/SERVICES (B)	QUANTITY ORDERED (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)	QUANTITY ACCEPTED (G)
	52.232-33 PAYMENT BY ELECTRONIC FUNDS TRANSFER-CENTRAL CONTRACTOR REGISTRATION (OCT 2003)					

TOTAL CARRIED FORWARD TO 1ST PAGE (ITEM 17(H))

NSN 7540-01-152-8082

OPTIONAL FORM 348 (Rev. 2/89)
Prescribed by GSA
FAR (48 CFR) 53.215-1(c)

SEP-22-2004 13:15 P.14

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PURCHASE/SERVICE/STOCK REQUISITION

ENTERED

Req. #D18002

BPA and Call No. Amendment #1

HFD-101

TO: Office of Acquisitions & Grants, HFA-531

REQUEST FOR: ☐ PURCHASE ☒ SERVICE ☐ STOCK ISSUE ☐ MATERIAL RELEASE

REQUISITIONING ORGANIZATION: CDER/OND/Office of Drug Evaluation I/Immediate Office

CONTROL AREA: 0730 DATE: 5/20/04 OBJECT CLASS: 25.2Z

FOR INFORMATION CALL: Tammy Russell TELEPHONE: 443-5392 APPROPRIATION: 7540600 22320Q10

DELIVER TO: Columbia University
Department of Psychiatry
1051 Riverside Drive, Box 42
New York, New York 10032

CAN: 6992762 D-18002

DATE REQUIRED: ASAP

ITEM NO.	DESCRIPTION (INCLUDE STOCK NUMBER, MODEL/PART NO., ETC.)	QUANTITY REQUIRED	UNIT OF ISSUE	COST UNIT	COST TOTAL
	AMENDMENT TO Professional Service Contract for "Suicide Panel of Experts" INCREASE OF FUNDS				10,600.00
	DUNS # 621889815 Federal ID # 135598093-A7				
	Contact Information: Columbia University Department of Child Psychiatry 1051 Riverside Drive, Box 74 New York, NY 10032 Attn: Kelly Posner, M.D. Phone: 212-543-5504 Fax: 212-543-6660 Email address: PosnerK@child.cpmc.columbia.edu				
	Period of Performance: 200 additional hours needed for contract				

I certify that the property/services requested are required for Government business, and are not available from current stock or current needs.

PERSON AVAILABLE (Signature/Title): Tammy Russell, Management Officer, ODEI — DATE: 5/20/04 — TOTAL: $10,600.

APPROVED BY (Signature/Title): Russell Katz, M.D. Director, Div of Neuropharm — DATE: 5/21/04

RECOMMENDED APPROVAL (Signature/Title): Robert Temple, M.D. Dep Director, ODEI — DATE: 5/26/04

APPR. (Signature/Title): Robert Temple, M.D. Director, ODEI — DATE: 5/27/04

PROPERTY MANAGEMENT OFFICER (Signature) — DATE

RECEIVING OFFICIAL - I certify that the quantities indicated in the "Quantity Received" column have been received in good order or as annotated.

RECEIVING OFFICIAL (Signature/Title) — DATE

ORDER NO. (PO, BO, PURCHASE, ETC.) — ORDER DATE

INVOICE NO. — INVOICED DATE

TO OAGS ml

Additional Work Required:

(1) Careful review of adverse event dictionaries for these trials to ensure that important events were not missed (60 hours)

(2) Review of a sample of CRFs to check on the completeness of the narratives (60 hours)

(3) Classification of additional narratives from a large NIMH-sponsored adolescent depression study that would give us more data to include in our analysis (30 hours)

(4) Work on developing a guidance document for better ascertainment for suicidality in future studies (50 hours)

Total of 200 hours at @$53.00/hour = $10,600.00

The Honorable John D. Dingell
Ranking Member
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Dingell:

Thank you for the letter of September 14, 2004, that included questions pertaining to the September 9, 2004 hearing before the Subcommittee on Oversight and Investigations entitled, "Publication and Disclosure Issues in Anti-Depressant Pediatric Clinical Trials." Your letter included questions from yourself and Representative Bart Stupak. Your questions are repeated below followed by our answers.

1. Why did Organon not receive pediatric Exclusivity for their drug Remeron?

The Pediatric Exclusivity Board, the group within the Food and Drug Administration (FDA or the Agency) that makes pediatric exclusivity determinations, concluded that Organon did not fairly respond to the terms of the Written Request (WR) for Remeron (mirtazapine) and, therefore, Organon was not granted pediatric exclusivity.

2. How does the Agency react to a question, raised by at least one drug firm, of whether it is ethical to perform a long-term safety study if a clinical trial shows no efficacy in children?

Long-term safety data on antidepressant drugs are still needed for children because, even if an antidepressant is not approved for use in children, these drugs continue to be used off-label in a significant number of pediatric patients. Safety data are collected through controlled efficacy trials. FDA believes that longer-term safety data should be generated in longer-term open extensions from these trials and/or in separate longer-term open safety studies.

3. Does the FDA have sufficient authority, under the Best Pharmaceuticals for Children Act, to require that drugs be studied to its satisfaction?

The Best Pharmaceuticals for Children Act (BPCA) contains a voluntary incentive program that was not intended to be a requirement. FDA has authority under the Pediatric Research Equity Act (PREA) to require sponsors to conduct pediatric studies for certain drugs.

The pediatric exclusivity program that began under FDAMA, and was reauthorized under BPCA, is a *voluntary* incentive program for drug products that have patent and/or exclusivity protection. Under this program, the Agency issues a Written Request to a sponsor for a drug with marketing exclusivity or patent protection. The Written Request proposes studies that FDA believes will provide useful information about the drug's safety and effectiveness in children, but it does not require that the sponsor conduct these

studies. If the sponsor conducts pediatric studies, and FDA determines that the sponsor has fairly responded to the terms of the Written Request (regardless of the results of the studies), the sponsor will receive 6 months of additional marketing exclusivity for that product. As of September 1, 2004, the program has resulted in 110 pediatric exclusivity determinations and 79 products with pediatric labeling.

Under BPCA, there are two other mechanisms for conducting studies in the pediatric population.

- The first mechanism is for drugs *without* patent or marketing protection and for which studies in the pediatric population are still needed. The National Institutes of Health (NIH), in consultation with FDA, develops, prioritizes, and publishes an annual list of such drugs. From this list, FDA issues Written Requests to all companies with approved applications for these drugs. If all of the companies decline to conduct studies, the Written Requests can be referred to the NIH to be transformed into requests for contract proposals. The fulfillment of these contracts is dependent on the availability of NIH funding as well as on interest expressed by an independent investigator to conduct the studies as described in the Written Request.

- The second mechanism is for drugs *with* patent and marketing protections that are held by sponsors who have declined to conduct the studies described in the Written Request. The BPCA states that if there is a continuing need to conduct studies, these Written Requests will be referred to the Foundation of the NIH for funding. Funding for these studies, however, is dependent on the Foundation's resources.

4. You testified that the FDA actively works to post summaries of pediatric trials in a timely manner. We know you did not in all but one of the drugs explored at this hearing. What other studies, which also have failed to show efficacy, has the FDA not yet released? Please provide a list of drugs that have failed to show efficacy in clinical trials in pediatric populations, as well as the dates FDA received the study results.

To better understand this issue, some background on disclosure is important. Under its regulations, FDA generally may not disclose to the public data and information in an unapproved application, which includes pediatric labeling supplements. In keeping with FDA's regulations, a sponsor submitting pediatric studies to FDA in response to a FDAMA Written Request (i.e., a Written Request issued before the enactment of BPCA in January 2002) understood that FDA generally would not disclose the study results prior to approval. Upon approval, however, FDA regulations provide that a summary of the studies upon which the approval is based will be made public. See 21 CFR 314.430.

When BPCA was enacted in January 2002, it contained a special disclosure provision relating to the summaries of pediatric studies performed in response to a Written Request. Specifically, the BPCA requires that no later than 180 days after the submission of a

pediatric study report, FDA will make publicly available a summary of the medical and clinical pharmacology reviews of the pediatric studies submitted in response to a Written Request. This means that BPCA changed the normal disclosure practice with regard to these studies. Prior to the BPCA (i.e., under Section 111 of FDAMA), studies submitted in response to a Written Request were still considered confidential until a supplemental application was approved. After the BPCA, however, summaries of studies submitted in response to a Written Request are made available no later than 180 days after submission of the report to FDA.

The BPCA is silent on whether the new provisions added in BPCA (including the disclosure provisions in Section 9) apply to Written Requests previously issued under FDAMA. Therefore, it was unclear to sponsors whether studies requested under FDAMA but submitted after the enactment of the BPCA would be governed by FDAMA or the BPCA. Because of this substantial change to the pediatric exclusivity program, FDA notified sponsors in a July 2002 letter that outstanding FDAMA Written Requests were considered to be reissued as of that date under the BPCA. The letter stated that any studies submitted after that point in response to the reissued Written Request would be subject to the terms of the BPCA, including the provisions governing public availability of study summaries.

As of September 17, 2004, 42 summaries were posted on CDER's pediatric website:

- 40 submissions were received AFTER the July 2002 letter putting all remaining outstanding Written Requests under BPCA. Two are still under review; 38 remain.
- Of the remaining 38, 4 were NDAs, one of which was withdrawn. Only summaries of supplements, not new NDAs, must be posted under Section 9 of the BCPA.
- That left 34 applications required to be posted. In addition, we posted summaries for 8 other applications for which summaries were not required to be posted under BPCA, but for which the sponsors agreed to the posting. In total, 42 summaries were posted on the pediatric website.

Regarding specific information on the list of drugs that have failed to show efficacy, we currently do not separately track the results of the studies that have failed to establish efficacy. All information that we are able to post regarding information about pediatric trials is posted on the web as indicated above.

5. I understand that the FDA has possession of studies that show that at least some of the antidepressants, under discussion in this hearing, are not effective in some of the trial of adults with Major Depressive Disorder (MDD). Please tell us which of these drugs, that were not shown to be effective in pediatric studies, were also submitted with one of more failed trials to FDA for adults populations suffering from MDD.

There are no studies that show the drugs to be ineffective, however, there are many trials that do not demonstrate effectiveness. Placebo-controlled trials in major depressive disorder in adults frequently fail to distinguish active drug from placebo, even for antidepressant drugs that are known to be effective in this population. The overall failure rate for such trials in drugs that are recognized as effective in adult depression is roughly 50 percent. There were, in fact, failed trials in all of the adult programs for the six antidepressants (Zoloft, Paxil, Celexa, Remeron, Serzone, Effexor) for which the pediatric depression trials also were not able to document effectiveness. There were also failed trials in the adult depression program for Prozac, the one drug for which the pediatric depression program was successful.

6. **You testified that the FDA asked manufacturers to change the labels of ten drugs to include stronger cautions and warnings about the need to monitor patients for worsening of depression and the emergence of suicidal behavior and ideation? You further state that the new warning language has now been added to the labels for seven of these products and that sponsors of the other three drugs have also agreed to adopt the language. Which three drugs have yet to make the appropriate changes to their labels? Why have they not changed their labels? Do they have a time limit for making these changes?**

By mid-August, 2004, the suicidality warning language had been implemented for the remaining three drugs for which such language had been requested.

7. **Please identify each official in the Office of Drug Safety, in the review division referred to as Neuropharm, or anywhere else in the Center for Drug Evaluation and Research, that reviewed, recommended (or failed to recommend), approved, concurred in the approval, or otherwise participated in the decision to request that Wyeth Laboratories moderate its labeled warning, or proposed labeled warning, regarding the dangers of Effexor in children and adolescents.**

The following FDA staffs were involved in the labeling decision regarding the suicidality language for the drug Effexor:

- Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (DNDP)
- Thomas Laughren, M.D., Team Leader, Psychiatric Drug Products (DNDP)
- Paul Andreason, M.D., Team Leader, Psychiatric Drug Products (DNDP)

Wyeth did make a change under what is known as "changes being effected (CBE)" in an August 22, 2003, labeling supplement. They added the following sentence under "Precautions, Usage in Children/Pediatric Use:"

> "In pediatric clinical trials, there were increased reports of hostility and especially in Major Depressive Disorder, suicide-related adverse events such as suicidal ideation and self-harm."

Companies are permitted to make such changes without prior approval, and this change remained in effect until late spring, 2004. At that time, when FDA was adding class language to all of the current generation of antidepressants, it was noted that there might be a discrepancy between Wyeth's language in the Precautions section and FDA's proposed Warning statement, given that the statement included language that "a causal role for antidepressants in inducing such behaviors has not been established," where "behaviors" included emergence of suicidality.

Although the Wyeth language was considered quite vague, it could be interpreted as suggesting causality. Thus, it was decided that, as an interim measure, while the analysis of the pediatric suicidality data was being completed to determine whether or not there was a causal relationship, it would be best to remove the vague language in the Precautions section and add the more prominent Warning statement. There was unanimous consensus in the review division that the Warning statement better represented the current state of knowledge about these data. It should be noted that this new language encouraged observation for emergence of both suicidality and hostility. It should also be noted that a Warning statement, especially one containing bolded language, is expected to have more impact on prescribing. In any case, it was recognized that, in a short period of time, the analysis of the suicidality data would be completed, the results would be presented to the advisory committees, and the Agency would be in a position to write a more definitive statement in labeling with regard to causality.

8. **Please identify each official in the Office of Drug Safety, in the review division referred to as Neuropharm, or anywhere else in the Center for Drug Evaluation and Research, that reviewed, recommended (or failed to recommend), approved, concurred in the approval, or otherwise participated in the decision to request that GlaxoSmithKline to label their drug, Paxil, as having failed to show efficacy in at least one pediatric trial.**

The following FDA staffs were involved in the regulatory action for the pediatric supplement for the drug Paxil:

- Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (DNDP)
- Thomas Laughren, M.D., Team Leader, Psychiatric Drug Products (DNDP)
- Andrew Mosholder, M.D., Clinical Reviewer, Psychiatric Drug Products (DNDP)

Dr. Mosholder conducted the primary review of the supplement. Drs. Katz, Laughren, and Mosholder all participated in the decision of how best to characterize the negative efficacy findings in Paxil labeling, and were in agreement on the action taken. In considering the labeling language that was implemented for Paxil regarding these negative findings, it is important to distinguish between the kind of information the agency considers informative for labeling and disclosure of information more broadly, e.g., on a website or in a publication. The agency is, of course, fully supportive of

companies providing full information about their trials in venues where it is possible to give more complete information. The difficulty with labeling is that there is limited space to provide much detail. In the case of negative efficacy trials in a condition such as depression, where interpretation of such an outcome is difficult, the brief mention of negative trials without further qualification might be misunderstood to mean that lack of efficacy has been proven. At the time this labeling was implemented in response to the pediatric supplement, it was DNDP's policy to ask companies whose efficacy trials had been negative to use the standard language that "effectiveness in the pediatric population has not been established." An alternative approach now being implemented is to provide brief details on the number of trials conducted and to note whether or not, in the aggregate, such trials support a claim for the condition being studied.

9. **Please identify each official in the Office of Drug Safety, in the review division referred to as Neuropharm, or anywhere else in the Center for Drug Evaluation and Research, that reviewed, recommended (or failed to recommend), and/or approved the decision not to require Forest Laboratories to label their drug, Celexa, as having failed to show efficacy in a pediatric trial.**

The following FDA staff were involved in the regulatory action for the pediatric supplement for the drug Celexa:

- Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (DNDP)
- Thomas Laughren, M.D., Team Leader, Psychiatric Drug Products (DNDP)
- Earl Hearst, M.D., Clinical Reviewer, Psychiatric Drug Products (DNDP)

Dr. Hearst conducted the primary review of the supplement. Drs. Katz, Laughren, and Hearst all participated in the decision of how best to characterize the efficacy findings in Celexa labeling, and were in agreement on the action taken, i.e., to ask the sponsor to use the standard language that "effectiveness in the pediatric population has not been established."

10. **Please identify each official in the Office of Drug Safety, in the review division referred to as Neuropharm, or anywhere else in the Center for Drug Evaluation and Research, that reviewed, recommended (or failed to recommend), and/or approved the decision not to require Bristol-Myers Squibb to label their drug, Serzone, as having failed to show efficacy in a pediatric trial.**

The following FDA staff were involved in the regulatory action for the pediatric supplement for the drug Serzone:

- Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (DNDP)
- Thomas Laughren, M.D., Team Leader, Psychiatric Drug Products (DNDP)

- Andrew Mosholder, M.D., Clinical Reviewer, Psychiatric Drug Products (DNDP)

Dr. Mosholder conducted the primary review of the supplement. Drs. Katz, Laughren, and Mosholder all participated in the decision of how best to characterize the efficacy findings in Serzone labeling, and were in agreement on the action taken, i.e., to ask the sponsor to use the standard language that "effectiveness in the pediatric population has not been established."

11. Please identify each official in the Office of Drug Safety, in the review division referred to as Neuropharm, or anywhere else in the Center for Drug Evaluation and Research, that reviewed, recommended (or failed to recommend), and/or approved the decision not to require Organon, to label their drug, Remeron, as having failed to show efficacy in a pediatric trial.

The following FDA staff were involved in the regulatory action for the pediatric supplement for the drug Remeron:

- Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (DNDP)
- Thomas Laughren, M.D., Team Leader, Psychiatric Drug Products (DNDP)
- Ann-Kathryn Maust, M.D., Clinical Reviewer, Psychiatric Drug Products (DNDP)

Dr. Maust conducted the primary review of the supplement. Drs. Katz, Laughren, and Maust all participated in the decision of how best to characterize the efficacy findings in Remeron labeling, and were in agreement on the action taken, i.e., to ask the sponsor to use the standard language that "effectiveness in the pediatric population has not been established."

12. Please identify each official in the Office of Drug Safety, in the review division referred to as Neuropharm, or anywhere else in the Center for Drug Evaluation and Research, that reviewed, recommended (or failed to recommend), and/or approved the decision not to require Pfizer, to label their drug, Zoloft, as having failed to show efficacy in a pediatric trial.

The following FDA staff were involved in the regulatory action for the pediatric supplement for the drug Zoloft:

- Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (DNDP)
- Thomas Laughren, M.D., Team Leader, Psychiatric Drug Products (DNDP)
- Andrew Mosholder, M.D., Clinical Reviewer, Psychiatric Drug Products (DNDP)

Dr. Mosholder conducted the primary review of the supplement. Drs. Katz, Laughren, and Mosholder all participated in the decision of how best to characterize the efficacy findings in Zoloft labeling, and were in agreement on the action taken, i.e., to ask the

sponsor to use the standard language that "effectiveness in the pediatric population has not been established."

13. **Please identify each official in the Office of Drug Safety, in the review division referred to as Neuropharm, or anywhere else in the Center for Drug Evaluation and Research, that reviewed, recommended (or failed to recommend), and/or approved the decision not to require Wyeth to label their drug, Effexor, as having failed to show efficacy in a pediatric trial.**

The following FDA staff were involved in the regulatory action for the pediatric supplement for the drug Effexor XR:

- Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (DNDP)
- Paul Andreason, M.D., Team Leader, Psychiatric Drug Products (DNDP)
- Glenn Mannheim, M.D., Clinical Reviewer, Psychiatric Drug Products (DNDP)

Dr. Mannheim conducted the primary review of the supplement. Drs. Katz, Andreason and Mannheim all participated in the decision of how best to characterize the efficacy findings in Effexor XR labeling, and were in agreement on the action taken, i.e., to ask the sponsor to use the standard language that "effectiveness in the pediatric population has not been established."

The following are questions submitted on behalf of Representative Stupak:

1. **In the 9/9/2004 hearing and at this year's Advisory Committee hearings, FDA officials have said repeatedly that the data sets they have in which to determine the safety and efficacy of antidepressants to treat depression in children are too small. What changes need to be made to the Written Requests for pediatric trials in order for FDA officials to better determine efficacy and safety? What has FDA learned from its review of antidepressants about how this system should be changed? What changes have you implemented or will you implement? Does legislation need to be enacted to make the changes necessary?**

As FDA noted at the Advisory Committee (AC) meeting and elsewhere, adult depression trials fail about half the time to distinguish active drug from placebo for drugs that are known to be effective. It is likely that some aspect of trial conduct explains the high failure rate. One approach to differentiating between trials that fail to demonstrate effectiveness for conduct reasons and those that fail to demonstrate the drug truly does not work is to include an active control group in a trial. With the approval of Prozac for pediatric depression, FDA will ask sponsors in all future written requests for pediatric depression trials to include a Prozac arm. Then, if neither Prozac nor the other drug is effective, we should be able to conclude that the trial was defective and did not adequately test the effectiveness of the drug.

FDA will also require other changes in pediatric depression drug development programs. For some years, FDA has been urging that depression trials use more than one dose and this recommendation is often followed. None of the pediatric trials, however, included more than a single dose FDA is now routinely asking for dose-finding trials to ensure that a full dose range is explored in the definitive trials. In addition, FDA will insist on use in trials of a more structured approach to identifying suicidality (a set of targeted questions, for example), other than waiting for the events to be reported.

None of these new measures for improving the conduct of pediatric depression trials would require any legislative action.

2. **Please provide the Committee with the number of spontaneous adverse events classified as suicide, suicidal behavior and ideation reported to the FDA through MedWatch for each year since the drugs Wellbutrin, Celexa, Prozac, Luvox, Serzone, Paxil, Remeron, Zoloft, and Effexor have been approved for use in adults. Please classify adverse events by age group (adult, adolescents, and children). Please also explain how the FDA has followed up on these reports and classified these events.**

The requested data and classification are attached. ODS prepared a review of the pediatric MedWatch data for the February 2004 AC meeting which analyzed the total number of reports for all drugs and the serious reports suggestive of suicidality for all the drugs. The report noted the particular challenge of analyzing adverse event reports of suicide with antidepressants, which are used to treat illnesses that are themselves associated with a risk for suicidal behavior. For this reason the report concluded that clinical trial data were the preferred method for assessing the suicidal risk of antidepressants.

Since the February AC meeting, ODS has worked with the rest of CDER in addressing pediatric suicidality concerns by 1) working on the March warning to clinicians, 2) reanalyzing the clinical trial data in children, 3) participating in the AC meeting in September, 4) participating in the AC follow-up and the proposed relabeling of the SSRIs, and 5) developing a draft Medication Guide to go out to patients. Finalization of the black box warning and Medication Guide is anticipated in December. Ongoing surveillance by ODS of the MedWatch reports for all adverse events continues as usual.

3. **In Dr. Dianne Murphy's testimony before the Advisory Committee on September 13, 2004, she stated that over 293 Written Requests for products to be studied in children have been made by FDA since 1994, and that studies have been submitted on over 110 products. Please account for the 183 products that have had Written Requests issued, but have not had studies submitted. How many of those 293 Written Requests were unanswered? How many products have studies underway that have not been submitted to the FDA?**

For clarification, Dr. Murphy's slide provided a history from 1994 to the present regarding Pediatric Initiatives. Section 111 of FDAMA, enacted in 1997, included the pediatric exclusivity incentive program. The first Written Request (WR) was not issued until 1998.

BCPA was passed in January 2002. Before BPCA was enacted, sponsors were not required to inform FDA if they were going to respond or perform the studies defined in the WR. Under BPCA, once a sponsor has been issued a WR, they are to notify FDA within 180 days if they intend to perform the studies requested.

In July 2002, FDA issued a letter to all sponsors who had been issued a WR and for which studies had not already been submitted, stating that their WRs were effectively re-issued under BPCA and were subject to the provisions of BPCA. This would include both the provisions on responding within 180 days and the disclosure provisions.

To account for the 183 Written Requests for which studies have not been submitted, we are providing the following information:

- 27 of the sponsors who were issued Written Requests between 1998 and 2002 (under FDAMA and prior to BPCA enactment) did not respond to the Request; the due date for submission of studies has expired and, therefore, these Written Requests are no longer in effect.
- 100 Written Requests issued under BPCA have studies that are planned or ongoing;
- 41 Written Requests issued under BPCA were declined or no response was submitted;
- 5 Written Requests were rescinded by FDA for safety reasons; and
- 10 Written Requests are currently awaiting the sponsors' response (within the 180 due date).

4a. Dr. Murphy testified that 76 label changes have been made. Why have only 76 labels been changed? What is the status of the other 24 label changes?

Please note that the 76 label changes referred to by Dr. Murphy in her testimony were based on data as of August 1, 2004.

As of September 1, 2004, studies have been completed on 110 products. Seventy-nine products have had labeling changes, reflecting approval actions, and 31 products have not had labeling changes.

Below is a breakdown of the 31 products without labeling changes:

- 23 were reviewed but received actions other than approval, so labeling changes were not made (14 not approvable actions and 9 approvable actions);
- 5 products were withdrawn by the sponsor (therefore no labeling changes made);
- 1 product had two determinations but one labeling change; and

- 2 products have labeling changes pending.

Once a sponsor submits an application to FDA (supplement or original NDA) and a pediatric exclusivity determination is requested, an exclusivity decision must be made within 90 days. Supplements submitted in response to a Written Request are given priority review and must have an action on approvability within 6 months. Therefore, an exclusivity determination must be made three months before an action is taken on the supplement. If the supplement is approved, it must be accompanied by a label. If the product is not approved, there usually is not a labeling change unless there are safety issues.

4b. Why has the FDA only posted 41 summaries on its Web site when over 110 products have studies completed and 79 products have label changes?

To better understand this issue, some background on disclosure is important. Under its regulations, FDA generally may not disclose to the public data and information in an unapproved application, which includes pediatric labeling supplements. In keeping with FDA's regulations, a sponsor submitting pediatric studies to FDA in response to a FDAMA Written Request (i.e., a Written Request issued before the enactment of BPCA in January 2002) understood that FDA generally would not disclose the study results prior to approval. Upon approval, however, FDA regulations provide that a summary of the studies upon which the approval is based will be made public. See 21 CFR 314.430.

When BPCA was enacted in January 2002, it contained a special disclosure provision relating to the summaries of pediatric studies performed in response to a Written Request. Specifically, the BPCA requires that no later than 180 days after the submission of a pediatric study report, FDA will make publicly available a summary of the medical and clinical pharmacology reviews of the pediatric studies submitted in response to a Written Request. This means that BPCA changed the normal disclosure practice with regard to these studies. Prior to the BPCA (i.e., under Section 111 of FDAMA), studies submitted in response to a Written Request were still considered confidential until a supplemental application was approved. After the BPCA, however, summaries of studies submitted in response to a Written Request are made available no later than 180 days after submission of the report to FDA.

The BPCA is silent on whether the new provisions added in BPCA (including the disclosure provisions in Section 9) apply to Written Requests previously issued under FDAMA. Therefore, it was unclear to sponsors whether studies requested under FDAMA but submitted after the enactment of the BPCA would be governed by FDAMA or the BPCA. Because of this substantial change to the pediatric exclusivity program, FDA notified sponsors in a July 2002 letter that outstanding FDAMA Written Requests were considered to be reissued as of that date under the BPCA. The letter stated that any studies submitted after that point in response to the reissued Written Request would be subject to the terms of the BPCA, including the provisions governing public availability of study summaries.

As of September 17, 2004, 42 summaries were posted on CDER's pediatric website:

- 40 submissions were received AFTER the July 2002 letter putting all remaining outstanding Written Requests under BPCA. Two are still under review; 38 remain.
- Of the remaining 38, 4 were NDAs, one of which was withdrawn. Only summaries of supplements, not new NDAs, must be posted under Section 9 of the BCPA.
- That left 34 applications required to be posted. In addition, we posted summaries for 8 other applications for which summaries were not required to be posted under BPCA, but for which the sponsors agreed to the posting. In total, 42 summaries were posted on the pediatric website.

5. Dr. Dianne Murphy testified before the Advisory Committee on September 13, 2004 that "Under FDA's general disclosure provisions for approved applications, the summary for Prozac is available" on the FDA website. Why has the FDA not used those same disclosure provisions to publish the summaries of pediatric trials of other drugs?

As noted, clinical trial information is disclosed for products once they are approved. Prozac was the only product approved for use in children and that is why "[u]nder FDA's general disclosure provisions for approved applications, the summary for Prozac is available on the FDA Web site." This is a not pediatric-specific issue.

With regard to pediatric uses of the drugs cited in your letter, although there is no requirement to do so under BPCA (in some cases because the studies were done before the BPCA was enacted), we have posted summaries of our reviews of the pediatric studies of all nine of the drugs cited in your letter.

Thank you for the opportunity to testify before the Committee and submit these answers for inclusion in the record. If there are further questions, please let us know.

Sincerely,

Patrick Ronan
Assistant Commissioner
for Legislation

Enclosure

FDA Statement for the Record
Before the Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
September 23, 2004

Per your request, we have restated your questions below followed by our response.

Walden #1: What is the "legal barrier" and regulation that prevents the FDA from compelling companies to put out information on negative clinical trials, especially within labeling.

The Trade Secrets Act, 18 U.S.C. § 1905, prohibits the disclosure of trade secret and confidential commercial information (including "confidential statistical data") by a federal employee "in any manner or to any extent not authorized by law." Additionally, the Freedom of Information Act, 5 U.S.C. § 552, contains an exemption protecting, among other things, "trade secrets and commercial or financial information" obtained from a person, that is privileged or confidential. 5 U.S.C. § 552(b)(4).

With specific regard to confidential commercial information, including data or results from clinical trials submitted to FDA by IND or NDA sponsors, FDA has several applicable regulations. *See, e.g.,* 21 C.F.R. § 20.61(b) (governing confidential commercial information generally) and 21 C.F.R. §§ 312.130, 314.430 (governing specific types of agency records relating to human drugs).

Under these laws and regulation, FDA has long considered information regarding an unapproved new drug application (including, for example, in a supplemental new drug application for a new indication) to be confidential commercial information under the Trade Secrets Act and FOIA. The release of such information is likely to cause substantial competitive harm to the position of the person from whom the information was obtained. Consequently, FDA's regulations state that FDA will not even acknowledge the existence of an IND or NDA unless its existence previously has been publicly disclosed or acknowledged by the sponsor. 21 C.F.R. §§ 312.130(a), 314.430(b). Even if the sponsor has publicly disclosed or acknowledged the existence of the IND or NDA, no data or information is generally available from that IND or NDA until the NDA has been approved. 21 C.F.R. § 314.430(d).

In summary, for applications other than those submitted under of the Best Pharmaceuticals for Children Act, the Agency generally may not publicly disclose information contained in investigational new drug applications, unapproved new drug applications, or unapproved supplemental new drug applications. Only after a new drug application or supplemental new drug application is approved can the Agency make public certain summary information regarding the safety and effectiveness of the product for the approved indication.

Walden #2: Has the FDA ever told a company not to disclose the fact that clinical trials were performed and failed to show efficacy?

FDA does not tell companies not to disclose the fact that clinical trials were performed and failed to show efficacy. However, it is important to distinguish between the type of information we consider informative for labeling, on the one hand, and disclosure of information more broadly, on the other (e.g., on a website, in a publication, etc.) FDA fully supports companies providing full information about their trials in venues where it is possible to give more complete information. The difficulty with labeling is that there is limited space to provide much detail. In the case of negative efficacy trials related to a condition such as depression, where interpretation of such trial outcomes is difficult, the brief mention of negative trials without further qualification can be misunderstood to mean that lack of efficacy has been proven. Alternatively, we have generally asked companies whose efficacy trials have been negative to use the standard language that "effectiveness in the pediatric population has not been established." An alternative approach we are now considering is to mention, and perhaps briefly describe, negative trials, but to add language noting the difficulty in interpreting such an outcome.

With regard to the seven pediatric programs in major depressive disorder, there were six for which this was an issue. The seventh program involved Prozac, which was approved for pediatric depression, and the trials supporting this claim are therefore fully described in labeling.

- Paxil—GSK did not propose any language describing its negative trials in labeling. Thus, its label has the standard language that effectiveness in the pediatric population has not been established.

- Zoloft—Pfizer proposed language supporting a claim for pediatric depression, and it was only at the end of a long paragraph promoting the results of their pooled analysis as positive where they mentioned that 1 of the 2 studies was negative. In fact, both studies were negative by themselves. Based on the concern that we expressed in the first paragraph of our response to this question, the Zoloft labeling currently contains the standard language that effectiveness in the pediatric population has not been established.

- Celexa—Forest also proposed language supporting a claim for pediatric depression, and in fact, their language only described their one positive study. However, our standard for the approval of a claim for pediatric depression is two positive studies. Therefore, we responded with the standard language indicating that effectiveness in the pediatric population has not been established. In this case, it would be problematic to describe both the positive and negative study, because we would, by doing so, be giving them a claim. However, we might simply note that two trials were conducted but further indicate that they did not meet our standard for approval for this claim.

- Effexor XR; Serzone; Remeron—Sponsors for these 3 drugs did propose very brief description of their negative trials, and we opted instead to give them the standard language that effectiveness in the pediatric population has not been established.

Bass #1: Is it normal to have a sole source contract for drug use as was the case with the Columbia study?

Under certain circumstances, sole source contracts are appropriate. FDA procurement guidelines provide that the Agency can use a sole source provided there is justification. Tab A contains a copy of the purchase order for this contract including the "sole source justification."

Bass #2: Has the FDA ever used a sole source contract before?

FDA has used sole source contracts in the past.

Bass #3: Was the Columbia University contract put through checks on "conflicts of interest"?

A conflict of interest check was not done in this case because this would not have been an issue in this contract. The data provided to Columbia for reclassification were double blinded, meaning there was no way to tell which event was related to which product produced by which manufacturer. Furthermore, in this case, Columbia University research scientists convened a panel of ten experts from outside of Columbia University. FDA had financial information on two of these experts because they were government employees previously screened for conflicts of interest. We do not have this information for the other individuals under contract to perform the classification project, as these individuals were not being asked to interpret data, only to classify cases, and they did not know whether the patient received a placebo or with what product the patient may have been treated. Also, they were not working under the direct supervision of any FDA employee and Federal conflict of interest statutes do not apply to their work.

Bass #4: What are the "standard procedures" (quoting Woodcock) for such an arrangement similar to Columbia University's?

Tab B contains a copy of FDA's guidelines on noncompetitive acquisitions.

Bass #5: Do some members of the Columbia University have financial relationships with drug companies that manufacture anti-depressants?

This issue is addressed in our response to question 3.

Tab	Document Description	Date
	GlaxoSmithKline	
1	Press Release - "GSK Clarifies Availability Of Clinical Trial Data On Paroxetine In Adolescent and Paediatric Patients"	6/10/2004
2	Press Release - "GSK Announces Major Advance In On-Line Access To Clinical Trial Information"	6/18/2004
3	GSK Website "Fact Sheet" RE: Use of Paxil in Pediatric Patients	No Date
4	GSK Website - Paroxetine and Pediatric and Adolescent Clinical Trial Data Overview	7/15/2004
5	Paxil: Study 329 Report Synopsis (selected pages)	11/24/1998
6	Paxil: Study 377 Report Synopsis (selected pages)	12/8/1998
7	Paxil: Study 701 Report Synopsis (selected pages)	7/20/2001
8	Poster Presentation Adolescent Depression: Efficacy of Paroxetine (ENCP Conf), Paris,	October-98
9	Poster Presentation Paroxetine in Adolescent Depression - World Congress Psych. Mtg, Hamburg, Germany	1999
10	Poster Presentation: Efficacy of Paroxetine and Imipramine in the Treatment of Adolescent Depression, Keller et al, American Psychiatric Assoc., Toronto, Can. (abstract)	1998
11	Attorney General of New York Complaint Against GlaxoSmithKline	6/2/2004
12	CMAJ Article- Drug Company Experts Advised Staff to Withhold Data About SSRI Use in Children	3/2/2004
13	Seroxat/Paxil Adolescent Depression - Executive Summary (Internal Document)	Oct-98
14	SmithKline Beecham - Fax to Thomas Laughren, M.D. (FDA) RE: Paxil	7/9/1999
15	Article "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial," Keller, et al. J.AM. ACAD. Child Adolesc. Psychiatry	July-01
16	Study 377. "Presentation at Annual Academy of Child and Adolescent Psychiatry (AACAP) Chicago, IL.	October 19-21,1999
	Forest Labs	
17	Article: Celexa: "A Randomized, Placebo-Controlled Trial of Citalopram for the Treatment of Major Depression in Children and Adolescents" (Am. Journal of Psychiatry)	6/6/2004
18	Slide Show Presentation at Am. Academy of Child & Adoles. Psychiatry re: Celexa by Dr. Jeffrey Jonas (Forest Labs)	10/16/2003
19	Excerpt of Danish Text and Translation Referencing Celexa Trial	No Date
20	Editorial - The "File Drawer" Phenomenon: Suppressing Clinical Evidence	2/17/2004
21	New York Times Article - A Medical Journal Quandary: How to Report on Drug Trials	6/21/2004
22	New York Times Article - Drug Maker Acknowledges Some Negative Test Results	6/26/2004
23	Forest Labs - Study Report for Protocol - A Randomized, Double-Blind, Placebo-Controlled Eval. Of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression	4/8/2002
24	Integrated Clinical Study Report - Investigational Product Citalopram	3/21/2002
25	Press Release: Forest Announces Results of Recently Completed Lexapro ® Pediatric Depression Clinical Trial	6/24/2004
26	Press Release: Forest Discusses Disclosure of Citalopram Clinical Trial Data in Children and Adolesents	6/24/2004
27	Agreement with NY AG's Office	9/7/2004
	Bristol-Myers	
28	NCDEU Poster Abstracts - Session II 64 Efficacy and Safety of Nefazadone in the Treatment of Adolescents with Major Depressive Disorder (NIMH Conference)	June 12,2002
29	Small Version of Poster in #27	June 12,2002
30	Article: "Nefazodone Pharmacokinetics in Depressed Children and Adolescents", Findling et	8/1/2000

Tab	Document Description	Date
31	Final Study Report: Nefazodone Protocol: CN104141 (Selected Pages)	2/27/2002
32	Final Study Report: Nefazodone Protocol: CN104187 (Selected Pages)	3/26/2002
33	Efficacy and Safety of Nefazodone in Adolescent with MDD - Rynn, et. al. - American	May-04
	Wyeth	
34	Poster Abstract Presentation: "Efficacy and Safety of Venlafaxine ER in Children and Adolescents With Major Depressive Disorder" (2 MDD RCT Studies)	May-04
35	Poster Abstract Presentation: "Long-Term Efficacy and Safety of Venlafaxine ER in Children and Adolescents With Major Depressive Disorder" (Open Label MDD Extension Trial)	May-04
36	Poster Abstract Presentation: "Venlafaxine ER in the Treatment of Children and Adolescents With Generalized Anxiety Disorder"	May-04
37	Poster Abstract Presentation: "Venlafaxine ER in Children and Adolescents with SAD"	May-04
38	Study Report - Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents with Major Depression: Final Report - Protocol No.: 0600B1-394-US (selected pages)	7/1/2002
39	Study Report - Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents with Major Depression: Final Report - Protocol No.: 0600B1-382-US (selected pages)	7/23/2002
40	HHS Letter to Kenneth R. Bonk - Wyeth Pharmaceuticals Re: Labelling Changes	5/1/2004
41	Dear Healthcare Letter - Re: Pediatric Use of Effexor	8/22/2003
42	August 2003 - Response Letter - Re: Use of Venlafaxine	August-04
	Organon	
43	Oral Presentation by Emslie at Am Ac. Clinical Psychiatry Conf., Hawaii	10/25/2001
44	Clinical Trial Report - Remeron (selected pages)	April-01
45	American Society of Clinical Pharmacology and Therapeutics Vol. 71, Number 2	
	Pfizer	
46	Final Study Report: Sertraline Protocol: A0501001 (selected pages)	10/3/2001
47	Final Study Report: Sertraline Protocol: A0501017 (selected pages)	10/10/2001
48	Article: "Efficacy of Sertraline in the Treatment of Children and Adolescents with Major Depressive Disorder," Wagner et al (JAMA)	8/27/2003
	Eli Lilly	
49	Principles of Medical Research Clinical Trial Registry	
50	Press Release: Lilly to Disclose Results of All Clinical Trials For Marketed Products	8/3/2004
51	Abstract "TADS" Randomized Controlled Trial (JAMA)	August-04
	PhRMA	
52	PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results	No Date
53	WSJ Article - "New Web Site To Offer Results of Drug Studies"	9/7/2004
	AMA	
54	Report of the Council on Scientific Affairs - CSA Report 10-A-04	Jun-04
55	Release: AMA Recommends That DHHS Establish a Registry For All U.S. Clinical Trials	6/15/2004
56	Release: AMA Encouraged By Early Signs of Industry Support For National Clinical Trials Registry	6/18/2004
	FDA	
57	"Best Pharmaceuticals for Children Act"	1/3/2002

Tab	Document Description	Date
58	Memorandum - Dept.of Health and Human Services - From Thomas P. Laughren, M.D. Subject - Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee	1/5/2004
59	Food and Drug Modernization Act (FDAMA) Section 113: Status Report on Implementation	7/6/2004
60	Sample Written Request for Pediatric Study on Antidpressants	
61	FDA Response to Question 11 of Committee's March 24 letter Re: Pediatric Studies	
	FDA - Reviews and Evaluations of Clinical Data	
62	Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies	8/23/2004
63	Review of Clinical Data - Citalopram - Celexa	8/20/2004
64	Review of Clinical Data - Mirtazapine - Remeron	8/20/2004
65	Review of Clinical Data - Nefazodone - Serzone	8/20/2004
66	Review of Clinical Data - Paroxetine - Paxil	8/20/2004
67	Review of Clinical Data - Sertraline - Zoloft	8/20/2004
68	Review of Clinical Data - Venlafaxine - Effexor	June-04
69	FDA Powerpoint - Re: Drug Utiliazation for Antidepressants Among Children & Adolescents	2/2/2004
	Miscellaneous	
70	PhRMA Clinical Study Results Database Proposal	No Date
71	Drug Company Sales Chart	No Date
72		
73		
74		

Press Release

1

GlaxoSmithKline

Issued – Thursday 10 June 2004, London UK and Philadelphia, USA

GlaxoSmithKline Clarifies Availability Of Clinical Trial Data On Paroxetine In Adolescent and Paediatric Patients

GlaxoSmithKline's policy is to ensure transparency of the clinical data the company collects on its marketed medicines. Specifically, we endorse the PhRMA principles that call for timely publication of meaningful trial results.

With regard to clinical trial data on paroxetine, GSK has already provided data that were collected during clinical trials in adolescent and paediatric patients to the US, UK, European and other regulatory agencies.

In addition, data have previously been made available to healthcare professionals through publication in peer-reviewed journals, poster presentations at scientific meetings, and medical letters to physicians. This approach is accepted standard practice for making data available.

However, in order to clarify the nature of these data, GSK will shortly be making available summaries of the safety and efficacy data from individual reports of the clinical studies conducted with paroxetine in adolescent and paediatric patients, as well as a bibliography of public communications derived from these studies, and the US letter to physicians summarising these data. This information will be available through the media room on the company's corporate website (www.gsk.com).

Paroxetine has not been approved in Europe or North America for treatment of patients younger than 18 years of age. It is GlaxoSmithKline's policy not to promote off label use of any of our medicines.

GlaxoSmithKline is one of the world's leading research-based pharmaceutical and healthcare companies. For more information on GlaxoSmithKline visit www.gsk.com.

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Press Release

2

GlaxoSmithKline

Issued -- Friday 18 June 2004, London

GlaxoSmithKline Announces Major Advance In On-Line Access To Clinical Trial Information

GlaxoSmithKline (GSK) announced today that it will create an electronic database to enable dissemination over the Internet of information about GSK-sponsored clinical trials.

The database, to be called the GSK Clinical Trial Register, will provide summaries of trial protocols and corresponding results for GSK-sponsored trials of marketed medicines. In addition, the register will provide references to publications that have appeared in the medical literature. The register will be accessible to physicians and the public.

"The GSK Clinical Trial Register will be a major advance in providing on-line access to information to support patient care, facilitating access to study summaries by putting them on a single Internet site," said Dr. Tadataka Yamada, chairman, Research & Development, GSK. "It is important to emphasize, however, that prescribing information approved by regulatory agencies must continue to guide appropriate use of our medicines."

GSK will continue to communicate clinical data in journals, at scientific meetings, and in letters to healthcare professionals.

The register has been under consideration and development for several months; its availability will be announced when it first appears on the GSK corporate Web site.

GlaxoSmithKline is one of the world's leading research-based pharmaceutical and healthcare companies. For more information on GlaxoSmithKline visit www.gsk.com.

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Glaxo website "Fact sheet"
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RE: USE OF PAXIL CR® OR PAXIL® IN PEDIATRIC PATIENTS

SUMMARY

- Paxil CR® (paroxetine HCl) Controlled Release and Paxil® (paroxetine HCl) are not approved by the US Food and Drug Administration (FDA) for use in treating any indications in the pediatric patients (less than 18 years of age: children and adolescents).

- A search of the published literature identified several studies discussing the use of *Paxil* in pediatric patients (children and adolescents) for the treatment of major depressive disorder (MDD), obsessive compulsive disorder (OCD), social anxiety disorder or panic disorder. Patient ages ranged 5 to 18 years and the dosage of *Paxil* ranged 5 to 80 mg/day. No studies were identified that discussed the use of *Paxil* for the treatment of generalized anxiety disorder (GAD) or posttraumatic stress disorder (PTSD) in pediatric patients. No studies were identified examining *Paxil CR* in pediatric patients.

- From an efficacy standpoint, trials in pediatric patients have shown *Paxil* to be statistically superior to placebo in the treatment of OCD and social anxiety disorder. The studies did not show a benefit for the treatment of MDD in pediatric patients. Conclusions regarding the efficacy and safety of *Paxil CR* and *Paxil* in pediatric patients for the treatment of panic disorder, GAD, and PTSD await further study.

- On March 22, 2004, the FDA issued a Talk Paper and Public Health Advisory to further caution clinicians, patients, families and caregivers of patients about the need to closely monitor both adults and children with depression being treated with antidepressants, especially at the beginning of treatment, or when the doses are changed with either an increase or decrease in the dose (1). The FDA asked manufacturers of 10 antidepressant drugs to change their products' labeling to recommend monitoring all patients for worsening of depression and the emergence of suicidal ideation, regardless of the cause of such worsening. These changes have now been finalized. Please see complete Warnings (Clinical Worsening and Suicide Risk) and Precautions (Information for Patients) sections of the prescribing information for details.

- The FDA has been closely reviewing the results of antidepressant studies since June 2003 to evaluate reports that may suggest an increased risk of suicidal thoughts and actions in patients when given antidepressants (2, 3). However, it is not yet clear whether antidepressants contribute to the emergence of suicidal thinking and behavior.

- In the GlaxoSmithKline pediatric trials, which included more than 1100 patients (aged 7 to 18 years) treated with *Paxil*, no patients committed suicide. In pooled analyses of the pediatric placebo-controlled trials, a difference was seen between *Paxil* and placebo in suicidal thinking and suicide attempts. The incidence of adverse events possibly related to suicidal behavior while on therapy (treatment phase plus taper phase) was 2.4% (18/738) of patients treated with *Paxil* compared to 1.1% (7/647) for placebo. The incidence of adverse events possibly related to suicidal behavior while on therapy plus 30 days of follow-up (treatment phase, taper phase and follow-up period), was 3.4% (25/738) of patients treated with *Paxil* and 1.2% (8/647) in the placebo group. Please refer to Table 4 for incidence of events by disorder.

- In additional analyses of the depression rating scale suicide items, no statistically significant difference was seen between *Paxil* and placebo. Please refer to Table 5 for these results.

Some information contained in this response may be outside the approved Prescribing Information for *Paxil CR* or *Paxil*. This response is not intended to offer recommendations for administering *Paxil CR* or *Paxil* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of *Paxil CR* or *Paxil*, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for *Paxil CR* or *Paxil*.

BACKGROUND

In the US, major depressive disorder (MDD) has a lifetime prevalence of 16.2% and a 12-month prevalence of about 6.6% in adults (4). The average age of onset is during the late twenties, however by adolescence the prevalence of depression is approximately 5% (5, 6). After puberty, depression occurs twice as often in females than males (4, 7). Major depressive disorder is strongly associated with anxiety disorders in adults and pediatrics (8). Obsessive compulsive disorder (OCD) is rare in children, however by late adolescence the prevalence is similar to that of adults. The incidence of social anxiety disorder in pediatrics may be as high as 4% based upon DSM-IV criteria. The prevalence of depression and anxiety disorders increases around the time of puberty. Depression and anxiety disorders in pediatric patients may continue into adulthood if left untreated.

Important Prescribing Information (9, 10)

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Prescriptions for *Paxil CR* or *Paxil* should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms.

It should be noted that *Paxil CR* and *Paxil* are not approved for use in treating any indications in the pediatric population.

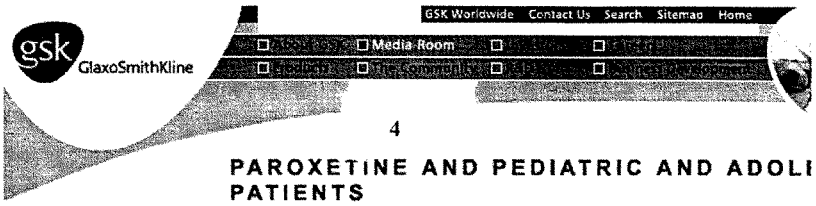
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that *Paxil CR* or *Paxil* is not approved for use in treating bipolar depression.

PUBLISHED LITERATURE

A search of the published literature identified several studies and case reviews discussing the use of *Paxil* in pediatric patients for the treatment of MDD, obsessive compulsive disorder (OCD), social anxiety disorder, or panic disorder. In the identified data, patient ages ranged from 5 to 18 years and the dosage of *Paxil* ranged 5 to 80 mg/day. A study evaluating *Paxil* therapy in adolescents with MDD and co-morbid ADHD was also identified. No studies or case reports were identified that discussed the use of *Paxil* for the treatment of generalized anxiety disorder (GAD) or posttraumatic stress disorder (PTSD) in pediatric patients. No studies were identified examining *Paxil CR* in pediatric patients. An overview of the use of paroxetine in the treatment of mood and anxiety disorders in pediatric patients has been published (11). A retrospective review of the treatment of paroxetine use in pediatric patients has been conducted (12).

Placebo-Controlled Clinical Trials

Tables 1, 2 and 3 summarize the placebo-controlled trials for *Paxil* in pediatric patients.



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PAROXETINE AND PEDIATRIC AND ADOLI PATIENTS

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Overview

GlaxoSmithKline has conducted a series of clinical studies to determine the efficacy and safety of paroxetine in treating children and adolescent patients with major depressive disorder, obsessive compulsive disorder and social anxiety disorder/social phobia. In the interest of further making the results of these studies available to all interested parties, GSK is posting to this Web page the following documents:

Clinical Study Reports
These are the formal study reports, which are the basis of submissions to the FDA, EMEA, MHRA and other regulatory agencies for all the studies of paroxetine in children and adolescents. They are presented here in two parts, the report Synopses, and the Full Reports (text and associated tables). [Because their size is many hundreds of pages, the appendices, which include line listings of raw data, the original protocol and its amendments, records of IRB approvals, etc., are not included. Names of investigators and sites have been redacted to preserve confidentiality.]

Bibliography of publications
This is a list of all the publications in peer-reviewed journals and poster presentations at scientific meetings which have been derived from GSK-sponsored studies of paroxetine in adolescents and children.

Medical Information Letter
This letter is sent to healthcare professionals in the United States who request information about paroxetine and its use in children and/or adolescents.

Paroxetine has not been approved in Europe or North America for the treatment of patients younger than 18 years of age.

Latest News:

GlaxoSmithKline availability of clin on paroxetine in paediatric patien

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Study Synopsis a
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PAXIL: Study 329 (MDD)
pg 1-4, 9

Report Synopsis

Title

A Multi-center, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression - Acute Phase (29060/329)

Investigators and Centers

Investigators from 10 centers in the United States and 2 in Canada participated in the study. All were affiliated with either a university or a hospital psychiatry department and had extensive experience in treating adolescent patients.

Publications

Keller MB, Ryan ND, Birmaher B, Klein RG, Strober M, Wagner KD, Weller EB, Paroxetine and Imipramine in the Treatment of Adolescent Depression. Abstract NR206, Annual Meeting of the American Psychiatric Association (APA), Toronto Ontario, Canada, 2 June 1998.

Wagner KD, Birmaher B, Carlson G, Clarke G, Emslie G, Geller B, Keller M, Klein R, Kutcher, S, Papatheodorou G, Ryan N, Strober M, Weller E, Safety of Paroxetine and Imipramine in the Treatment of Adolescent Depression. Abstract 69, Annual Meeting of New Clinical Drug Evaluation Program (NCDEU), Boca Raton, Florida, USA, 11 June, 1998,

Study Dates

The first patient received study medication on 20 April 94, the final patient was enrolled on 15 March 1997. The final study visit for the acute phase occurred on 07 May 1997, the final study visit for the continuation phase occurred on 15 February 1998.

Objectives

The primary objective was to compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression.

The secondary objectives were as follows: to identify predictors of treatment outcomes across clinical subtypes of major depressive disorder; to provide information on the safety profile of paroxetine and imipramine when these agents were given for an extended period of time; to estimate the rate of relapse among imipramine, paroxetine and placebo responders who were maintained on treatment.

This report presents the results from the 8 week acute phase. Findings from the continuation phase, which include long term safety and the analysis of relapse, will be reported separately.

Study Design

This was a multi-center, double-blind, placebo controlled, parallel group trial of the efficacy and safety of treatment with paroxetine or imipramine compared with placebo in adolescents with major depressive disorder. The study plan included two phases, an acute phase in which patients were treated for 8 weeks and a continuation phase in which responders had the option to continue to receive blinded study medication for an additional 6 months. Eligible patients were randomized to treatment with paroxetine, imipramine or placebo for 8 weeks; clinic visits for efficacy and safety assessments were made weekly. At the completion of the 8 week study, patients who met specific criteria for a clinical response could be continued on the same medication in a double-blind manner for a 6 month continuation treatment phase; clinical visits were made monthly.

Study Population

Eligible patients were adolescents (12 years 0 months through 18 years 11 months inclusive), were currently in an episode of major depression (DSM-III-R criteria) for at least 8 weeks, and had a total score $\geq$ 12 on the 17-item Hamilton Depression Scale (HAM-D).

Treatment and Administration

Test product: Paroxetine was supplied as film coated, capsule shaped tablets, yellow containing 10 mg (batch no U95085) and pink containing 20 mg (batch no. U95086).

Reference therapies: Imipramine (50 mg) was bought commercially and supplied as green film coated round tablets (batch nos. U95121, U-93135, and U-93139). "Paroxetine placebos" (batch no. U95084) matched the paroxetine 20 mg tablets, and "imipramine placebos" (batch no. U95087) matched the imipramine tablets.

All tablets were over-encapsulated in bluish-green capsules to preserve blinding. Patients took their study medication twice daily, once in the morning and once at night. Total daily doses of imipramine were 50, 100, 150, 200, 250, and 300 mg for dosing levels 1 to 6, respectively. Daily doses of paroxetine were 20 mg for levels 1 to 4, 30 mg for level 5, and 40 mg for level 6. At the beginning of the study, all patients were started at level 1 and titrated up to level 4 at weekly intervals, regardless of response. Non-responders could be titrated up to level 5 or 6 during the next 4 weeks.

Evaluation Criteria

Efficacy Parameters: The efficacy assessments in the trial included the Hamilton Rating Scale for Depression (HAM-D), the 9-item depression subscale of the Schedule for Affective Disorders and Schizophrenia for School-age Children - Lifetime Version (K-SADS-L), the Clinical Global Improvement (CGI), and the following functional and quality of life assessments: the Self Perception Profile (SPP), the Autonomous Functioning Checklist (AFC), and the Sickness Impact Profile (SIP).

The protocol defined the primary efficacy parameters as the change from baseline in the HAM-D total score, and the proportion of responders defined as patients with a 50% reduction in the total HAM-D or a score of 8 or less. Secondary parameters included the change in baseline in the K-SADS-L depression subscale, the mean CGI score, and the functional/quality of life instruments. An analytical plan developed prior to opening of the blind also described additional outcome measures including patients in "remission" (a score of 8 or less on the HAM-D total), and the mean change in the depressed mood items from the HAM-D and the K-SADS-L instruments.

Safety Parameters: Adverse experiences, vital signs and body weight; clinical laboratory evaluations, and electrocardiograms (EKGs).

Other Parameters: Plasma paroxetine and serum IMI and DMI concentrations were determined at the completion of 4 and 8 weeks of treatment.

Statistical Methods

All patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment were included in the ITT efficacy population. Statistical conclusions concerning the efficacy of paroxetine and imipramine were made using data obtained from the last observation carried forward (LOCF) and observed cases (OC) datasets. The last observation carried forward consisted of each patient's last on-therapy assessment during the acute phase. All hypotheses were two sided. The comparisons of interest were paroxetine vs. placebo and imipramine vs. placebo at week 8 LOCF. Hypotheses concerning these comparisons were tested at the alpha level of 0.05. No comparisons were made between paroxetine and imipramine. Interactions were considered significant at the 10% level of significance. Continuous efficacy variables were analyzed by analysis of variance using the general linear model (GLM) procedure of SAS with effects for treatment and investigator. Categorical data were analyzed by logistic analysis using the categorical modeling procedures (CATMOD) of SAS with effects for treatment and investigator. Covariate analyses were also carried out using the general linear model procedures. For the covariate analyses, each analysis used a model including effects for treatment, covariate, and treatment by covariate interaction.

Patient Disposition and Key Demographic Data

Two hundred and seventy five patients were enrolled in the acute phase and randomized to the three treatment regimens: 93 paroxetine, 95 imipramine, 87 placebo. The baseline demographic features and the clinical features of depression of the three treatment groups were comparable at entry. Over 70% of the paroxetine and the placebo patients completed the 8-week acute phase. In contrast, 60% of imipramine patients completed the acute phase. The most common reason for early withdrawal for the imipramine group was adverse events.

Laboratory Tests:

The number of patients identified with laboratory values of clinical concern was low in all treatment groups. None were considered to be of clinical significance.

Conclusions

This study supports that paroxetine is beneficial in treating adolescents with major depression although the support is derived mainly from secondary measures. The superiority of the paroxetine response over placebo appears less than seen in adults; this may be a result of the weekly supportive psychotherapy sessions allowed by the protocol producing a large "placebo" response. The safety profile of paroxetine in the adolescent appears similar to that reported in adults. The study provided little support for the benefit of imipramine in treating adolescent depression.

PAxil: Study 377
pgs 173.

Report Synopsis

Study Title

A Double-blind, Multicentre Placebo Controlled Study of Paroxetine in Adolescents with Unipolar Major Depression

Investigator(s) and Center(s)

The study was carried out in 33 centres in Belgium, Italy, Spain, United Kingdom, Holland, Canada, South Africa, United Arab Emirates, Argentina and Mexico.

Publication

None published as of August 1998.

Study Dates

26th April 1995 to 15th May 1998.

Objective(s)

The primary objective of the study was to compare the efficacy of paroxetine and placebo in the treatment of adolescents with unipolar, major depression.

The secondary objective of this study was to assess the safety and tolerability of paroxetine in adolescents with unipolar, major depression.

Study Design

This was a multicentre, double-blind, randomised, parallel group, placebo controlled study to compare the efficacy and safety of paroxetine (20-40mg daily, flexible dose) and placebo in the treatment of adolescents with unipolar, major depression as defined by DSM-IV criteria. After Screening patients entered a 2 week, single-blind, placebo run-in period. Eligible patients were then randomised to receive paroxetine (20-40mg daily, flexible dose) or placebo (2:1 randomisation) for a period of 12 weeks. Patients returned to the clinic at the end

of Weeks 1, 2, 3, 4, 6, 8 and 12 for assessments of efficacy, safety, concomitant medications and general compliance with study procedures. Patients withdrawing prematurely from the study received 2 week run out medication. At the end of the study all patients were down-titrated off study medication over a period of 2 weeks and returned to the clinic for a last assessment of safety at the end of Week 14.

Study Population

Male or female patients aged between 13 years and 18 years 11 months at Screening, with a current diagnosis of unipolar, major depression as defined by DSM IV criteria, a C-GAS score <69 and a MADRS score ≥16 were eligible to enter the study.

Treatment and Administration

Study medication was formulated as capsules for oral administration twice a day. Batch numbers: paroxetine 10mg – M94002 and M96328; paroxetine 15mg – M94003; paroxetine 20mg – M94004, M95004 and M96330; placebo – CT2/4301 and M96332

Evaluation Criteria

Efficacy Parameters

The primary efficacy parameters were the proportion of patients with a 50% or greater reduction in MADRS score between baseline and study endpoint, and the change from baseline to study endpoint in K-SADS-L depression subscale. The secondary efficacy variables were: change from baseline in MADRS total score; change from baseline in CGI severity of illness score; CGI global improvement score; change from baseline in BDI and change from baseline in MFQ. All primary and secondary variables were analysed at Weeks 6, 8 and study endpoint. Please note: the protocol states analysis of the secondary variables at week 6 and endpoint only. An amendment to the reporting and analysis plan prior to database freeze added week 8 as a time point for analysis, this should have been reflected in the protocol as a protocol modification.

Safety Parameters

Safety parameters consisted of adverse experiences and assessment of vital signs and laboratory data.

Statistical Methods

The proportion of patients responding (≥50% reduction in MADRS total score) was analysed using logistic regression (PROC LOGISTIC of SAS). The model included treatment group, country group, and covariates of age and baseline score. Odds ratios and 95% confidence intervals were presented. The effect of adding treatment by country group interaction into the model was assessed with the above terms in the model. If the treatment by country group interaction was not statistically significant ($p \geq 0.1$), it was dropped from the model. Treatment by covariate and covariate by covariate interactions were assessed in a similar way.

The mean change from baseline in K-SADS-L depression subscale score, MADRS, BDI and MFQ total scores were analysed using analysis of covariance (PROC GLM of SAS) with factors treatment, country group, age and baseline score. Least squares means were compared at the 5% level and 95% confidence intervals presented for treatment differences. The effect of adding treatment by country group interaction into the model was assessed with the above terms in the model. If the treatment by country group interaction was not statistically significant ($p \geq 0.1$), it was dropped from the model. Treatment by covariate and covariate by covariate interactions were assessed in a similar way.

The changes from baseline in the CGI severity of illness (an ordered categorical rating scale) were analysed non parametrically using the Wilcoxon Rank Sum test (PROC NPAR1WAY of SAS). No adjustment was made for country grouping or covariates. The CGI global improvement scores were compared using Cochran-Mantel-Haenszel chi-square tests (stratifying by country group) at the 5% level using PROC FREQ of SAS.

Patient Disposition and Key Demographic Data

Patient disposition and key demographic data are shown below.

Withdrawals Due to Adverse Experiences

For all randomised patients, 22 out of 187 (11.8%) patients in the paroxetine group withdrew due to adverse experiences compared to 7 out of 99 (7.1%) in the placebo group. This difference was not statistically significant.

Vital Signs

Changes in mean vital signs values between baseline and week 12 were small for both treatment groups and of no clinical concern, and there were no differences between the treatment groups regarding vital signs values meeting sponsor-defined clinical concern criteria.

Laboratory Tests

Similar proportions of patients in the two treatment groups had one or more laboratory value meeting sponsor-defined clinical concern criteria (paroxetine 29.1%, placebo 33.3%).

Conclusion(s)

The results failed to show any superiority for paroxetine over placebo in the treatment of adolescent depression. A significant age by treatment interaction was detected in both of the primary efficacy variables and most of the secondary, indicating evidence of a different treatment effect dependent on age. Therefore conclusions drawn on the data presented overall should be treated with caution.

Paroxetine was well tolerated with no unexpected finding regarding adverse experiences, vital signs or laboratory values.

PAXIL · STUDY 701 (MDD)
Pgs 1, 2 - 5

Report Synopsis

Study Title: A Randomized, Multicenter, 8-Week, Double-blind, Placebo-Controlled Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Major Depressive Disorder (29060/701)

Investigators and Centers: The study was conducted in 40 centers in the US and 1 in Canada.

Publication: No publication as of 20 July 2001.

Study Dates: The first dose of randomized study medication was administered on 20 March 2000 and the last dose of study medication (excluding Taper) was administered on 24 January 2001.

Objectives: To compare the efficacy of paroxetine versus placebo in the treatment of children and adolescents with Major Depressive Disorder (MDD), as measured by the change from Baseline in the Children's Depression Rating Scale–Revised (CDRS–R) Total Score at Week 8 last observation carried forward (LOCF) endpoint.

To compare the safety and tolerability of paroxetine versus placebo in the treatment of children and adolescents with MDD.

Study Design: This was an 8-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose trial in children (ages 7 through 11) and adolescents (ages 12 through 17). The randomization scheme was stratified by age subgroup.

Study Population: Male and female outpatients, 7 to 17 years of age, who met Diagnostic and Statistical Manual version IV (DSM-IV) criteria for Major Depressive Disorder (single episode [296.2] or recurrent [296.3]) and who satisfied all other entrance criteria were eligible for the study. Each age subgroup was to account for at least 40% of the total number randomized.

Treatment and Administration: Both double-blind medications, i.e., paroxetine and placebo, were in the form of white oval, film-coated tablets for oral administration once daily. They were identical in size, shape and color. All active tablets contained 10 mg paroxetine. Batch numbers were U99074 and U00001 for paroxetine 10 mg and U96161 for placebo.

Following a 1-week Screening Phase, eligible patients were randomly assigned (1:1) to paroxetine or placebo. All randomized patients initiated therapy at Dose Level (DL) 1 (10 mg/day or matching placebo) for the first week of therapy. The dose could be titrated up in 10 mg weekly increments after the initial dose level, up to a maximum of 50 mg per day (DL 5), according to the judgment of the investigator based on efficacy and tolerability of the study medication. Dose reductions were allowed for an adverse event (AE); such a reduction was permitted only once. A Taper Phase with a gradual reduction of study medication was required for all patients on DL 2 or higher at the end of the study. Total study duration per patient, including Taper Phase, was a maximum of 15 weeks.

Evaluation Criteria

Efficacy Parameters: The primary efficacy variable was the change from Baseline in the CDRS–R total score.

The two treatment groups showed no marked imbalances in any of the patient characteristics, although there was a slightly higher proportion of patients with comorbid psychiatric illnesses in the paroxetine group than in the placebo group.

Demography and Baseline Characteristics (ITT Population)

	Paroxetine	Placebo	Total
Age Group: Total	101	102	203
Females:Males	48:53	47:55	95:108
Mean age (SD): years	11.9 (3.00)	12.1 (2.95)	12.0 (2.97)
White: n (%)	76.2%	82.4%	79.3%
Baseline CDRS–R Total Score: Mean (SD)	60.7 (9.37)	62.6 (8.96)	61.7 (9.19)
Psychiatric Comorbidity Yes:No	28:73	18:84	46:157
Age Group: Children	49	47	96
Females:Males	23:26	18:29	41:55
Mean age (SD): years	9.2 (1.28)	9.4 (1.28)	9.3 (1.28)
White: n (%)	69.4%	83.0%	76.0%
Age Group: Adolescents	52	55	107
Females:Males	25:27	29:26	54:53
Mean age (SD): years	14.4 (1.60)	14.5 (1.72)	14.4 (1.66)
White: n (%)	82.7%	81.8%	82.2%

Efficacy Results

Datasets: Primary inferences from efficacy analyses were based on the ITT population at Week 8 LOCF. In addition, the primary efficacy variable was analyzed using the Per Protocol (PP) population.

Primary Efficacy Variable: Analysis of the primary endpoint provided no evidence that paroxetine was more efficacious than placebo in the treatment of MDD in the pediatric population. Although there was a large mean change from Baseline in CDRS–R total score in paroxetine-treated patients, there was also a large placebo effect. The adjusted mean difference between paroxetine and placebo in change from Baseline in CDRS–R total score at Week 8 LOCF for the ITT population was 0.8 points in favor of placebo (95% confidence interval [-3.09, 4.69], $p = 0.684$). This result was supported by the analysis of the PP population and the analysis of the Week 8 OC dataset in each population.

There was evidence of a statistically significant treatment by age group interaction ($p = 0.049$), indicating varying treatment effect across the age groups; therefore the analysis was carried out separately for each age group. Children (ages 7 through 11) exhibited a 5.3-point difference in favor of placebo in the CDRS–R total score change from Baseline, although this difference was not statistically significant ($p = 0.054$). Adolescents (ages 12 through 17) exhibited a 2.6-point difference in favor of paroxetine in the CDRS–R total score change from Baseline; again this difference was not statistically significant ($p = 0.375$).

Secondary Efficacy Variables: None of the secondary efficacy variables (CGI Severity of Illness, CGI Global Improvement, GAF) provided evidence that paroxetine is more efficacious than placebo in the treatment of children and adolescents with MDD.

Other Efficacy Variable: Analysis of the additional variable of interest (KADS, adolescents only) provided no evidence of a statistically significant benefit of paroxetine over placebo.

Electrocardiograms: No abnormal ECGs (as assessed by the investigator) were seen at Week 8 or Early Withdrawal in either treatment group.

Conclusions

The results of this study failed to provide evidence for the primary and secondary endpoints that paroxetine is more efficacious than placebo in treating children and adolescents with MDD.

Paroxetine was generally well tolerated in this pediatric population compared to placebo, with no unexpected adverse events or findings in laboratory tests, vital signs, or ECGs. More paroxetine patients than placebo patients withdrew due to adverse events, and more children than adolescents withdrew due to AEs in the paroxetine group. The safety profile appeared similar to that previously reported for adults except that there were few gender-specific adverse events.

ECNP
Oct-Nov 98
Paris

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FEB 11
Rob MacRae

Adolescent depression: efficacy of paroxetine

Ray Berard, Neal Ryan*
William Slater Centre for Adolescents, Department of Psychiatry, UCT Medical School/Groote Schuur Hospital, Cape Town, South Africa.
*University of Pittsburgh School of Medicine, Pittsburgh, USA.

Introduction

- Depression in adolescents is a common problem; life-time prevalence rates of over 15% have been reported (1). 'Masking' of symptoms and a typical presentation such as hyperphagia, hypersomnia and externalisation can complicate the diagnosis. In addition, the use of rating scales to aid in detection and monitoring of treatment can be problematic as many have not been validated for this age group.
- Failure to diagnose and treat effectively can lead to the development of comorbid anxiety disorders, the impairment of cognitive and psychosocial functioning, and a high risk of suicide.
- Because of the chronic nature of depression, treatment needs to be well tolerated, with minimal disruptive effects on lifestyle. Antidepressants with concomitant efficacy against anxiety disorders provide the clinician with the option of monotherapy in patients presenting with these disorders.
- Few trials have been conducted to investigate antidepressant efficacy in this group of patients, and most have failed to show significant benefits over placebo (2). Small open-label studies have shown paroxetine to be effective in treating depression in adolescents (3). Reported here are the results of a study which compared the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression.

Methods

- This was a double-blind, multi-centre, parallel-group, placebo-controlled study conducted in 12 centres in North America. Patients were randomised to receive either paroxetine (n=93), imipramine*(n=95) or placebo (n=87). Patients randomised to paroxetine treatment began on 20 mg/day. Patients randomised to imipramine began on 50 mg/day, titrated up to 200 mg/day by week 4 (Figure 1). If no response had been observed by 4 weeks of treatment, the respective doses were titrated upwards during the remaining 4 weeks, to a maximum of 40 mg/day paroxetine and 300 mg/day imipramine.

Results

- The three treatment groups were balanced with respect to demographic variables (Table 1).

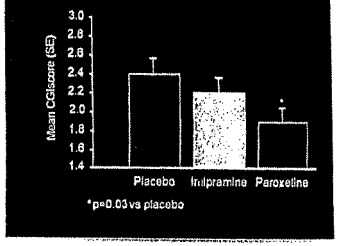
Table 1. Patient demographics and clinical characteristics at entry

	Paroxetine n=93	Imipramine n=95	Placebo n=87
Mean age, years (SD) Female (%)	14.8 (1.6) 62	14.9 (1.7) 59	15.1 (1.6) 66
Duration of current depressive episode (months) mean (SD)	14.4 (17.5)	14.2 (17.9)	12.6 (16.6)
Age at first episode (years) mean (SD)	13.2 (2.8)	13.2 (2.7)	13.5 (2.3)
Patients with >1 prior episode (%)	18	20	22
Mean HAM-D score at entry (SD)	19.0 (3.8)	18.1 (3.9)	19.0 (3.7)

Primary efficacy parameters

- By week 4, approximately half the patients in each treatment group were classed as responders (Figure 2). This proportion increased further during the study and by week 8 there was a statistically significantly greater number of responders in the paroxetine group compared with placebo (81% vs 65%). The imipramine group did not separate from placebo for this efficacy parameter (73% vs 65%).

Figure 4. Mean CGI global improvement score (SE) at week 8

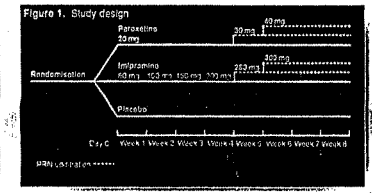


- A progressive reduction in mean scores on the K-SADS-L depression 9-item scale was observed during the course of the study in all three treatment arms. The mean decrease from baseline at week 8 was greate in the paroxetine group, but this did not reach statistical significance.

Safety

One hundred and ninety patients completed the 8-week study (Table 2). Tl included 72% of patients receiving paroxetine, 60% of those receiving imipramir and 76% of those receiving placebo. Thirty-two percent of the treatment discontinuations in the imipramine group were due to adverse events, compar with 10% and 7% in the paroxetine and placebo groups, respectively.

Figure 1. Study design



- The Clinical Management for Adolescent Depression Manual was used to define the level of psychosocial supportive therapy permitted between patients and investigators. Interpersonal, cognitive or behavioural psychotherapy was not permitted.
- Adolescents (aged between 12 years and 18 years 11 months) who were currently experiencing an episode of major depression (DSM-III-R criteria) of a minimum duration of 8 weeks, and diagnosed using the Schedule for Affective Disorders and Schizophrenia for School-age Children - Lifetime version (K-SADS-L), were recruited to the study. In addition, patients had to have a total score of ≥12 on the 17-item Hamilton Depression Scale (HAM-D) and a severity score of <60 on the Child Global Assessment Scale.

Efficacy parameters

- Primary:
  - the proportion of responders with a ≥ 50% reduction in the total HAM-D score or a HAM-D score of ≤8 at week 8;
  - change from baseline in HAM-D total score at week 8.
- Secondary:
  - mean Clinical Global Impression (CGI) global improvement scores;
  - change from baseline on the 9-item depression subscale of the K-SADS-L at week 8.

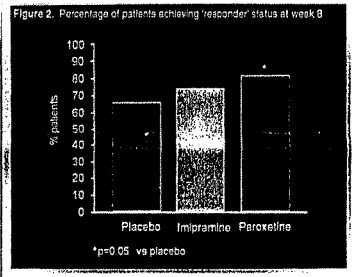
Safety assessments

- Adverse events were monitored by non-leading questions. Clinical laboratory tests were performed at the screening visit and at the end of the study. Treatment discontinuations due to either adverse events or lack of drug efficacy were also recorded.

Statistical methods

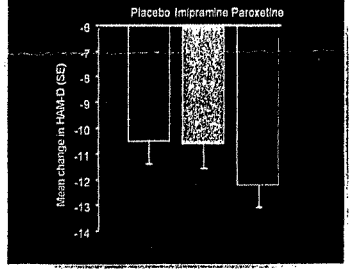
- Statistical conclusions concerning the efficacy of paroxetine and imipramine were made using data obtained from the last assessment of the intention-to-treat population (observed cases). Changes from baseline to endpoint in HAM-D score, CGI Improvement Scale scores and changes from baseline in the 9-item depression subscale of the K-SADS-L were analysed using a 2-factor analysis of variance. The proportion of patients who responded to treatment were analysed using logistic analysis implemented in the SAS procedure Categorical Modelling. Pair-wise comparisons between the two active agents and placebo were made at the 0.05 level of significance using the Least Square Means procedure.

Figure 2. Percentage of patients achieving 'responder' status at week 8



- After 8 weeks of treatment, patients receiving paroxetine experienced a greater decrease in total HAM-D score than the placebo group (Figure 3). This difference showed a trend towards statistical significance. The change in HAM-D score in the imipramine group was comparable with that of placebo.

Figure 3. Mean change from baseline (SE) in total HAM-D score at week 8



Secondary efficacy parameters

- Progressive improvement in mean CGI scores (global improvement item), with continuing treatment, occurred in all groups. At week 8, a statistically significantly greater improvement was observed in paroxetine-treated patients, compared with those receiving placebo (Figure 4). There was no significant difference between the imipramine and placebo groups.

Table 2. Treatment discontinuations

	Paroxetine	Imipramine	Placebo
No. entered	93	95	87
Completed 6 weeks (%)	72	80	76
Reason for withdrawal (%)			
Adverse event	10	32	7
Lack of efficacy	4	1	7
*Other reason**	14	7	10
Mean dose (mg) (SD)	29.0 (8.5)	206 (64.0)	0

*Other includes patients withdrawn for protocol violations and lost to follow-up

Conclusions

- Paroxetine provides effective treatment for major depression in adolescents.
- Paroxetine is better tolerated than imipramine. Three times as many patients discontinued imipramine than paroxetine, secondary to adverse events.
- The large 'placebo' response occurring in adolescents may result from psychosocial supportive therapy provided by the investigators.
- There was little support for the use of imipramine in this vulnerable population, which is in agreement with smaller trials.

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2. Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D. *Br Med J* 1995; 310: 897-901.
3. Ramos PR, de Dios Vega JL, Cabases JSS, Sordo LS, Sanz MJM. *Eur J Clin Res* 1996; 8: 49-61.

PAROXETINE IN ADOLESCENT DEPRESSION

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Introduction

Adolescent depression is a common problem. Most estimates of prevalence are around 5%,[1] but rates as high as 9-17% have also been reported.[2]

Depression during adolescence can disrupt normal psychosocial and educational functioning at a crucial time in development - the transition from childhood to adulthood.

Suicide is a serious risk factor with unrecognised/untreated depression in adolescents. Approximately 60% of adolescent suicide attempts are made by individuals with depression,[3] and the rate of suicidal behaviour in adolescents appears to be increasing.[4]

Despite the high prevalence and associated serious consequences, adolescent depression remains under recognised and undertreated. This poster reviews the issues relating to recognition and management of adolescent depression and presents recent data from clinical studies with paroxetine in this patient group.

Adolescent depression: a difficult diagnosis?

Adolescents are a heterogeneous population, and depression in these subjects can be difficult to diagnose due to differences in presenting symptoms, such as antisocial or impulsive behaviour. Younger adolescents with depression often show irritable mood, persistent boredom, lack of energy, poor performance at school, long periods of time spent with a pet, and preoccupation with somatic symptoms. Older adolescents with depression most commonly show apathy, fatigue, diminished ability to concentrate, preoccupation with death/suicide, and low self-esteem.[4]

While 'adult' rating scales such as the Hamilton Depression Rating Scale (HAM-D) are considered valid for assessing depression in older adolescents (age 16-18 y), they have not been exclusively studied in the whole adolescent age group. Therefore, specialised screening tests have been developed for diagnosis of depression in adolescents (and children) (Table 1).

Table 1. Screening for depression in adolescents

Validated rating scales
Clinician-rated
Diagnostic Interview Schedule for Children (DISC-2.3)
Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL)
Patient-rated
Children's Depression Inventory (CDI)
Revised Psychiatric Adolescent Depression Scale (RADS)

The problem of comorbidity

Adolescent depression is often compounded by other psychiatric disorders and/or behavioural problems (Table 2). It has been suggested that over 95% of children and adolescents with depression have one other psychiatric disorder, and over 80% have two.[5]

Table 2. Common comorbidities of adolescent depression

Comorbidity
Anxiety disorders
Social anxiety disorder
Agoraphobia
Obsessive compulsive disorder
Antisocial behaviour
Conduct / oppositional disorders
Attention deficit / hyperactivity
Eating disorders
Substance abuse

The presence of comorbid conditions increases the severity and can worsen the prognosis of the depression. In these cases, the need for recognition and treatment of adolescent depression becomes even greater.

Pharmacotherapy: clinical studies of paroxetine

SSRIs have been widely investigated for treatment of depression and are generally regarded as first-line therapy. Several studies have examined the antidepressant efficacy of the SSRI paroxetine in adolescent subjects (Table 3).[6-8]

Table 3. Clinical studies of paroxetine in adolescent depression

Age group	Study design	n	Dose (mg/day)	Response rate[a] (scale)
12 y to 18 y 11 mo	Double-blind, placebo-controlled, 8 wks of treatment	275	20-40	40%[] 8 (HAM-D)
≤ 14 y	Open-label[b]	15	10-25	100% 7 (CGIS)
11y to 17y	Retrospective[c]	25	10-40	76% 6 (ICD-10)

[a] Responders defined by:
- A 50% reduction in HAMD score or a HAMD score of ≤ 8 at endpoint.
- [b] Reduction in CGIS on a graded scale ≥4
- [c] After 8 weeks treatment, no primary symptoms observed and ≤ 4 secondary symptoms observed, with a severity of mild to moderate

[] vs 59% imipramine, 51% placebo

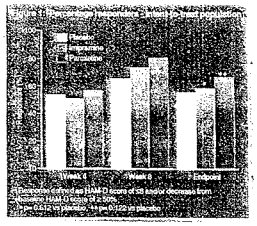
CGIS - Clinical Global Severity scale

ICD-10 - International Classification of Diseases 10

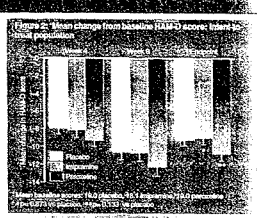
In the largest trial with paroxetine, 275 adolescents with depression who were currently experiencing an episode of major depression (DSM-III-R criteria) diagnosed using the Schedule for Affective Disorders and Schizophrenia for School-age Children - Lifetime version (K-SADS-L), were recruited by 12 centres in the USA.[6] Subjects had to have a HAM-D score of ≥12 and a severity score of ≤60 on the Child Global Assessment Scale (C-GAS).

Patients were randomised (1:1:1) for 8 weeks treatment with: flexible-dose paroxetine 20-40 mg/day, flexible-dose imipramine 200-300 mg/day, or placebo.

- The demographic characteristics of the three groups were comparable.
- By week 8, there were significantly more HAM-D 'responders' in the paroxetine group compared with placebo (p=0.051) (Figure 1). At this timepoint, the imipramine group also showed an improved response compared with placebo, but this was not statistically significant (p= 0.369).



- The paroxetine group experienced a greater reduction from baseline HAM-D score at all timepoints, compared with placebo. Reductions were less marked in the imipramine group and were similar to that observed with placebo at the end of the study (Figure 2).



- By the end of the study, the proportion of patients who experienced remission of depression (HAM-D score ≤ 8) was significantly greater with paroxetine (63%) compared with placebo (46%, p=0.019). The imipramine treatment group did not separate from placebo with respect to remission (50%, p=0.574 vs placebo).
- The large 'placebo response' observed in adolescents may be attributed to the psychosocial supportive therapy provided by the investigators.
- Paroxetine was well tolerated and had a lower incidence of withdrawals due to adverse events compared with imipramine.

Conclusions

- Adolescent depression can have serious consequences, as individuals are at a critical stage of emotional, social, and educational development.
- Paroxetine is effective in the treatment of adolescent depression and is better tolerated than imipramine.
- Paroxetine has the additional advantage of being an efficacious treatment for common psychiatric comorbidities of depression, such as social anxiety disorder and obsessive compulsive disorder.

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Summary

The CARE study is a 12-month randomized evaluation of the Depression Management Program (DMP) compared with Usual Care (UC). We identified patients with depression by administering the SCID, via telephone interview, to high utilizers of ambulatory services in three large HMOs. Patients screening positive for major depression or depression in partial remission received a HAMD assessment two weeks later. Patients meeting study eligibility criteria, including a HAMD score of 15 or higher, were asked to complete four follow-up telephone interviews over the next year. We randomized 407 consenting patients, 218 to the DMP and 189 to UC. DMP patients initiated treatment with their primary care physicians and nonresponders received increasing levels of psychiatric care. DMP patients received the Rhythms patient education program at the first visit. DMP follow-up visits and prescription refills were also tracked to improve compliance. UC patients received the care available without the DMP. The data are from unblinding the first six months of clinical data and are based upon intent to treat. Baseline HAMDs were 19.1 for DMP and 19.2 for UC. Improvements in HAMD scores were significantly greater in the DMP group at six weeks and all later assessments ($p < 0.05$) by ANOVA. Six-month HAMD scores were 11.8 for DMP vs. 15.2 for usual care. At six months DMP patients reported better physical functioning and mental health and general health perceptions than UC on the SF-20 ($p < 0.05$). At least three antidepressant prescriptions were filled in the first six months by 68.4% of DMP patients vs. 18.5% in UC ($p < 0.05$). There were three or more specialty mental health visits in the first six months by 13.3% of DMP patients vs. 9.5% in UC ($p < 0.05$). Data on indirect costs and 12-month data will soon be available and presented.

Sponsor: Pfizer Pharmaceuticals

References:

1. Katzelnick, DJ, Kobak, KA, Greist, JH, Jefferson, JW, Henk, HJ: Effect of primary care treatment of depression on service use by patients with high medical expenditures. Psychiatric Services 1997;48:59–64.
2. Henk, HJ, Katzelnick, DJ, Kobak, KA, Greist, JH, Jefferson, JW: Medical costs attributed to depression among patients with history of high medical expenses in a health maintenance organization. Arch Gen Psychiatry 1996;53:899–904.

NR206 Tuesday, June 2, 9:00 a.m.-10:30 a.m.

Paroxetine and Imipramine in the Treatment of Adolescent Depression

Martin B. Keller, M.D., Department of Psychiatry, Butler Hospital/Brown Univ., 345 Blackstone Boulevard, Providence RI 02906; Neal D. Ryan, M.D., Boris Birmaher, M.D., Rachel G. Klein, Ph.D., Michael Strober, Ph.D., Karen D. Wagner, M.D., Elizabeth B. Weller, M.D.

Educational Objectives:

This presentation will provide information on the efficacy of paroxetine and imipramine in the treatment of major depression in adolescent outpatients.

Summary:

The efficacy of paroxetine and imipramine in adolescents meeting DSM-IV criteria for major depression was assessed in a double-blind, placebo-controlled trial in 275 outpatients between the ages of 12 and 19. Patients were treated for eight weeks with doses of 20 mg of paroxetine and 200 mg of imipramine. Titration to 40 mg of paroxetine and 300 mg of imipramine was permitted for patients judged to be nonresponders. Patients were seen weekly and assessments included the 17-item Hamilton Depression Scale (HAM-D), the 7-point Clinical Global Impression of Improvement (CGI), and the 9-item depression section of the Kiddie SADS (K-SADS). Remission was defined as a score of 8 or less on the HAM-D. Among the imipramine patients, 32% withdrew for an adverse event. This compares with 10% and 7% for the paroxetine and placebo patients, respectively.

Patients treated with paroxetine demonstrated significant improvement over placebo on measures of affect, global improvement, and remission of depressive symptoms. In contrast, there was no separation from placebo on any clinical measures in patients treated with imipramine. These results support that paroxetine is an effective treatment for major depression in an adolescent outpatient population.

References:

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NR207 Tuesday, June 2, 9:00 a.m.-10:30 a.m.

Depressive Symptoms: A Risk for Mortality in Elderly

Junji Takeshita, M.D., Department of Psychiatry, University of Hawaii, 45-710 Keaahala Road, Kaneohe HI 96744; Kamal Masaki, M.D., Iqbal Ahmed, M.D., Daniel Foley, M.S., Yuan Qing Li, M.S.C., Daryl Fujii, Ph.D., G. Webster Ross, M.D., Helen Petrovitch, M.D., Lon White, M.D.

Educational Objectives:

At the conclusion of this presentation the participant should be able to describe how the presence of depressive symptomatology is a significant predictor of mortality in elderly men; and describe how appropriate treatment of depression may result in decreased mortality and improved quality of life.

Summary:

Objective: To evaluate the predictive value of depressive symptomatology as a risk factor for mortality in elderly men.

Methods: At the fourth examination (1991–1993) of the Honolulu Heart Program longitudinal cohort, the presence of depressive symptoms was assessed using an 11-question version of the CES-D (Center for Epidemiology Surveys-Depression) Scale, hereafter called CESD-11. A total of 3741 men aged 71 to 93 were examined and followed prospectively for an average of five years for all-cause mortality. Presence of depressive symptomatology was defined as a score of ≥ 9 points on the CESD-11.

Results: A total of 3263 subjects completed the CESD-11 and 321 (10%) had depressive symptomatology. Of those without depressive symptoms, 20% (584/2942) died during the five year follow-up period compared with 25% (81/321) of those with these symptoms. Five-year, age-adjusted mortality rates in those with and without depressive symptoms were 56.4 and 43.6 per 1000 person-years, respectively. Using Cox proportional hazards models, after adjusting for age, the relative risk for mortality with depressive symptoms was 1.30 ($p = 0.026$).

Conclusions: These data suggest that the presence of depressive symptomatology is a significant predictor of mortality in elderly men. Appropriate treatment of depression may result in decreased mortality and improved quality of life.

SUPREME COURT OF THE STATE OF NEW YORK
COUNTY OF NEW YORK

THE PEOPLE OF THE STATE OF NEW YORK, by ELIOT SPITZER, Attorney General of the State of New York,

Plaintiff,

against -

GLAXOSMITHKLINE, plc., d/b/a/ GlaxoSmithKline,

SMITHKLINE BEECHAM CORPORATION, d/b/a/ GlaxoSmithKline,

Defendants.

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COMPLAINT
Index No.

TO: THE SUPREME COURT OF THE STATE OF NEW YORK

The People of the State of New York, by their attorney, Eliot Spitzer, Attorney General of the State of New York, allege the following upon information and belief:

PRELIMINARY STATEMENT

1. GlaxoSmithKline, plc and SmithKline Beecham Corporation (doing business as GlaxoSmithKline and together referred to as "GSK") are collectively a pharmaceutical manufacturer with net income (adjusted earnings) in 2002 of over $6.9 billion. GSK has engaged in repeated and persistent fraud by misrepresenting, concealing and otherwise failing to disclose to physicians information in its control concerning the safety and effectiveness of its antidepressant medication paroxetine HCL ("paroxetine") in treating children and adolescents with Major Depressive Disorder ("MDD"). GSK sells paroxetine in the United States under the names Paxil® and Paxil CR™. Until 2003, GSK had market exclusivity for paroxetine in the US.

2. Paroxetine has been approved by the United States Food and Drug Administration ("FDA") as safe and effective for treating various indications in adults, including MDD, social anxiety disorder, general anxiety disorder and obsessive compulsive disorder ("OCD"). Paroxetine has not been approved for any condition or illness in children or adolescents. However, New York, like other states, permits physicians to prescribe FDA-approved drugs for conditions or diseases for which FDA approval has not been obtained when, through the exercise of independent professional judgment, the physician determines the drug in question is an appropriate treatment for an individual patient. This practice is referred to as "off-label" use, and prescribing paroxetine for children and adolescents is an off-label use.

3. Approximately 2.1 million prescriptions for paroxetine were written for children and adolescents in the United States during 2002. Nearly 900,000 of these prescriptions were for youngsters whose primary diagnosis was a mood disorder, the most common of which is depression. It is estimated that one-third of such prescriptions are written by non-psychiatrists, many by family practitioners and pediatricians. Prescriptions for paroxetine to treat mood disorders in children and adolescents translated into US sales for GSK of approximately $55 million in 2002

4. GSK has misrepresented information concerning the safety and efficacy of paroxetine for treating MDD in children and adolescents. GSK has allowed positive information about pediatric use of paroxetine to be disclosed publically, but has withheld and concealed negative information concerning the safety and effectiveness of the drug as a treatment for pediatric MDD. Thus, GSK has prevented physicians from properly and independently exercising their professional judgment on behalf of their child and adolescent patients with MDD. GSK's acts have deprived these youngsters of the benefit of their physicians' independent professional judgment.

5. The Attorney General of the State of New York brings this action to stop GSK's illegal and deceptive actions, to obtain restitution for the New York children and adolescents with MDD for whom paroxetine has been prescribed, for disgorgement of profits, and for all other proper relief.

JURISDICTION AND PARTIES

6. The Attorney General is authorized to seek a judgment which enjoins repeated or persistent fraudulent or illegal business acts or practices, including any misrepresentation, concealment or suppression of a material fact, and which awards damages and restitution for such acts. N.Y. Executive Law § 63(12).

7. GlaxoSmithKline, plc is a public limited company organized under the laws of England and Wales. SmithKline Beecham Corporation is a Delaware corporation, which is a wholly owned subsidiary of GlaxoSmithKline, plc. (Defendant GlaxoSmithKline, plc includes all of its predecessors and its past and current components, including SmithKline Beecham Corp.) GSK regularly conducts business within the State of New York and derives substantial revenues from goods consumed in New York.

FACTUAL ALLEGATIONS

Background

8. The FDA approves drugs for human use, based on whether they are safe and effective as determined through scientifically conducted clinical studies. Efficacy is assessed by whether the drug is superior to placebo (dummy pills) and whether that superiority is statistically significant, *i.e.*, the difference in the outcome could not be explained by chance alone. To provide solid evidence of a drug's efficacy, and therefore its benefit to patients, a study needs to be randomized, placebo-controlled and double-blind. The FDA approves a drug for specific

conditions or diseases and for specific populations, such as children and adolescents ("pediatric population") or adults.

9. The FDA has approved paroxetine as safe and effective in treating various indications in adults, but not for any illness or condition in children and adolescents.

10. The FDA does not regulate the practice of medicine. Within New York, as in other states, the regulation of the practice of medicine is solely the responsibility of the State.

1. New York physicians, like other physicians, owe their patients fiduciary and professional obligations to exercise their independent professional judgment in making treatment recommendations and to recommend only those treatments that are appropriate for the individual patient. Conversely, patients (and, in the case of children and adolescents, their parents and guardians) rely on the professional judgment of their physicians in deciding whether to consent to and purchase a treatment.

12. The State of New York, like other states, permits licensed physicians who practice medicine within its borders to prescribe a drug for conditions or diseases for which FDA approval has not been obtained when, in the physician's professional judgment, it is an appropriate treatment for the individual patient, provided the drug has already been approved by the FDA for some other use. This judgment is based on the balance between (a) the benefit the patient is likely to derive from the treatment, including the harm or benefit, if any, of providing no treatment or an alternative treatment, and (b) the risk that the proposed treatment will cause the patient harm and the nature and severity of that harm.

13. In deciding whether to prescribe a drug for an off-label use, physicians usually rely on their assessment of information received from other sources. Such information must be accurate and provide an unbiased picture of a drug's safety and efficacy in treating a condition. If the information is false or misleading, the physician cannot accurately assess the crucial risk-

benefit balance for the patient or exercise professional judgment that is independent. Consequently, the physician cannot act in accordance with the professional and fiduciary obligations owed to the patient.

14. Concealing or providing inaccurate or biased information that is material to a prescribing decision misleads the physician and the patient who relies on that physician's professional judgment.

GSK's Studies Concerning the Safety and Efficacy of
Paroxetine in Treating Children and Adolescents with MDD

15. GSK conducted three randomized, placebo-controlled, double-blind clinical studies to assess the safety and efficacy of paroxetine in treating children and adolescents diagnosed with MDD. These studies are referred to by GSK as studies 329, 377 and 701

16. GSK management approved the final clinical reports for studies 329 and 377 in 1998 and for study 701 on July 31, 2001

17. GSK has represented that studies 329, 377 and 701 were "well designed and appropriate to investigate whether paroxetine was efficacious in children and adolescents with MDD." The FDA has also referred to them as "well-controlled trials."

18. GSK conducted two additional studies that were extensions of studies 329 and 701. The extension of study 329 (final clinical report approved by GSK on October 31, 2001), which included only youngsters with MDD, was not randomized. It was designed to evaluate relapse rate and longer-term safety, not efficacy. Study 716 (final clinical report approved by GSK on September 16, 2002), was not randomized, placebo-controlled or blind (all participants received paroxetine during the extension) and included participants from completed studies of pediatric patients with MDD (study 701) or OCD. It examined the longer-term safety of paroxetine.

a. Efficacy

19. GSK's studies did not demonstrate that paroxetine is efficacious in treating children and adolescents with MDD.

20. Two of the three GSK placebo-controlled studies (377 and 701) failed to show that paroxetine was more effective than placebo or that there was any evidence of efficacy for treating MDD in children and adolescents.

21. Study 377 found that "[n]o clinically or statistically significant differences were detected between paroxetine and placebo in either of the [two] primary efficacy variables," or on any of the secondary measures.

22. In study 701, placebo actually outperformed paroxetine on the primary efficacy measure and there were no statistically significant differences between paroxetine and placebo on any of the secondary measures.

23. Another placebo-controlled trial, study 329, presented a mixed picture of paroxetine's efficacy in treating MDD in a pediatric population. Before study 329 began, GSK specified seven measures of efficacy, two of which it identified as "primary" endpoints and five as "secondary" endpoints. The efficacy of paroxetine was not measured as superior to placebo at a level of statistical significance on either of the primary measures. It was measured as superior to placebo on three of the five secondary ones, as well as on an endpoint that was added to the analysis.

b. Safety

24. GSK's studies showed the possibility of a link between paroxetine and an increased risk of suicidal thoughts and acts in adolescents. Combined, studies 329, 377, and 701 showed that certain possibly suicide-related behaviors were approximately two times more likely

in the paroxetine group than the placebo group. The extension phase of study 329 and study 716 provided support for the presence of such a risk in youngsters taking paroxetine.

25. In the five studies (329, 377, 701, 329-extension and 716), GSK coded suicidal thinking and acts, as well as mood swings, crying and similar behaviors, as "emotional lability."

26. In study 329, emotional lability was recorded for 6.5 percent of the participants on paroxetine (for five of six of these youngsters, the events were classified as "serious") and only 1.1 percent in the placebo group (also "serious").

27. In study 377, emotional lability occurred in 4.4 percent of the paroxetine group, while it occurred in 3.2 percent in the placebo group. In study 701, emotional lability occurred in 3.6 percent of the paroxetine group participants who remained in the study for the tapering-off or follow-up periods, while it occurred in 1.4 percent of the same group of participants who took placebo.

28. In the 329 extension study, emotional lability was found in 7.7 percent of the youth on paroxetine (four individuals) and 3.0 percent of the placebo group. The reported incident for three of the four paroxetine youngsters was intentional overdose, and the youth from the placebo group was reported as suicidal and homicidal. The adverse events for these four participants were categorized as serious.

29. In study 716, which had no placebo group, emotional lability occurred in 6.8 percent of the participants (children and adolescents) with a primary diagnosis of MDD and in 12.5 percent of the adolescents with MDD.

GSK's Presentation of Positive Information and
Misrepresentation and Suppression of Negative Information

30. Because its studies failed to demonstrate efficacy for paroxetine in treating MDD in children and adolescents and suggested a possible increased risk of suicidal thinking and acts

for these youth, GSK sought to limit physicians' access to only the most favorable aspects of the data from these studies. To accomplish this, GSK embarked on a campaign both to suppress and conceal negative information concerning the drug and to misrepresent the data it did reveal concerning the drug's efficacy and safety.

a. GSK's Release of Study 329 and Concealment of the Unfavorable Studies

31. An internal GSK document from 1998 concluded that, in light of the mixed efficacy outcomes from study 329 and the entirely negative results of study 377, GSK's "target" was "[t]o effectively manage the dissemination of these data in order to minimise any potential negative commercial impact."

32. As part of its campaign to "manage the dissemination of these data," the document recommended that GSK prepare and cause the publication of a full article on the only study with some favorable conclusions, study 329.

33. Thereafter, and in accordance with the recommended plan, an article that described and analyzed the results of study 329 was published in a professional journal. The authors of this article included two GSK employees who authored GSK's final clinical report for study 329.

34. Although it allowed the data from study 329 to be published, GSK concealed and suppressed studies 377 and 701, which failed to show that paroxetine was more effective than placebo in treating MDD in children and adolescents.

35. While information from study 377 was presented at a medical convention in 1999, neither study 377 nor study 701 has ever been published, and they remain unavailable to physicians, as are the results of the extension phase of study 329 and study 716. (Interim results from study 716 were presented at a medical conference in 2002.)

36. The data in studies 377 and 701, as well as the data from the extension phase of study 329 and study 716, are material to the risk-benefit balance and, therefore, to a physician's decision whether to prescribe paroxetine for a child or adolescent with MDD. This is especially true in light of the publication of study 329.

b. GSK's Provision of Misinformation to its Sales Force, Which Is the Company's Liaison to Physicians

37. GSK has repeatedly misrepresented the safety and efficacy outcomes from its studies of paroxetine as a treatment for MDD in a pediatric population to its employees who promote paroxetine to physicians. These sales representatives are the GSK personnel who routinely have personal contact with the physicians who decide whether to write prescriptions for paroxetine.

38. On a cover memo that transmitted the published article concerning study 329 to "All Sales Representatives Selling Paxil," Zachary Hawkins, GSK Paxil Product Management, stated, "***Paxil* demonstrates REMARKABLE Efficacy and Safety in the treatment of adolescent depression.**" (Type face as in original.)

39. Study 329 did not demonstrate remarkable efficacy and safety in treating adolescent depression. Although the memo contained the boiler-plate language, "FYI *Article will be stamped: This article is for pharmaceutical consultants' Information only. Do not use it with, or distribute it to physicians*," it is clear that this was the intent. GSK would have had no reason to provide this information to sales representatives other than to use it to falsely characterize study 329 in their communications with physicians. Indeed, it appears that these sales representatives had paroxetine "targets" for psychiatrists who treat only children and adolescents, because GSK informed its sales force that these targets would be eliminated in 2003.

40. In December 1999, Dr. Karen Wagner, one of the authors listed on the published article concerning study 329, spoke at a meeting of GSK Neuroscience consultants, at which she discussed study 329. She was quoted by an internal GSK newsletter as having said, "We can say that paroxetine has both efficacy and safety data for treating depression in adolescents." Although study 377 had also been completed when this newsletter was distributed, its negative results were not mentioned.

c. GSK's Misrepresentations in its Medical Information Letters: November 2001 through January 2003

41. GSK provides information concerning off-label uses of its drugs to physicians through its Medical Information Letters, but only when the physician makes an unsolicited request for the information.

42. As of November 2001, GSK had completed and approved the final clinical reports on studies 329, 377 and 701, and the extension phase of study 329. GSK issued Medical Information Letters in November 2001 and January 2003, both of which misrepresented the information concerning the safety and efficacy of paroxetine for treating MDD in children and adolescents as GSK knew it at the time. GSK enclosed the published article concerning study 329 with some of the Medical Information Letters.

43. Neither of these Medical Information Letters reported the four efficacy outcomes from study 329 that were not statistically significant. Nor did the Medical Information Letters refer to the fact that study 329 had an extension phase in which the rate of relapse did not differ between the paroxetine and placebo groups. While all of the efficacy outcomes from study 377 were negative, the Letters only reported one of them, stating it was numerically superior to placebo but not statistically significant. The Medical Information Letters failed to communicate GSK's own conclusion that there was no clinical significance, as well as no statistical

significance, in the outcomes from study 377. Nor did these Medical Information Letters include any reference to study 701 in which placebo outperformed paroxetine. Each of these Medical Information Letters, however, reported open label (non-placebo-controlled) studies with positive efficacy results.

44. GSK reported emotional lability data from its MDD paroxetine studies in only one of the two Medical Information Letters it sent to physicians during this period. Even when GSK reported the emotional lability information in one Letter, which was exclusively from study 329, it did so only for the paroxetine group. Without the comparative data from the placebo group, these data on possibly suicide-related thinking and acts lost much of their meaningfulness.

45. The Medical Information Letter that reported emotional lability data from study 329 also provided information on other categories of adverse events observed during study 716. This Letter, however, did not inform physicians that in study 716 emotional lability was experienced by 6.8 percent of the participants (children and adolescents) with a primary diagnosis of MDD and in 12.5 percent of the adolescents with MDD. Extension study 329 was not mentioned in any of the Medical Information Letters, although in this study emotional lability was observed in 7.7 percent of the paroxetine group versus 3.0 percent in the placebo group.

GSK's Disclosure of the Studies to Regulatory
Agencies and its Admissions Concerning Efficacy and Safety

46. In 2002, as part of its application for FDA approval of paroxetine to treat OCD in children and adolescents, GSK submitted the final clinical reports for studies 329, 377 and 701, which assessed the safety and efficacy of paroxetine in the treatment of MDD in pediatric patients. GSK subsequently provided these materials to the drug-regulatory agencies of other countries.

47. The studies raised issues for all the drug-regulatory agencies regarding the efficacy and safety of pediatric use of paroxetine for treating MDD.

48. In documents submitted in response to safety and risk-benefit issues raised by various drug-regulatory agencies, including the FDA, the UK's Medicines and Healthcare products Regulatory Agency ("MHRA") and the European Agency for the Evaluation of Medicinal Products ("EMEA"), GSK admitted that studies 329, 377 and 701 "all failed to separate paroxetine from placebo overall and so do not provide strong evidence of efficacy in this indication."

49. On June 10, 2003, the MHRA stated that its analyses of GSK's studies suggested the risk of self-harm and potential suicidal behavior of youngsters with MDD was between 1.5 and 3.2 times greater for the paroxetine group than for placebo. The MHRA reported that its Committee on Safety of Medicines advised that paroxetine "should not be used in children and adolescents under the age of 18 years to treat depressive illness." The agency also added a contraindication for this use on the paroxetine labeling in the UK, which would substantially curtail its use as a treatment for pediatric MDD. The Irish Medicines Board followed suit in December 2003.

50. In response to the MHRA's June 10, 2003 warning, GSK admitted in a letter to physicians in the UK that the "clinical trials in children and adolescents under 18 years of age failed to demonstrate efficacy in Major Depressive Disorder and that there was a doubling of the rate of reporting of adverse events in the paroxetine group compared with placebo, including ... emotional lability."

51 In a press release GSK issued in the UK, the company admitted that, in its studies of youngsters with depression, it had observed "a difference between [paroxetine] and placebo in terms of suicidal thinking or attempts, particularly in adolescents."

52. In a submission GSK made to the EMEA and subsequently sent to the FDA on November 17, 2003, GSK admitted that the risk-benefit balance for treating pediatric MDD patients using paroxetine was unfavorable. Citing the overall lack of statistical significance in the efficacy outcomes from studies 329, 377 and 701 and the possibly increased risk of suicidal thinking and acts for these youth, especially for older adolescents, GSK stated, "it must be concluded that the benefit-risk balance is in favour of not treating children and adolescents [diagnosed with MDD] with paroxetine." GSK also stated in this submission, "in view of a safety signal concerning a possible increase in suicidal behaviour, particularly in adolescents with MDD, the use of paroxetine in children and adolescents with MDD cannot be recommended."

53. On June 19, 2003, the FDA issued a Talk Paper, which stated that it was reviewing the data from studies of paroxetine use in children and adolescents with MDD to assess possible increased risk of suicidal thinking and attempts in this population. Noting the absence of evidence of efficacy, the FDA also stated that although the review of the safety data was not complete, "FDA is recommending that Paxil not be used in children and adolescents for the treatment of MDD." In a second Talk Paper in October 2003, the FDA did not retract its finding that "***three*** well-controlled" clinical trials of paroxetine did not establish its efficacy in treating MDD in the pediatric population, but it noted the scientific fact that the lack of evidence of efficacy in any "***particular***" study is not "***definitive***" evidence that the drug is not effective. (Emphasis added.) It also stated that the possibility of a link between paroxetine and an increased risk of suicidal thoughts and acts was under agency review and advised that paroxetine and other drugs in its class (Selective Serotonin Reuptake Inhibitors or "SSRIs") be used with caution. The FDA strengthened its advice to use SSRIs with caution in a third FDA Talk Paper issued March 22, 2004.

54. On July 15, 2003, after discussions with Health Canada, the Canadian regulatory agency, GSK issued a public advisory "alerting patients, their parents or guardians, and healthcare professionals that until further information is available Paxil should not be given to pediatric patients (children and adolescents under 18 years of age), due to concerns of a possible increased risk of suicidal thinking, suicidal attempts or self-harm. Paxil must not be used in pediatric patients with major depressive disorder, due to the additional fact that studies have failed to show that Paxil was effective in this patient population."

55 On April 22, 2004, the Committee for Proprietary Medicinal Products of the EMEA announced that, following its review of scientific data, it was recommending to the European Commission that paroxetine not be prescribed for pediatric patients.

GSK's Continued Suppression and Misrepresentations

56. Despite its 2003 admissions to regulatory agencies and to the public in the UK and Canada, and despite the agencies' negative assessment of efficacy and articulated safety concerns about the use of paroxetine by children and adolescents with MDD, GSK continues to misrepresent and conceal information in an ongoing effort to encourage physicians to prescribe paroxetine to these youngsters.

57. For example, GSK revised its Medical Information Letter three times after the FDA's first Talk Paper in June 2003. While these Letters included all of the data from study 329, none cited the existence of the extension phase of this study, which showed no difference in relapse rate between paroxetine and placebo. One of these three 2003 Medical Information Letters did not report any additional information concerning emotional lability beyond what was reported in the earlier Medical Information Letters that pre-dated any of the Talk Papers. None of the Letters reported the particularly negative emotional lability data from study 329-extension and

study 716, although they cited other non-randomized studies that had no placebo control. Moreover, all of these communiques to physicians referenced the FDA Talk Papers, but one failed to acknowledge the absence of evidence of efficacy from the clinical studies, which the FDA's first Talk Paper had noted.

58. GSK also issued a fourth Medical Information Letter explicitly responding to the FDA's first Talk Paper, which omitted any reference to the agency's finding of no evidence of paroxetine's efficacy in treating MDD in a pediatric population. This Medical Information Letter was specifically focused on the use of paroxetine to treat children and adolescents with MDD, and stated: "GlaxoSmithKline stands firmly behind Paxil as a safe and effective medication that continues to help millions of patients suffering from mood and anxiety disorders. We will continue to work with the FDA on the safety evaluation." In the context of this document, the quoted statement appeared to announce GSK's position concerning paroxetine as a treatment for MDD in a pediatric population, suggesting it is safe and effective for this use.

59. GSK further controlled physicians' access to negative information about paroxetine as a treatment for MDD in children and adolescents by controlling the information provided to its own personnel. While GSK attached the FDA's June 19, 2003 Talk Paper to a July 15, 2003 internal company newsletter, it instructed the sales representatives that the copy of the Talk Paper was **"for your information only, and it** [sic] **not to be used with your customers."** (Emphasis in original.) This 2003 newsletter also informed the sales personnel, who communicate directly with physicians, that study 329, as described in the published article, was able to establish efficacy despite a high placebo-response rate. At most, study 329 presents a mixed picture on efficacy.

60. Although, in response to the British and Canadian regulatory actions, GSK distributed letters to the physicians in those countries informing them that clinical studies had

failed to demonstrate the efficacy of paroxetine in MDD in the pediatric population and that there was a doubling of the rate of reporting of adverse events, including emotional lability, it did not provide American physicians with this same information. Instead, it sent the Medical Information Letters, with their omissions of material information, to only those physicians who specifically requested information concerning paroxetine use as a treatment for MDD in children and adolescents.

61 GSK took affirmative steps to conceal negative information about the use of paroxetine to treat MDD in children and adolescents from the American public. Unlike GSK's June 10, 2003 press release in Britain, which disclosed that GSK had "seen a difference between [paroxetine] and placebo in terms of suicidal thinking or attempts [in its MDD studies] particularly in adolescents," GSK's June 19, 2003 American press release noted only that "there is no evidence that Paxil is associated with an increased risk of suicidal thinking or acts in adults" and that "not a single person [who participated in the pediatric paroxetine trials] committed suicide." The American press release provided no safety or efficacy information material to treatment decisions for pediatric patients with MDD.

GSK's Prevention of Physicians' Exercise of
Independent Professional Judgment on Behalf of Their Patients

62. Virtually all physicians have access to the results of study 329 through the published article. GSK's failure to disclose to these physicians the findings of studies 377 and 701 and the safety outcomes of studies 329-extension phase and 716, created the false impression that, based on the scientific evidence in GSK's control, there is no question about paroxetine's safety and efficacy in treating MDD in children and adolescents and, therefore, the risk-benefit balance is well settled and generally favorable for this off-label use. This impression was reinforced by GSK's mischaracterization of much of the information it did disclose, its further

concealment and suppression of negative information, and its paroxetine-related targeting of psychiatrists who treat only pediatric patients.

63. GSK misled and deceived physicians and consequently the patients who relied on their professional judgment. GSK deprived physicians of the information needed to evaluate the risks and benefits of prescribing paroxetine for children and adolescents with MDD. By doing so, GSK deceived these physicians, irrespective of whether or not they would have prescribed paroxetine if GSK had disclosed the material facts that were known at the time.

CAUSE OF ACTION
REPEATED AND PERSISTENT FRAUD

64. Executive Law § 63(12) authorizes the Attorney General to bring an action to enjoin and obtain restitution and damages for "repeated fraudulent acts or ... persistent fraud .. in the carrying on, conducting or transaction of business," including "any deception, misrepresentation, concealment [or] suppression" of a material fact.

65. By engaging in the acts and practices described above, GSK has engaged in and continues to engage in repeated fraudulent acts or persistent fraud in violation of Executive Law § 63(12).

PRAYER FOR RELIEF

WHEREFORE, the People of the State of New York respectfully request that a judgment and order be entered that:

A. Permanently enjoins GSK from engaging in the deceptive, fraudulent and unlawful practices alleged herein;

B. Directs GSK to pay restitution and damages to all aggrieved consumers, including those not known at the time the order is entered, which restitution and damages shall include, but

not be limited to, disgorgement of all profits GSK derived from the sale of Paxil® or Paxil CR™ in the State of New York for a child or adolescent with depressive disorder;

C. Awards Plaintiffs costs, including additional costs in the amount of $2,000 pursuant to C.P.L.R. § 8303(a)(6); and

D. Grants all other relief that is just and proper.

Dated: New York, New York
June 2, 2004

Respectfully submitted,

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PHARMACEUTICAL INDUSTRY

ANALYSIS

Drug company experts advised staff to withhold data about SSRI use in children

An internal document advised staff at the international drug giant GlaxoSmithKline (GSK) to withhold clinical trial findings in 1998 that indicated the antidepressant paroxetine (Paxil in North America and Seroxat in the UK) had no beneficial effect in treating adolescents.

Paroxetine is 1 of 6 drugs in the class of selective serotonin reuptake inhibitors (SSRIs) that Britain and the US have since banned for pediatric use because of increased risk of suicide. On Feb. 2, Health Canada issued a public warning that the pediatric use of 7 antidepressants — paroxetine, bupropion (Wellbutrin), citalopram (Celexa), fluvoxamine (Luvox), mirtazapine (Remeron), sertraline (Zoloft) and venlafaxine (Effexor) — should proceed only after consultation with the treating physician "to confirm that the benefits of the drug still outweigh its potential risks."

The GSK internal document obtained by *CMAJ* offers a glimpse into the inner workings of a drug giant. Entitled "Seroxat/Paxil Adolescent Depression: Position piece on the phase III clinical studies," the confidential document was prepared by the Central Medical Affairs team (CMAt), a division of SmithKline Beecham (which subsequently merged with Glaxo Wellcome to form GSK).

The document provides guidance on how to manage the results of 2 clinical trials conducted into the efficacy of paroxetine (Seroxat). Given that the clinical trials results were, according to the document, "insufficiently robust" to support an application to regulatory authorities for a label change approving Seroxat for use in pediatric depression, CMAt recommended the firm "effectively manage the dissemination of these data in order to minimize any potential negative commercial impact."

Sales for Seroxat amounted to almost $4.97 billion worldwide in 2003.

Study 329, conducted in the US from 1993–1996, was the largest trial to date on using an SSRI in a pediatric population. According to the document, the results indicated paroxetine was no more effective than placebo. In the other trial, Study 377, carried out in Europe, South America and elsewhere, placebo was actually more effective than the antidepressant.

The CMAt document advised that "Positive data from Study 329 will be published in abstract form at the [European College of Neuropsychopharmacology] meeting" in November 1998 and that "a full manuscript ... will be progressed." It also stated that "It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine."

GSK spokeswoman Jill McKinlay-Morris said that "the memo draws an inappropriate conclusion and is not consistent with the facts." She didn't elaborate on that point, but went on to say "GSK abided by all regulatory requirements for submitting safety data. We also communicated safety and efficacy data to physicians through posters, abstracts, and other publications."

Study 329 was eventually published (*J Am Acad Child Adolesc Psychiatry* 2001;40[7]:762-72) in 2001. The authors concluded that paroxetine is "generally well tolerated and effective for major depression in adolescents." Among the 93 adolescents taking Seroxat, there were 5 serious cases of "emotional lability" (e.g., suicidal ideation/gestures). Among the 95 patients taking the comparison treatment, imipramine (Tofranil), there was 1 such case, and among the 89 subjects receiving placebo there was also 1. According to the article, only 1 serious adverse event — headache in 1 patient — was considered by the treating investigator to be related to paroxetine treatment.

A 1993–1996 industry study showed that paroxetine was no more effective than placebo in treating pediatric depression.

Britain's Medicines and Healthcare products Regulatory Authority (MHRA) advised doctors in June 2003 that paroxetine should not be prescribed to patients under the age of 18 because evidence from various clinical trials showed that episodes of suicidal behaviour were between 1.5 and 3.2 times higher in children taking the drug than in those receiving placebo. Several nations, including the US, France and Ireland, quickly followed suit.

The MHRA subsequently reviewed and banned the pediatric use of 6 other SSRIs (exempting fluoxetine [Prozac]) and is now reviewing their use among adults. The US Food and Drug Administration is now reviewing pediatric trials of 8 antidepressants. It's been estimated that as many as 11 million American, and 3 million Canadian children are taking antidepressants. — *Wayne Kondro*, Ottawa, and *Barbara Sibbald*, CMAJ

DOI:10.1053/cmaj.1040236

October 1998

SEROXAT/PAXIL ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies

13

EXECUTIVE SUMMARY

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and the United Arab Emirates, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.

October 1998

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies
FOR INTERNAL USE ONLY

SITUATION

2 SB sponsored, placebo-controlled, phase III clinical trials have been conducted, Study 329 (US) and Study 377 (Europe, South America, South Africa and Saudi Arabia), in order to assess the efficacy and safety of Seroxat/Paxil (up to 40mg/day) in the treatment of adolescents (aged between 13 and 18 years and 11 months) with unipolar major depressive disorder (diagnosed according to DSM IIIR, Study 329 or DSM IV criteria, Study 377).

Study 329 was a placebo-controlled, imipramine comparator study with an 8 week acute treatment phase followed by a 6 month extension phase. The acute phase has completed and the extension phase is due to complete at the end of 1998. 275 patients were recruited to the study. Results from the acute phase of this study show that there were no statistically significant differences from placebo on either of the primary efficacy parameters (change from baseline in HAMD total scores and the proportion of responders-where response was defined as a ≥50% reduction from baseline in HAMD score or a HAMD score ≤8 at endpoint). However, trends in favour of paroxetine compared with placebo were seen across all the indices of depression (change from baseline in HAMD total [p=0.133], HAMD responders [p=0.112], CGI [p=0.094] and K-SADS [p=0.065] scores) and statistically significant differences from placebo were observed in the proportion of patients in remission (defined as a HAMD score of ≤8 at endpoint). In general, the response to imipramine was similar to that for placebo. The 6 month extension phase has now completed and is scheduled to report at the end of 1998.

Study 377 was a 12 week placebo-controlled study, conducted in 276 adolescents with major depression. There was a high placebo response rate in this study and no statistically or clinically significant differences from placebo were observed on either of the primary efficacy variables (proportion of patients achieving a ≥50% reduction from baseline in total MADRS scores and change from baseline in the K-SADS-L depressive subscale score). The only differences from placebo (secondary efficacy variables) were seen in a subgroup of patients who were ≥16 years of age.

Possible explanations for the high placebo response include,

1) The large number of study visits
2) the duration of the assessments
3) The fact that concomitant psychotherapy was not excluded
4) Question marks about the adequacy of using currently available diagnostic criteria and rating scales in younger patients
5) Adolescents may be more susceptible to a placebo effect
6) Developmental issues. Children and adolescents may respond in a pharmacologically different manner due to quantitative and/or qualitative differences in neurotransmitter/receptor systems.

Conclusions from these studies;

- There were no differences in the safety profile of Seroxat/Paxil in adolescents when compared to that already established in the adult population

- The efficacy data from the above clinical trials are insufficiently robust to support a regulatory submission and label change for this patient population.

OTHER DATA:

Ongoing studies: SB France are conducting a locally funded double-blind, comparative study of Seroxat/Paxil with clomipramine in adolescents with major depression (Study 511). In addition, a study in adolescents with OCD (Study 453) is underway in the US. This study comprises a 16 week open label Seroxat/Paxil treatment phase, followed by double-blind, randomisation to paroxetine or placebo for a further 16 weeks of treatment. The regulatory acceptability of these 2 studies needs to be established.

Published data: A review of the literature shows that 2 studies assessing the use of paroxetine in the treatment of 34 adolescents and children with depression have been published (Rey-Sanchez and Gutierrez-Cesares, 1997; Findling et al; 1996).

The first study (Rey-Sanchez and Gutierrez-Cesares, 1997) was a retrospective survey of data from 25 adolescents (aged 13-17 years) treated with paroxetine. Patients were diagnosed according to ICD 10 criteria. In 13 of the patients unipolar major depression was not the primary diagnosis. 17 patients received paroxetine as a monotherapy, 8 also received concomitant psychotropic medications (n=7 benzodiazepines, n=1 haloperidol). Paroxetine was administered at doses of 10mg (14 patients) or 20mg/day (11 patients). No specific depression rating scales were used, response was based on clinical judgement. 76% patients

had a satisfactory response (11 complete remission, 8 improved with residual symptoms). A lack of satisfactory response in was observed in 6 (24%) patients. Eight patients reported side effects (somnolence or sleep disorders n=6, asthenia n=4, nausea n=3, tachycardia n=2, diarrhea n=2, headache n=2, orthostatic hypotension n=1, restlessness n=1). Two patients were withdrawn due to one due to anxiety, one due to hypotension and dizziness)

The second study (Findling et al; 1996) was conducted in 9 patients aged between 7-15 years (children and adolescents) meeting DSM IV criteria for a major depressive disorder. Symptomatology was assessed using HAM-D for subjects aged 13 to 15 years, and the childhood depression rating scale (CDRS) subjects aged 12 or younger. Paroxetine was initially given at a dose of 10mg/day. This was escalated to 20mg/day if the patient had not responded after 4 weeks of treatment. 8/9 patients responded to treatment with paroxetine. Three patients had complete remission, 5 patients had a >50% reduction in total CDRS score from baseline. CGI improved in all patients. One patient withdrew from the study at week 2 due to an adverse experience. This patient was found to have elevated serum paroxetine levels and was a poor 2D6 metaboliser. Assessment of pharmacokinetic parameters in this study showed that paroxetine had a similar half life to that reported in the adult population (15.7h [sd 9.0h] vs 24h, respectively).

COMPETITOR ACTIVITIES:

Lilly are believed to be in near to completing their phase III clinical trials in adolescent depression. One relatively large placebo-controlled 8 week study with an open 12 month follow-up period conducted in 96 patients (aged 8-18 years) has recently been published (Emslie et al; 1997 and 1998). These data show that 56% (27/48) patients on fluoxetine (20mg/day) compared with 33% (16/48) patients on placebo were rated as much or very much improved on the CGI at Week 6 ($p=0.02$. In the 12 month follow-up period, 85% (n=74) patients recovered from the depressive episode (47 on fluoxetine, 22 on placebo and 5 on other antidepressants or lithium). Twenty nine (39%) of the patients (36% of those who had recovered on fluoxetine [17/47] and 41% of those who had recovered on placebo [9/22] had a recurrence of depression during the 12 month follow-up (a higher recurrence rate than seen in adults). Other published data on fluoxetine are from small open studies or individual case reports (Colle et al; 1994).

Pfizer already have positive data (including PK data) and are licenced in the US for the treatment of adolescent OCD. In addition, Pfizer are also believed to be conducting clinical trials in adolescent depression. Available published data are

limited, derived from small open studies in adolescent depression (McConville et al; 1996; Tierney et al; 1995)

TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

PROPOSALS

- Based on the current data from Studies 377 and 329, and following consultation with SB country regulatory and marketing groups, no regulatory submissions will be made to obtain either efficacy or safety statements relating to adolescent depression at this time. However data (especially safety data) from these studies may be included in any future regulatory submissions, provided that we are able to go on and generate robust, approvable efficacy data. The rationale for not attempting to obtain a safety statement at this time is as follows;

  i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use

  ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.

- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

- The regulatory acceptability of Studies 511 and 453 and any other data in this patient population will continue to be investigated

SB
SmithKline Beecham
Pharmaceuticals

Facsimile Transmittal

To:	Thomas Laughren, M.D.
Fax #:	301-594-2859
Date:	July 9, 1999
Pages:	(number of pages including cover page) 23

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From: Thomas F. Kline, Assistant Director
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Dear Dr. Laughren,

As a follow-up to your brief discussion with Dr. Raj Kumar at the DIA meeting in Baltimore, we would be very grateful for clarification of your advice concerning pediatric exclusivity studies per the Division's letter dated May 18, 1999.

As you know, we submitted two protocols, No. 329 and 453, for pediatric depression and OCD respectively, which were conducted and completed in the USA.

- The design of the OCD study 453 is both scientifically valid and clinically relevant and clearly established the effectiveness of paroxetine in this population as:

  a) We see a clear effect of paroxetine in the 16 week open label phase of the study with a clinical response i.e. improvement in 70-90% of the study population.

  b) When the patients were randomized to continue in a double-blind manner to either paroxetine or placebo, a number of outcome measures, including CY-BOCS showed a clinical benefit of paroxetine over placebo.

Therefore, in this adequate and well- designed study, the data by itself provides evidence for the usefulness of paroxetine in the treatment of OCD in the pediatric-adolescent population. Based on these findings we would propose to add the information to our current labeling for Paxil (paroxetine HCl).

- Safety: The safety of paroxetine has been established in the adolescent population in study 329 and in both children under and over the age of 12 years in the OCD trial 453. Our conclusion are that there seems to be no adverse findings unique to these populations or these age ranges.

Do you concur with our findings that the usefulness and the safety of paroxetine in patients with OCD has been established and would fulfill the requirement to effect a labeling statement and fulfill the exclusivity requirements?

- On the basis of study 329 we acknowledge that we have not established efficacy in children under the age of 12 years of age, however, the data suggests that we have established the usefulness of paroxetine in the patient population.(Given there are no unique adverse events in this population and there are no clinical reasons to believe that paroxetine would not be useful in children with major depressive episode under the age of 12 years).

Do you concur with our findings?

Thank you for the clarification, and please see the attached synopses for studies 453 and 329.

Sincerely,

Thomas Kline
Assistant Director
U.S. Regulatory Affairs

Celexa : US Study (MDD)
Forest Labs

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Article

A Randomized, Placebo-Controlled Trial of Citalopram for the Treatment of Major Depression in Children and Adolescents

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Objective: Open-label trials with the selective serotonin reuptake inhibitor citalopram suggest that this agent is effective and safe for the treatment of depressive symptoms in children and adolescents. The current study investigated the efficacy and safety of citalopram compared with placebo in the treatment of pediatric patients with major depression.

Method: An 8-week, randomized, double-blind, placebo-controlled study compared the safety and efficacy of citalopram with placebo in the treatment of children (ages 7–11) and adolescents (ages 12–17) with major depressive disorder. Diagnosis was established with the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version. Patients (N=174) were treated initially with placebo or 20 mg/day of citalopram, with an option to increase the dose to 40 mg/day at week 4 if clinically indicated. The primary outcome measure was score on the Children's Depression Rating Scale—Revised; the response criterion was defined as a score of ≤28.

Results: The overall mean citalopram dose was approximately 24 mg/day. Mean Children's Depression Rating Scale—Revised scores decreased significantly more from baseline in the citalopram treatment group than in the placebo treatment group, beginning at week 1 and continuing at every observation point to the end of the study (effect size=2.9). The difference in response rate at week 8 between placebo (24%) and citalopram (36%) also was statistically significant. Citalopram treatment was well tolerated. Rates of discontinuation due to adverse events were comparable in the placebo and citalopram groups (5.9% versus 5.6%, respectively). Rhinitis, nausea, and abdominal pain were the only adverse events to occur with a frequency exceeding 10% in either treatment group.

Conclusions: In this population of children and adolescents, treatment with citalopram reduced depressive symptoms to a significantly greater extent than placebo treatment and was well tolerated.

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Up to 5% of children and 8% of adolescents meet diagnostic criteria for depression, with the incidence of depression increasing markedly after puberty (1–4). The mean duration of pediatric depressive episodes is 9 months, and there is substantial risk for relapse (4, 5). Like depression in adults, pediatric depression is associated with significant social and functional impairment. School performance, peer relationships, and family functioning all are affected negatively in children and adolescents with depression (6), and risk of suicide is increased (7). Furthermore, depression in children and adolescents frequently continues into adulthood, resulting in considerable morbidity and mortality (8).

Although childhood depression is increasingly being recognized, few randomized, placebo-controlled trials of antidepressant pharmacotherapy have been reported in this population, and those that have appeared in the literature have had mixed results. For example, trials with tricyclic antidepressants have not demonstrated superiority over placebo (9). However, several recently published studies have suggested that selective serotonin reuptake inhibitors (SSRIs) may be effective and well tolerated in children and adolescents. In double-blind, placebo-controlled trials, fluoxetine (10, 11) and sertraline (12) have shown efficacy in the treatment of children and adolescents with major depression, as has paroxetine for the treatment of depressed adolescents (13). The use of SSRIs in children and adolescents has increased dramatically as a result of these trials, case reports, and open-label studies. Indeed, approximately 70% of family physicians and pediatricians in one mail survey reported prescribing SSRIs to children and adolescents with psychiatric disorders, including depression (14).

Citalopram, an SSRI shown to be effective in the treatment of depression in the adult population (15–17), appears well suited for use in children and adolescents because it has a favorable side effect profile, a low potential for drug-drug interactions, and is relatively safe in overdose (18, 19), which is of concern in this population (7).

TABLE 1. Demographic and Clinical Characteristics of Children and Adolescents With Major Depressive Disorder Randomly Assigned to 8 Weeks of Double-Blind Treatment With Citalopram or Placebo

Characteristic	Subjects Given Placebo (N=85)		Subjects Given Citalopram (N=89)	
	N	%	N	%
Male gender	39	45.9	42	47.2
Caucasian race	62	72.9	72	80.9
Disease course				
Recurrent	15	17.6	19	21.3
Single episode	70	82.4	70	78.7
	Mean	SD	Mean	SD
Weight (lb)	125.6	57.2	123.7	51.0
Age (years)	12.1	2.8	12.1	3.1
Duration of major depressive disorder (years)	2.2	1.9	2.3	2.0
Duration of episode (months)	18.6	16.4	20.8	21.4
Age at onset (years)	9.8	3.0	9.8	3.3

Additionally, open-label trials and case reports suggest that citalopram is effective in younger patients (20, 21).

The objective of the current randomized, double-blind, placebo-controlled, flexible-dose study was to compare the efficacy and safety of citalopram with placebo in the treatment of children and adolescents with major depressive disorder.

Method

Study Population

This study was conducted at 21 hospital, academic, and research centers in the United States. Children (ages 7–11) and adolescents (ages 12–17) who met DSM-IV criteria for major depressive disorder and whose current episode of major depressive disorder was at least 4 weeks in duration at baseline were eligible for participation. The Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) (22), a semistructured diagnostic interview, was used to establish that patients met DSM-IV criteria for major depressive disorder and to rule out other psychiatric diagnoses. A score of at least 40 on the Children's Depression Rating Scale—Revised (23, 24) was required at the screening and baseline visits.

Additional inclusion criteria were a normal physical examination, laboratory tests, and ECG results. Female patients of childbearing potential were required to have negative serum human chorionic gonadotropin levels at screening and be willing to practice a reliable method of birth control. Patients were required to provide assent prior to participation, and the parent or legal guardian had to provide written consent. A parent or caregiver was required to accompany the patient at each visit. The study protocol was approved by institutional review boards at each study center.

Patients were excluded from the study for any of the following reasons: 1) primary psychiatric diagnoses other than major depressive disorder; 2) a DSM-IV diagnosis of attention deficit hyperactivity disorder (ADHD), posttraumatic stress disorder, bipolar disorder, pervasive development disorder, mental retardation, conduct disorder, or oppositional defiant disorder; 3) any psychotic features; 4) any personality disorder that would interfere with study participation; 5) a history of alcohol or substance abuse within the past year; or 6) anorexia or bulimia within the past year. Initiation of psychotherapy or behavioral therapy 3 months prior to the screening visit or during the study was not allowed. Patients who were considered a suicide risk, who had made an active suicide attempt within the past year, or had been hospitalized because of an attempt also were excluded.

Patients who had been treated with any antidepressant or anxiolytic medication within 2 weeks of baseline (4 weeks for fluoxetine), had been treated with a neuroleptic or stimulant within 6 months prior to screening, or received an investigational drug 30 days prior to study entry were excluded. Concomitant treatment with certain prescription or over-the-counter medications (e.g., antipsychotics, anticonvulsants, sedatives, hypnotics, and cardiovascular agents, among others) also was prohibited per protocol.

Study Design

Following an initial screening visit and a 1-week, single-blind placebo lead-in period, patients returned for a baseline visit to determine whether they remained eligible to participate. Eligible patients were then randomly assigned in double-blind fashion to 8 weeks of citalopram or placebo treatment. Citalopram was initiated at 20 mg/day, with the potential to increase the dose to 40 mg/day anytime after week 4 if deemed clinically necessary. Subsequent to week 4, the dose could be decreased to 20 mg/day for tolerability reasons. Evaluations were scheduled after 1, 2, 4, 6, and 8 weeks of double-blind treatment.

The primary outcome measure in this study was the change from baseline in score on the Children's Depression Rating Scale—Revised at week 8 or upon termination. The Children's Depression Rating Scale—Revised was administered at each study visit. Response was defined as a score of ≤28 (indicating minimal residual symptoms). Secondary measures included Clinical Global Impression (CGI) improvement and severity ratings (25). At the final visit (week 8), a physical examination and laboratory tests were performed, and ECG results were obtained. Adverse events were spontaneously reported by patients or observed by investigators.

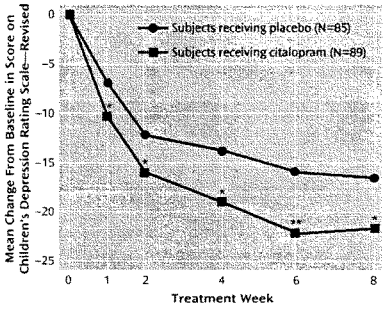
Statistical Analyses

Treatment differences in the primary efficacy outcome, baseline-to-endpoint change in score on the Children's Depression Rating Scale—Revised, in patients treated with citalopram versus patients treated with placebo were assessed using an analysis of covariance model, with treatment, study center, and age group as factors and the baseline score as covariate. A Cochran-Mantel-Haenszel test controlling for center and age group was applied for between-treatment comparison with respect to the response rate. These analyses were carried out using the last observation carried forward approach at week 8.

Results

A total of 178 patients (93 in the citalopram group and 85 in the placebo group) were randomly assigned to double-blind treatment. Four patients (three children and one adolescent), all randomly assigned to the citalopram group, were lost to follow-up and did not receive study medication. These patients were not included in the intent-to-treat analyses. Thus, the intent-to-treat population consisted of 89 patients (45 children and 44 adolescents) assigned to citalopram and 85 patients (38 children and 47 adolescents) assigned to placebo. Of these, 18 patients from each group discontinued double-blind treatment prematurely. Demographic and clinical characteristics of the patient population at baseline are summarized in Table 1. There were no significant differences in age,

FIGURE 1. Baseline-to-Endpoint Changes in Score on the Children's Depression Rating Scale—Revised in Children and Adolescents With Major Depressive Disorder Randomly Assigned to 8 Weeks of Double-Blind Treatment With Citalopram or Placebo



*p<0.05. **p<0.01.

gender, race, or weight between the placebo and citalopram groups. The mean age was 12.1 years in both treatment groups, and there were no differences between groups in the mean ages of children and adolescents. Additionally, responses to the K-SADS-PL (administered at the screening visit) indicated there were no clinically meaningful differences between the citalopram and placebo treatment groups in depression history. Ongoing secondary psychiatric disorders other than depression were reported in 23 patients, the most common diagnosis being dysthymia (citalopram group: 5.6%, placebo group: 1.2%) and enuresis (citalopram group: 4.5%, placebo group: 3.5%). A previous diagnosis of ADHD had been made in four citalopram-treated patients (4.5%) and one placebo-treated patient (1.2%); there were no reports of ongoing ADHD. Approximately 80% of the patients who participated in the study were experiencing a single episode of depression with a mean duration of 2 years. The mean duration of the current depressive episode was about 20 months. The age at onset was approximately 7 years for children and 12 years for the adolescent group. Twenty percent of the patients in the citalopram group and 18% of patients in the placebo group received previous antidepressant treatment, and approximately 15% of the patients in the citalopram group and 16% of the patients in the placebo group had a history of nonresponse to antidepressant treatment. Mean Children's Depression Rating Scale—Revised scores at baseline were 58.8 (SD=10.9) and 57.8 (SD=11.1) in the citalopram and placebo groups, respectively, indicative of moderately severe illness.

As noted in the Method section, investigators had the option to increase the dose of study medication to 40 mg/day citalopram or placebo equivalent any time after the week 4 visit. By the end of the study, medication dose had been increased in 53 placebo-treated patients (62.4%) and in 48 citalopram-treated patients (53.9%). In the citalopram group, the mean daily dose over the 8-week treatment period was 23.3 mg/day (SD=5.0) for the children and 24.4 mg/day (SD=5.0) for the adolescents.

TABLE 2. Treatment-Emergent Adverse Events[a] in Children and Adolescents With Major Depressive Disorder Randomly Assigned to 8 Weeks of Double-Blind Treatment With Citalopram or Placebo

	Patients Experiencing Event			
	Placebo Group (N=85)		Citalopram Group (N=89)	
Adverse Event	N	%	N	%
Rhinitis	5	5.9	12	13.5
Nausea	3	3.5	12	13.5
Abdominal pain	6	7.1	10	11.2
Influenza-like symptoms	0	0.0	6	6.7
Fatigue	1	1.2	5	5.6
Diarrhea	1	1.2	5	5.6
Back pain	3	3.5	5	5.6

[a] Adverse events listed are those that occurred with a frequency >5% in the citalopram group and that had an incidence in patients treated with citalopram that exceeded the incidence in patients treated with placebo.

Citalopram treatment showed statistically significant improvement compared with placebo on the Children's Depression Rating Scale—Revised as early as week 1 ($F=6.58$, df=1, 150, $p<0.05$), which persisted throughout the study (Figure 1). At week 8, the effect size on the primary outcome measure, Children's Depression Rating Scale—Revised (last observation carried forward), was 2.9. Additionally, at endpoint more citalopram-treated patients (36%) met the prospectively defined criterion for response than did placebo-treated patients (24%), a difference that was statistically significant ($\chi^2=4.178$, df=1, $p<0.05$). The proportion of patients with a CGI improvement rating ≤2 at week 8 was 47% for the citalopram group and 45% for the placebo group (last observation carried forward values). For the CGI severity rating, baseline values were 4.4 for the citalopram group and 4.3 for the placebo group, and endpoint values (last observation carried forward) were 3.1 for the citalopram group and 3.3 for the placebo group.

Citalopram treatment was well tolerated. All treatment-emergent adverse events that occurred with a frequency >5% in the citalopram group, and with an incidence in citalopram-treated patients that exceeded that in placebo-treated patients, are listed in Table 2. Of these, nausea, rhinitis, and abdominal pain were the only adverse events occurring in ≥10% of citalopram-treated patients. There were no reports of mania. The rate of discontinuation due to adverse events was comparable in the placebo and citalopram groups (5.9% versus 5.6%, respectively). The only adverse events that led to the discontinuation of more than one patient were aggravated depression (two placebo, no citalopram) and agitation (no placebo, two citalopram). No clinically significant ECG results, laboratory

values, or weight changes were found. No serious adverse events were observed in any patient treated with citalopram in this study.

Discussion

This randomized, placebo-controlled, double-blind trial provides evidence that citalopram produces a statistically and clinically significant reduction in depressive symptoms in children and adolescents. Specifically, citalopram was superior to placebo on the primary efficacy measure, score on the Children's Depression Rating Scale—Revised, as early as week 1 with efficacy continuing throughout the trial. Reported adverse events were mild, and the rate of discontinuation due to adverse events was similar in the placebo and citalopram groups.

The results of this trial are in agreement with previous open-label trials (20) and case reports (21), which suggest that citalopram is efficacious and safe in children and adolescents with depression. In the current trial, citalopram-treated patients demonstrated significant improvement in depressive symptoms compared with placebo at week 1, an earlier time point than has been reported in other published trials of SSRIs in children and adolescents (10–12), although one placebo-controlled trial demonstrated significance for fluoxetine at week 1 (11). This is a potentially important observation, since therapeutic treatment options in these young patients remain limited, and early amelioration of symptoms may serve to enhance adherence to an adequate course of therapy.

In our study, the prospectively defined criterion of response was an endpoint score of ≤28 on the Children's Depression Rating Scale—Revised. In the Emslie et al. study of fluoxetine (11), a Children's Depression Rating Scale—Revised endpoint total score ≤28 was defined as remission. It is noteworthy, therefore, that the rates of response for citalopram (36%) were similar to the remission rates for fluoxetine (41%).

It is tempting to speculate that similar clinical results would be achieved in children and adolescents treated with the recently developed single isomer compound escitalopram, since the serotonin reuptake activity of citalopram is attributable to its S-isomer (26). This hypothesis is being tested in a multicenter, randomized, double-blind study of escitalopram in pediatric patients that is currently under way.

The mean citalopram dose for children and adolescents over the 8-week trial was approximately 25 mg/day, which is similar to the minimum dose shown to be effective in adults (27). There were no serious adverse events observed in the citalopram group. In fact, the overall adverse event profile was similar to that reported in adult trials, with no new or unexpected adverse events reported. Notably absent in this population of children and adolescents were dizziness and somnolence, two events frequently reported by adult patients (18). In this study, psychiatric adverse events were reported infrequently by patients randomly assigned to citalopram. For example, adverse events associated with behavioral activation (such as insomnia or agitation) were not prevalent in this trial.

The consistent and significant reduction in Children's Depression Rating Scale—Revised score in citalopram-treated patients compared with placebo-treated patients at weeks 1, 2, and 4 suggests that citalopram, 20 mg/day, is an effective dose in this population, since the citalopram dose was fixed throughout the first 4 weeks of the trial.

Of interest, early and sustained improvements in Children's Depression Rating Scale—Revised scores were observed with citalopram treatment in this study despite a relatively high rate of placebo response (which is common in pediatric trials with antidepressants). The study was not powered sufficiently to detect treatment differences by age group. Other limitations include the low number of patients with comorbid conditions and concomitant medication use, both of which are common in younger patients. It is not known whether the presence of comorbid psychiatric disorders such as ADHD would have affected the observed outcomes of this trial; however, the exclusion criteria employed produced a study population comparable to those of Emslie et al. (11) and Wagner et al. (12).

In conclusion, citalopram treatment significantly improved depressive symptoms compared with placebo within 1 week in this population of children and adolescents. No serious adverse events were reported, and the rate of discontinuation due to adverse events among citalopram-treated patients was comparable to that of placebo. These findings further support the use of citalopram in children and adolescents suffering from major depression.

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Double-blind Study of Paroxetine in Adolescents with Unipolar Major Depression

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Funded by

SmithKline Beecham Pharmaceuticals

ABSTRACT

The primary objective of this international study is to compare the efficacy and safety of paroxetine and placebo in the treatment of adolescents with unipolar, major depression.

286 patients aged 13 to 18 years are screened using the DSM-IV, the Clinical Global Assessment Scale (C-GAS), and the Montgomery Asberg Depression Rating Scale (MADRS). Patients are randomized to receive paroxetine (20-40 mg daily) or placebo for 12 weeks. The primary efficacy parameters are the proportion of patients with a 50% or greater reduction in MADRS score and the change in Kiddie Sads-Lifetime (K-SADS-L) depression subscale, between baseline and endpoint.

No statistically significant differences are detected between paroxetine and placebo in either of the primary efficacy variables. The only statistically significant interaction found is treatment by age ($p=0.002$).

The results show no superiority for paroxetine over placebo in the treatment of adolescent depression. The significant age by treatment interaction indicates evidence of a different treatment effect dependent upon age (> 16 years old).

INTRODUCTION

Epidemiological research suggests an estimated prevalence rate for major depression in adolescents between 0.4% and 8.3%, with a lifetime prevalence rate of 15% to 20%, comparable to that of adults (Birmaher et al., 1996). In adolescents, twice as many females as males present with major depression (Lewinsohn et al., 1994).

Community and clinical studies have shown that the mean length of an episode of early onset major depressive disorder is 7 to 9 months. In a large community study of adolescents, the majority of depressive episodes were relatively brief with a median of 8 weeks. A substantial risk of recurrence exists (Birmaher et al., 1996; Goodyer et al., 1997; Harrington et al., 1990; Kovacs et al., 1984; Lewinsohn et al., 1994). Depressive episodes in adolescents are usually associated with school, family and social difficulties (Simeon, 1989).

To date, pharmacological, double blind trials comparing various tricyclic antidepressants to placebo for adolescent oupatients with major depression have reported no significant differences (Birmaher et al., 1998; Boulos et al., 1991; Geller et al., 1990; Kramer and Feguine, 1984; Kutcher et al., 1994; Kye et al., 1996).

Selective serotonin-reuptake inhibitors (SSRI) are widely used in the treatment of depression in adults. Treatment with selective serotonin-reuptake inhibitors in children and adolescents has produced promising reports. Open studies of fluoxetine have found significant improvements (Boulos et al., 1992; Colle et al., 1994; Jain et al., 1992). Only one published double-blind, placebo-controlled study of an SSRI (fluoxetine) has reported a statistically significant improvement in major depression (Emslie, 1997). Open trials of sertraline and paroxetine have suggested the medication may be efficacious in improving major depression (Ambrosini et al., 1999; McConville et al., 1996; Simeon et al., 1998; Rey-Sanchez & Gutierrez-Caseres, 1997; Tierney et al., 1995). Preliminary report (Keller et al., 1998, presented at APA, unpublished) from an 8 week multicentre, double-blind, placebo-controlled study of paroxetine and imipramine has suggested efficacy of paroxetine in treating unipolar major depression in 275 adolescents. Paroxetine was superior to placebo on measures of affect, global improvement and remission of depressive symptoms. Imipramine was not superior to placebo on any outcome measure.

OBJECTIVES AND HYPOTHESIS

The objective of this study was to compare the efficacy and safety of paroxetine and placebo in the treatment of adolescents with unipolar major depression. Additional objectives were to add to the understanding of pharmacotherapy in the treatment of adolescent major depression and to determine the feasibility of selective serotonin-reuptake inhibitor use in adolescent depression.

It was hypothesized that paroxetine would be safe, effective and superior to placebo in treating adolescent major depression.

METHODOLOGY

SUBJECTS

Study subjects were 286 adolescents of either gender between the ages of 13 and 18 years with a current DSM-IV diagnosis of unipolar, major depression, a Clinical Global Assessment score < 69, and a Montgomery Asberg Depression Rating Scale score ≥16.

STUDY DESIGN

The study was carried out in 33 centres in Argentina, Belgium, Canada, Holland, Italy, Mexico, South Africa, Spain, United Arab Emirates, and United Kingdom. The study was a multicentre, double-blind, randomized, parallel group, placebo controlled study to compare the efficacy and safety of paroxetine (20-40 mg daily, flexible dose) and placebo in the treatment of adolescents with unipolar, major depression as defined by DSM-IV criteria.

EFFICACY AND SAFETY PARAMETERS

Primary efficacy parameters were the proportion of subjects with a 50% or greater reduction in the MADRS score between baseline and study endpoint, and the change from baseline to study endpoint in K-SADS-L depression subscale. Secondary efficacy variables were: change from baseline in the MADRS total score; change from baseline in CGI severity of

illness score; CGI global improvement score; change from baseline in Beck Depression Inventory (BDI) and change from baseline in Mood and Feelings Questionnaire (MFQ). All efficacy variables (primary and secondary) were analyzed at weeks 6, 8 and study endpoint.

Safety parameters consisted of adverse experiences and assessment of vital signs and laboratory data.

STATISTICAL ANALYSES

The proportion of patients responding were analyzed using logistic regression. The model included treatment group, country group, and covariates of age and baseline score. Odds ratios and 95% confidence intervals were presented. The effect of adding treatment by country group interaction into the model was assessed with the above terms in the model. If the treatment by country group interaction was not statistically significant ($p \leq .01$), it was dropped from the model. Treatment by covariate and covariate by covariate interactions were assessed in a similar way.

The mean change from baseline in K-SADS-L depression subscale score, MADRS, BDI and MFQ total scores were analyzed using analysis of covariance with factors of treatment, country group, age and baseline score. Least squares means were compared at the 5% level and 95% confidence

intervals were presented for treatment differences. The effect of adding treatment by country group interaction into the model was assessed with the above terms in the model. If the treatment by country group interaction was not statistically significant ($p \leq .01$), it was dropped from the model. Treatment by covariate and covariate by covariate interactions were assessed in a similar way.

The changes from baseline in the CGI severity of illness were analyzed using the non-parametric Wilcoxin Rank Sum Test. No adjustment was made for country grouping or covariates. The CGI global improvement scores were compared using the Cochran-Mantel-Haenszel Chi-Square Tests (stratifying by country group) at the 5% level.

RESULTS

PATIENT DATA			
Number of Patients:	TREATMENT GROUP		Totals
	Paroxetine	*Placebo*	
Screened			324
Randomized	187	99	286
ITT pop.[1]	182	93	275
ITT compl.[2]	127	69	196
ITT Demography:			
# Females	122 (67%)	61 (65.6%)	
Age (X, sd)[3]	15.5, 1.6	15.8, 1.6	
Age Range[3]	13-19	13-18	
# Caucasian	126 (69.2%)	61 (65.6%)	

Notes:

ITT pop.[1]: International Treatment Trial study population

Eleven patients were not eligible for the ITT population, 5 from the paroxetine group (2 due to adverse events, 1 protocol violator, 1 lost to follow-up, 1 centre 007 patient) and 6 from the placebo group (1 due to lack of efficacy, 1 protocol violator, 1 lost to follow-up, 2 centre 007 patients, and 1 for another reason).

ITT compl.[2]: International Treatment Trial study completers

60 of the 187 (32.1%) randomized paroxetine patients withdrew from the study and 30 of the 99 (30.3%) randomized placebo patients withdrew from the study. Slightly more patients from the paroxetine group compared to the placebo group withdrew due to adverse events (11.8% and 7.1% respectively).

Age[3]: Age in years

PROPORTION OF PATIENTS WITH 50% OR GREATER REDUCTION FROM BASELINE IN MADRS TOTAL SCORES							
Data Set Time Point	TREATMENT GROUPS						
	Paroxetine		*Placebo*		Odds Ratio[1]	95% CI *Paroxetine/ Placebo*	P-value
	n/N	%	n/N	%			
LOCF Data Set, week 12[2]	107/ 177	60.5	53/ 91	58.2	1.109	0.653/1.884	0.702
OC Data Set, week 12[3]	94/ 126	74.6	47/ 66	71.2	1.161	0.590/2.285	0.666

Notes:

Odds Ratio[1] : Adjusted odds ratio

LOCF Data Set, week 12 [2] : LOCF is an efficacy data set termed "last observation carried forward". It is generated from the OC data set whereby missing data were estimated by extending forward the data from the previous visit. The primary analysis population for the study was the intention-to-treat population using the LOCF data set with the primary time point of interest being the 12th week.

OC Data Set, week 12[3] : OC is an efficacy data set termed "observed cases" consists of each patient's observed data at each visit.

No statistically significant treatment differences were observed at any time point. The above table demonstrates that at week 12 endpoint in the International Treatment Trial LOCF population, 60.5% of the paroxetine and 58.2% of the placebo patients had responded. These results were confirmed by the OC data set.

PROPORTION OF PATIENTS WITH A > 50% REDUCTION IN TOTAL MADRS SCORE BY AGE GROUP AT WEEK 12					
Data Set	*Paroxetine* Responders n/N (%)	*Placebo* Responders n/N (%)	Adjusted Odds Ratio	95% CI *Paroxetine/ Placebo*	P-value
Age Group < 16 years old					
LOCF	65/118 (55.1%)	37/57 (64.9%)	0.609	0.309/1.201	0.153
OC	56/80 (70.0%)	33/45 (73.3%)	0.815	0.355/1.870	0.629
Age Group > 16 years old					
LOCF	42/59 (71.2%)	16/34 (47.1%)			
OC	38/46 (82.6%)	14/21 (66.7%)			

*Note: Model could not be fitted due to lack of responders per treatment group*country group combination*

A statistically significant treatment by age interaction was found (p=.002). Re-analysis of the data set by age group found in this table shows that in the younger group the proportion of responders was higher in the placebo group, although this was not statistically significant. In the older age group, the proportion of responders was higher in the paroxetine group.

KIDDIE-SADS LIFETIME SCHEDULE DEPRESSION SUBSCALE SCORE AT WEEK 12					
Data Set	TREATMENT GROUPS				
	Paroxetine N/adjusted mean (SE)	*Placebo* N/adjusted mean (SE)	Difference in adjusted means	95% CI (*Paroxetine/ Placebo*)	P-value
LOCF	171/-9.3 (0.54)	88/-8.9 (0.70)	-0.408	(-2.007/ 1.192)	0.616
OC	126/-10.8 (0.49)	66/-10.2 (0.63)	-0.657	(-2126/ 0.812)	0.379

At endpoint, the difference between the treatment groups in adjusted means of -.041 in the ITT LOCF population did not achieve clinical or statistical significance. This was confirmed by the ITT OC data set.

CHANGE FROM BASELINE IN K-SADS-L DEPRESSION SUBSCALE SCORE BY AGE GROUP AT WEEK 12					
Data Set	*Paroxetine* N/adjusted mean (SE)	*Placebo* N/adjusted mean (SE)	Difference in adjusted means	95% CI (*Paroxetine /Placebo*)	P-value
Age Group < 16 years old					
LOCF	113/-8.4 (0.61)	55/-9.4 (0.83)	0.968	(-0.954/ 2.891)	0.321
OC	80/-10.1 (0.61)	45/-9.8 (0.77)	-0.285	(-2.141/ 1.571)	0.762
Age Group > 16 years old					
LOCF	58/-11.2 (1.25)	33/-8.4 (1.47)	-2.725	(-5.641/ 0.192)	0.067
OC	46/-12.1 (0.93)	21/-10.9 (1.20)	-1.161	(-3.681/ 1.358)	0.360

A statistically significant treatment by age interaction was found (p=.02). Re-analysis of the data set by age group found in this table shows that, although there were no overall treatment differences, in the older group of adolescents the mean change from baseline was larger in the paroxetine group.

SAFETY RESULTS

Adverse Experiences

Similar proportions of subjects from both treatment groups experienced adverse events (65.4% of paroxetine in comparison to 59.1% of placebo patients).

Serious Adverse Experiences

22 (12.1%) of subjects in the paroxetine and 6 (6.5%) of those in the placebo group experienced serious emergent adverse events. None of the events were fatal.

Withdrawals due to Adverse Experiences

For all randomized patients, 22/187 (11.8%) subjects in the paroxetine group withdrew due to adverse experiences compared to 7/99 (7.1%) from the placebo group. This difference was not statistically significant.

Vital Signs

Changes in mean vital signs values between baseline and week 12 were small for both treatment groups and of no clinical concern. There were no differences between the treatment groups regarding vital signs values meeting sponsor-defined clinical concern criteria.

Laboratory Tests

Similar proportions of patients in the two treatment groups had one or more laboratory values meeting sponsor-defined clinical concern criteria (29.1% for paroxetine and 33.3% for placebo).

LIMITATIONS

Limitations of the study include the following:

1) The 8 week (minimum) duration of the major depression episode may have been too short, biasing the sample towards those subjects with major depression episodes far less than the mean of 7 to 9 months reported in the literature. There may be a greater likelihood for those with shorter episodes of major depression to experience a natural resolution of the depression which may account for the strong placebo effect, especially in the younger adolescents.

2) The study did not preclude subjects receiving non-directive supportive therapy which has been shown to reduce self-reported depression in 36% of adolescents with major depression (Brent et al., 1997). It is, therefore, possible that at least part of the strong placebo effect may have resulted from treatment with supportive psychotherapy.

3) The 2 week placebo run-in period may have resulted in a selection bias towards those with less severe or shorter duration episodes of major depression since these subjects would be more likely to wait the 2 week period without treatment.

4) The statistical model did not fit the data well suggesting that further analysis using different methods or models may have been warranted.

CONCLUSIONS

No clinically or statistically significant treatment differences between paroxetine and placebo were detected between paroxetine and placebo in either of the primary efficacy variables.

No overall treatment differences between paroxetine and placebo were detected for any of the secondary efficacy variables.

There appeared to be a trend for a treatment by age interaction for the primary efficacy variables and most of the secondary efficacy variables suggesting that adolescents over the age of 16 may respond positively to paroxetine treatment. This is consistent with the preliminary results of the North American, multicentre, double-blind, placebo-controlled study of paroxetine and imipramine, also in an adolescent population with unipolar major depression, which were reported by Keller and colleagues at the 1998 APA.

Paroxetine was well tolerated with no unexpected findings regarding adverse experiences, vital signs or laboratory values.

It is important to report even negative findings, especially within the early investigative stages of pharmacological trials, as they add to our understanding of research methods and treatment, and may suggest future directions for research.

Further investigations of paroxetine should involve an examination of age and characteristics of major depressive disorder, including duration of depressive episode and treatment history, and how they impact on treatment efficacy in adolescents with unipolar major depression.

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Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

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ABSTRACT

Objective: To compare paroxetine with placebo and imipramine with placebo for the treatment of adolescent depression. **Method:** After a 7- to 14-day screening period, 275 adolescents with major depression began 8 weeks of double-blind paroxetine (20–40 mg), imipramine (gradual upward titration to 200–300 mg), or placebo. The two primary outcome measures were endpoint response (Hamilton Rating Scale for Depression [HAM-D] score ≤8 or ≥50% reduction in baseline HAM-D) and change from baseline HAM-D score. Other depression-related variables were (1) HAM-D depressed mood item; (2) depression item of the Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version (K-SADS-L); (3) Clinical Global Impression (CGI) improvement scores of 1 or 2; (4) nine-item depression subscale of K-SADS-L; and (5) mean CGI improvement scores. **Results:** Paroxetine demonstrated significantly greater improvement compared with placebo in HAM-D total score ≤8, HAM-D depressed mood item, K-SADS-L depressed mood item, and CGI score of 1 or 2. The response to imipramine was not significantly different from placebo for any measure. Neither paroxetine nor imipramine differed significantly from placebo on parent- or self-rating measures. Withdrawal rates for adverse effects were 9.7% and 6.9% for paroxetine and placebo, respectively. Of 31.5% of subjects stopping imipramine therapy because of adverse effects, nearly one third did so because of adverse cardiovascular effects. **Conclusions:** Paroxetine is generally well tolerated and effective for major depression in adolescents. *J. Am. Acad. Child Adolesc. Psychiatry*, 2001, 40(7):762–772. **Key Words:** paroxetine, imipramine, major depression, adolescent.

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The treatment of depression in adolescents is an area of burgeoning interest. Unfortunately, few well-controlled, large-scale, randomized clinical trials have been conducted in this population. Data from the 1,769 adolescents and

young adult participants in the National Comorbidity Survey (Kessler and Walters, 1998) indicate a lifetime prevalence rate of 15.3% for major depression, comparable with the 17% lifetime prevalence of depression in adults (Kessler et al., 1994). As with adults, the course of major depression in adolescents is often characterized by protracted episodes, frequent recurrence, and impairment in social and academic domains (Rao et al., 1995). Suicide is the third leading cause of death in adolescents, and depressive disorders are strongly correlated with suicide attempts (Eisenberg, 1984; Kovacs et al., 1993). Depressed adolescents grow up to be depressed adults and, compared with healthy controls, have higher rates of suicide, psychiatric and medical hospitalizations, and impairment in work, family, and social lives (Weissman et al., 1999).

The efficacy of tricyclic antidepressants has been investigated in at least 11 double-blind, randomized studies (Dulcan et al., 1998; Ryan and Varma, 1998), none demonstrating superiority of active treatment over placebo. However, methodological deficiencies in these studies, including very small sample sizes and diagnostic heterogeneity, limit statistical inference and generalizability of the findings. At the same time, cardiovascular effects and lethality in overdose associated with the tricyclic agents have greatly limited their use in clinical practice.

Since the selective serotonin reuptake inhibitors (SSRIs) became commercially available, the safety, tolerability, and efficacy of these agents in treating major depression in adolescents have been noted in several open-label reports (Ambrosini et al., 1999; Apter et al., 1994; Masi et al., 1997; McConville et al., 1996; Rey-Sanchez and Gutierrez-Casares, 1997; Rodriguez-Ramos et al., 1996; Simeon et al., 1998). Placebo-controlled trials, which remain the standard against which efficacy is determined, number only two, both with fluoxetine (Emslie et al., 1997; Simeon et al., 1990). A small study by Simeon and associates (1990) was negative. In contrast, a large-scale trial by Emslie and colleagues (1997) showed a 23% drug-placebo difference in overall clinical improvement. The findings of a third study, which used a historical case-control design (Strober et al., 1999), suggested greater efficacy of fluoxetine compared with imipramine in a severely ill, inpatient population of adolescents with major depression. We now report principal findings from the first double-blind, placebo-controlled comparison of an SSRI, paroxetine, and a placebo-controlled comparison with a tricyclic antidepressant, imipramine, in the treatment of adolescents with major depression.

METHOD

Study Design

This was an 8-week, multicenter, double-blind, randomized, parallel-design comparison of paroxetine with placebo and imipramine with placebo in adolescents with major depression. The trial was conducted at 10 centers in the United States and 2 in Canada. Four hundred twenty-five subjects were screened for eligibility, and 275 subjects were randomly assigned to experimental treatment. The trial was conducted in accordance with good clinical practices and the Helsinki Declaration. All subjects and their parent(s) provided written informed consent before entry into the study; the identity of all subjects is completely blinded in this report. Funding for this study was provided by GlaxoSmithKline; each author had access to data and signed off on the manuscript before it was submitted for publication.

Patient Eligibility

Male and female subjects, aged 12 through 18 years, fulfilling the *DSM-IV* (American Psychiatric Association, 1994) criteria for a current episode of major depression of at least 8 weeks in duration were enrolled. Major depression was diagnosed by a systematic clinical interview which used the juvenile version of the Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version (K-SADS-L) rating scale. The K-SADS-L was developed by one of the authors (R.G.K.) through modification of the adult SADS assessment technique (Endicott and Spitzer, 1978) by providing uniform anchors so that symptoms were specifically rated for clinical relevance and by adding items to generate *DSM-IV* diagnoses. The K-SADS-L uses separate patient and parent reports to assess lifetime presence of affective and schizophrenic disorders, as well as the full range of childhood and adolescent psychopathological conditions. In addition to fulfilling *DSM-IV* criteria for major depression, subjects were required to have a total score of at least 12 on the 17-item Hamilton Rating Scale for Depression (HAM-D), a score of less than 60 on the Children's Global Assessment Scale, and a score of at least 80 on the Peabody Picture Vocabulary Test. All subjects were medically healthy.

Potential subjects in the study were screened initially by telephone, and candidates who were considered likely to meet diagnostic criteria were evaluated at the study site. Adolescents and parents were interviewed separately. For those cases in which there existed a significant discrepancy between information provided by the adolescent and information provided by the parent, the clinician met with both to discuss the information obtained and then rendered a rating. Eligible subjects and their parent(s) were required to reach agreement with the site investigator that the subject had a disorder requiring treatment. In cases in which the diagnosis was not certain, audiotapes of the screening interview were to be reviewed and the diagnosis was to be verified further by an independent expert from another participating site prior to certifying study eligibility.

Subjects with a current or lifetime *DSM-IV* diagnosis of bipolar disorder, schizoaffective disorder, eating disorder, alcohol or substance use disorder, obsessive-compulsive disorder, autism/pervasive developmental disorder, or organic brain disorder were excluded from consideration. A diagnosis of posttraumatic stress disorder within 12 months of recruitment was also exclusionary, as was current suicidal ideation with intent or specific plan, a history of suicide attempts by drug overdose, any medical condition in which the use of an antidepressant was contraindicated, current psychotropic drug use, an adequate trial of antidepressant medication within 6 months of study entry, or exposure to investigational drug use either within 30 days of

study entry or within five half-lives of the drug. Females who were pregnant or breastfeeding and those who were sexually active and not using reliable contraception were also excluded.

Blinding, Randomization, and Treatment

All subjects underwent a 7- to 14-day screening phase to determine persistence and severity of entry diagnostic and eligibility criteria and to obtain baseline global functioning scores, physical examination, and clinical laboratory studies. Placebo was not administered during the screening phase. By means of a computer-generated list, subjects who still met entry criteria were randomly assigned to an 8-week course of treatment with paroxetine, imipramine, or placebo in a 1:1:1 ratio. Tablets were overencapsulated in matching Supro B locking capsules to preserve medication blinding. Subjects assigned to paroxetine treatment received 20 mg/day in the morning for weeks 1 through 4. Optional dosage increases to 30 mg of paroxetine per day (divided dose) were allowed at week 5 and to 40 mg per day (divided dose) at weeks 6 through 8 if deemed necessary by the treating clinician. Imipramine treatment was initiated with a forced titration schedule in which subjects received daily doses of 50 mg during week 1, 100 mg during week 2, 150 mg during week 3, and 200 mg during week 4. Thereafter, optional dosage increases to 250 mg/day (during week 5) and to 300 mg/day (during weeks 6 through 8) were allowed if judged necessary by the research study clinician. Imipramine administration was divided between morning and evening for all daily doses of 100 mg or greater.

Subjects were instructed to take their medication twice daily, once in the morning and again in the evening. The number of active drug or matched placebo capsules administered per day was identical for each treatment group during forced titration. During weeks 1 and 2, subjects in the paroxetine or imipramine groups received one active drug capsule in the morning and one active drug or matched placebo capsule in the evening. Subjects in the placebo group received one capsule in the morning and one in the evening. During week 3, subjects received one active drug capsule in the morning and two active drug or matched placebo capsules in the evening. At week 4, subjects received one active drug capsule plus one matched placebo capsule in the morning and two active drug or matched placebo capsules in the evening. Beginning at week 5, subjects either remained at the week 4 dose level (i.e., four capsules per day) or were titrated upward to five or six capsules per day. Subjects who completed the study were offered the option of continuing blinded treatment at the same dose for 6 additional months. If subjects withdrew from the study prematurely for any reason, the dose of medication was gradually tapered over a 7- to 17-day period.

Supportive case management was provided to all subjects at each weekly clinic visit according to the method described by Fawcett et al. (1987). Such management was limited to psychosocial interaction that enabled observation of treatment effects. Interpersonal or cognitive-behavioral psychotherapeutic interventions were strictly prohibited.

Efficacy and Safety Evaluation

After randomization, subjects were seen at weekly intervals and evaluated with standardized instruments and global assessments for efficacy. The protocol described two primary outcome measures: (1) response, which was defined as a HAM-D score of ≤8 or a ≥50% reduction in baseline HAM-D score at the end of treatment; and (2) change from baseline in HAM-D total score. Five other depression-related variables were declared a priori: (1) change in the depressed mood item of the HAM-D; (2) change in the depression item of the K-SADS-L; (3) Clinical Global Impression (CGI) improvement scores of 1 (very much improved) or 2 (much improved); (4) change in the nine-item depression subscale of the K-SADS-L; and (5) mean CGI improvement scores.

Assessment of multiple domains of functioning, general health, and behavior consisted of (1) Autonomous Function Checklist, completed by the parent, which assessed the subject's autonomy in performing daily activities (Sigafoos et al., 1988); (2) Self-Perception Profile, completed by the subject to measure self-esteem (Harter, 1988); and (3) Sickness Impact Scale, completed by the subject, to measure present health and quality of life (Bergner et al., 1981).

Adverse events, heart rate, blood pressure, and body weight were determined at each weekly visit. Rhythm strip electrocardiograms (ECGs) were obtained at each visit, and 12-lead ECGs were obtained during the screening phase and at weeks 4 and 8. Routine clinical laboratory studies were conducted during the screening phase and at week 8, or upon study withdrawal.

If changes in cardiovascular parameters occurred, then dosage reductions were required. Doses were reduced by 10 mg for paroxetine doses of 30 mg or 40 mg; subjects receiving 20 mg of paroxetine were withdrawn from the study. Similarly, imipramine doses of 250 mg or 300 mg per day were reduced by 50 mg, and subjects receiving ≤200 mg of imipramine were withdrawn from the study. Cardiovascular parameters necessitating dosage reduction or study withdrawal were defined prospectively as heart rate ≥110 beats per minute (bpm) at two consecutive visits or heart rate ≥130 bpm at a single visit; systolic blood pressure >140 mm Hg or diastolic blood pressure >85 mm Hg; PR interval ≥0.21 seconds; QRS interval ≥0.12 seconds and ≥150% of baseline; or QT_C interval ≥0.48 seconds.

Blood samples were obtained from all patients at weeks 4 and 8 for determination of plasma concentrations of imipramine, desmethylimipramine (the major, pharmacologically active metabolite of imipramine), and paroxetine. Subjects were withdrawn from the study if the combined imipramine and desmethylimipramine concentration exceeded 500 ng/mL.

Statistical Methods

A sample size of 90 patients per arm was required to provide approximately 80% power to detect an effect size of 0.4 between an active regimen and placebo with an α level of 5% (two-tailed). The change from baseline in the HAM-D total score was used.

The efficacy analyses were performed on the population of patients who were randomized and had at least one postbaseline efficacy evaluation. Two datasets from this population were examined: (1) a last observation carried forward dataset in which the last observation on treatment was carried forward to estimate missing data for patients who withdrew prior to completing 8 weeks of treatment, and (2) a completer dataset that examined results in patients who received study medication for the full 8 weeks. Missing data were not estimated for the completer dataset.

Continuous variables, such as changes from baseline to endpoint in the HAM-D total score, CGI improvement scale, and K-SADS-L, were analyzed by a two-factor analysis of variance using the general linear model procedure of the Statistical Analysis System (SAS). The model included terms for treatment and investigator. Categorical variables, such as percentage of subjects responding to treatment, were analyzed with logistic analysis implemented in the categorical modeling procedure (CATMOD) of the SAS; the model included effects for investigator and treatment. Pairwise comparisons between each active treatment and placebo were two-tailed and performed at an α level of .05. Data are reported as least square means (±SD or SE).

RESULTS

Treatment groups were similar with regard to demographic characteristics and psychiatric profile (Table 1). Most subjects had a first-degree relative with major depression and were experiencing their first episode of major depression. The mean duration of the current depressive episode was more than 1 year, with a mean baseline HAM-D total score between 18 and 19. Features of melancholic or endogenous depression were exhibited by 35% to 40% of patients, and 20% had features of atypical depression. Despite exclusion criteria that limited many comorbid conditions, psychiatric comorbidity was common. Comorbid anxiety disorders, such as separation anxiety and social anxiety disorder, and externalizing disorders were present at the time of screening in 19% to 28% of subjects.

Premature Discontinuation

A total of 190 subjects (69% of 275) completed the 8-week study. Premature withdrawal rates were 24% for placebo, 28% for paroxetine ($p = .60$ versus placebo), and 40% for imipramine ($p = .02$ versus placebo). Premature study discontinuation due to adverse effects occurred at a rate of 6.9% in the placebo group. Study withdrawal due to adverse effects was the most common reason for discontinuation in the paroxetine (9.7%; $p = .50$ versus placebo) and imipramine (31.5%; $p < .01$ versus placebo) groups, respectively. Cardiac adverse effects consisting of tachycardia (8 patients), postural hypotension (2), prolonged QT intervals (2), arrhythmia (1), atrioventricular block (1), abnormal ECG (1), extrasystole (1), and hypertension (1) led to withdrawal among 14% of subjects in the imipramine group (13 subjects). Protocol violation, including lack of compliance, was the most common reason for withdrawal in the placebo group (8.0%).

Efficacy Results

Of the depression-related variables, paroxetine separated statistically from placebo at endpoint among four of the parameters: response (i.e., primary outcome measure), HAM-D depressed mood item, K-SADS-L depressed mood item, and CGI score of 1 (very much

TABLE 1
Demographic Characteristics and Mean Baseline Depression Scores for 275 Randomized Subjects

Parameter	Paroxetine ($n = 93$)	Imipramine ($n = 95$)	Placebo ($n = 87$)
Gender, M/F	35/58	39/56	30/57
Age, mean ± SD (yr)	14.8 ± 1.6	14.9 ± 1.6	15.1 ± 1.6
Race, no. (%)			
White	77 (82.8)	83 (87.4)	70 (80.5)
African American	5 (5.4)	3 (3.2)	6 (6.9)
Asian American	1 (1.1)	2 (2.1)	2 (2.3)
Other	10 (10.8)	7 (7.4)	9 (10.3)
CGAS, mean ± SD	42.7 ± 7.5	42.5 ± 7.4	42.8 ± 8.3
Duration of current depressive episode, mean ± SD (months)	14 ± 18	14 ± 18	13 ± 17
No. of prior depressive episodes (%)			
0	81	79	77
1	12	14	14
≥2	7	6	8
First-degree relative with major depression (%)	86	90	95
Age at onset of first episode, mean ± SD (yr)	13.1 ± 2.8	13.2 ± 2.7	13.5 ± 2.3
Mean baseline HAM-D total score	18.98 ± 0.43	18.11 ± 0.43	18.97 ± 0.44
Features of melancholic or endogenous depression	36	35	40
Features of atypical depression (%)	25	16	9
Current comorbid psychiatric diagnosis (%)			
Any diagnosis	41	50	45
Anxiety disorder[a]	19	26	28
Externalizing disorder[b]	25	26	20

Note: CGAS = Children's Global Assessment Scale; HAM-D = Hamilton Rating Scale for Depression.
[a] Includes separation anxiety, panic ± agoraphobia, agoraphobia, social anxiety disorder, generalized anxiety disorder.
[b] Includes conduct disorder, oppositional defiant disorder, and attention-deficit/hyperactivity disorder.

improved) or 2 (much improved) and trended toward statistical significance on two measures (K-SADS-L nine-item depression subscore and mean CGI score) (Table 2). The response to imipramine was not significantly different from that for placebo across any of the seven depression-related variables.

A total of 63.3% of paroxetine subjects (57/90; $p = .02$ versus placebo), 50% of imipramine subjects (47/94; $p = .57$ versus placebo), and 46% of placebo subjects (40/87) achieved a HAM-D total score of ≤8 at endpoint (Fig. 1). The time course of response in mean HAM-D total score is shown in Figure 2. Among patients who completed 8 weeks of treatment, 76.1% of paroxetine subjects (51/67; $p = .02$ versus placebo), 64.3% of imipramine subjects (36/56; $p = .44$ versus placebo), and 57.6% of placebo subjects (38/66) achieved a mean HAM-D total score of ≤8. In the paroxetine group, 65.6% of patients were considered very much or much improved on the CGI ($p = .02$ versus placebo); rates for the imipramine and placebo groups were 52.1% ($p = .64$ versus placebo) and 48.3%, respectively. Improvement in baseline depressed mood as measured by the HAM-D and the K-SADS-L depressed mood items was significantly greater than placebo in the paroxetine group, but not significantly greater than placebo in the imipramine group. Improvements in the K-SADS-L depression subscore ($p = .07$) and mean CGI score ($p = .09$) trended toward statistical significance in the paroxetine group, but not in the imipramine group ($p = .98$ and $p = .90$, respectively) (Table 2).

Although neither paroxetine nor imipramine separated statistically from placebo across the nonsymptom measures of functioning, health, and behavior, improvements over baseline were achieved for each active treatment group. Placebo-treated subjects also improved along the behavioral measures, but to a lesser extent than patients in the active treatment groups.

Dosage Titration

Nearly half of subjects in the paroxetine group remained at the initial starting dose of 20 mg/day (48%). Mean dose at study endpoint for paroxetine was 28.0 mg (SD ±8.54 mg) and for imipramine was 205.8 mg (SD

TABLE 2
Mean Scores of Depression-Related Variables in Adolescents With Major Depression[a] Who Were Treated With Paroxetine, Imipramine, or Placebo

	Paroxetine				Imipramine				Placebo		
Variable	Mean	(SE)	*n*	*p*[b]	Mean	(SE)	*n*	*p*[b]	Mean	(SE)	*n*
HAM-D ≤8											
Week 8 endpoint	63.3%	(—)	90	.02	50.0%	(—)	94	.57	46.0%	(—)	87
HAM-D ≤8 or 50% reduction in baseline HAM-D											
Week 8 endpoint	66.7%	(—)	90	.11	58.5%	(—)	94	.61	55.2%	(—)	87
HAM-D depressed mood item											
Baseline	2.99	(0.08)	90		2.79	(0.08)	94		2.86	(0.08)	87
Week 8 endpoint	0.99	(0.14)	9	.001	1.17	(0.14)	94	.14	1.53	(0.14)	87
K-SADS-L depressed mood item											
Baseline	4.57	(0.09)	83		4.29	(0.09)	87		4.63	(0.09)	85
Week 8 endpoint	2.37	(0.18)	83	.05	2.52	(0.18)	87	.87	2.90	(0.18)	85
CGI score of 1 or 2[c]											
Week 8 endpoint	65.6%	(—)	90	.02	52.1%	(—)	94	.64	48.3%	(—)	87
K-SADS-L 9-item depression subscore											
Baseline	28.25	(0.52)	83		27.54	(0.51)	88		28.84	(0.52)	85
Week 8 endpoint	16.59	(0.84)	83	.07	17.99	(0.83)	88	.98	19.27	(0.83)	85
Mean CGI score											
Week 8 endpoint	2.37	(0.16)	90	.09	2.70	(0.15)	94	.90	2.73	(0.16)	87
HAM-D total score											
Baseline	18.98	(0.43)	90		18.11	(0.43)	94		18.97	(0.44)	87
Week 8 endpoint	8.24	(0.81)	90	.13	9.2	(0.81)	94	.87	9.88	(0.83)	87

Note: HAM-D = Hamilton Rating Scale for Depression; K-SADS-L = Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version; CGI = Clinical Global Impression.

[a] The last evaluation during treatment for subjects who did not complete the entire study (i.e., the last observation carried forward) is reported.

[b] The *p* values compare treatment difference in active versus placebo groups.

[c] CGI score of 1 = very much improved; CGI score of 2 = much improved.

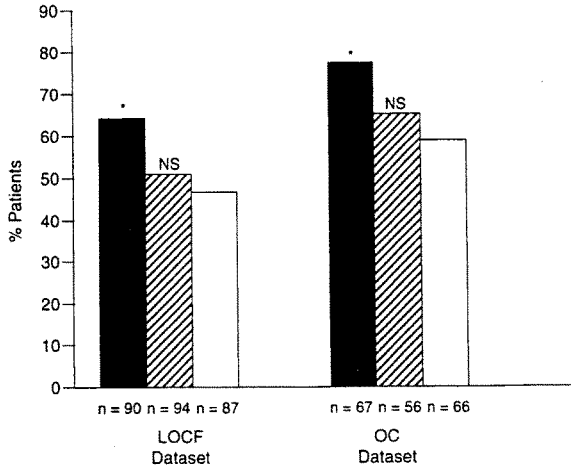

Fig. 1 Percentage of subjects treated with paroxetine (■), imipramine (▨), and placebo (□) who achieved a HAM-D total score ≤8 in the LOCF and completer (OC) subgroups at week 8. *p = .02; NS = $p \geq .44$. HAM-D = Hamilton Rating Scale for Depression; LOCF = last observation carried forward; OC = observed cases.

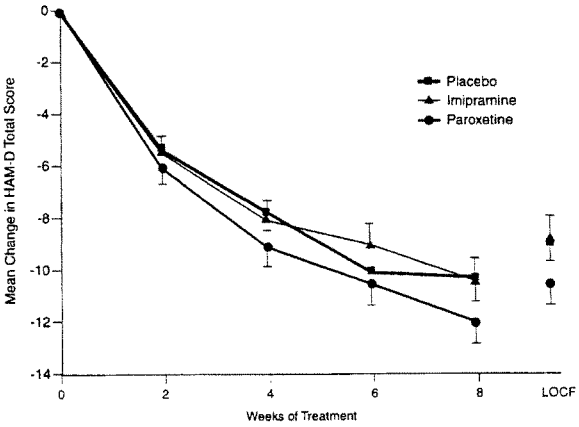

Fig. 2 Least square mean change HAM-D total score (±SEM) during an 8-week course of paroxetine (n = 90), imipramine (n = 94), and placebo (n = 87) administration in adolescents with major depression. HAM-D = Hamilton Rating Scale for Depression; LOCF = last observation carried forward.

±63.94 mg). The most common "doses" of placebo (administered as divided doses) were four capsules per day (31.0%) and six capsules per day (41.4%).

Adverse Effects

Paroxetine was generally well tolerated in this adolescent population, and most adverse effects were not serious. The most common adverse effects reported during paroxetine therapy were headache, nausea, dizziness, dry mouth, and somnolence (Table 3). These occurred at rates that were similar to rates in the placebo group with the exception of somnolence, which occurred at rates of 17.2% for paroxetine and 3.4% for placebo. Dizziness, dry mouth, headache, nausea, and tachycardia were most commonly reported during imipramine treatment. Tremor occurred in 10.8% of paroxetine-, 14.7% of imipramine-, and 2.3% of placebo-treated subjects.

Adverse effects in all treatment groups occurred most often during the first week of therapy. Dosage reductions were most often required for somnolence, insomnia, and restlessness among paroxetine-treated subjects. Dry mouth, constipation, and tremor were the most common adverse effects leading to imipramine dose reductions. Premature withdrawal from the study because of adverse effects occurred at rates of 9.7% for paroxetine, 31.5% for imipramine, and 6.9% for placebo. Clinically significant

TABLE 3
Adverse Effects Occurring in ≥5% of Subjects in the Paroxetine, Imipramine, and Placebo Groups

Adverse Effect	Paroxetine (n = 93)	Imipramine (n = 95)	Placebo (n = 87)
Cardiovascular system			
Tachycardia	2 (2.2)	18 (18.9)	1 (1.1)
Postural hypotension	1 (1.1)	13 (13.7)	1 (1.1)
Vasodilation	0 (0)	6 (6.3)	2 (2.3)
Chest pain	2 (2.2)	5 (5.3)	2 (2.3)
Digestive system			
Dry mouth	19 (20.4)	43 (45.3)	12 (13.8)
Nausea	22 (23.7)	23 (24.2)	17 (19.5)
Constipation	5 (5.4)	9 (9.5)	4 (4.6)
Decreased appetite	7 (7.5)	2 (2.1)	4 (4.6)
Diarrhea	7 (7.5)	3 (3.2)	7 (8.0)
Dyspepsia	6 (6.5)	9 (9.5)	4 (4.6)
Tooth disorder	5 (5.4)	2 (2.1)	2 (2.3)
Vomiting	3 (3.2)	8 (8.4)	6 (6.9)
Abdominal pain	10 (10.8)	7 (7.4)	10 (11.5)
Nervous system			
Dizziness	22 (23.7)	45 (47.4)	16 (18.4)
Emotional lability	6 (6.5)	3 (3.2)	1 (1.1)
Hostility	7 (7.5)	3 (3.2)	0 (0)
Insomnia	14 (15.1)	13 (13.7)	4 (4.6)
Nervousness	8 (8.6)	6 (6.3)	5 (5.7)
Somnolence	16 (17.2)	13 (13.7)	3 (3.4)
Tremor	10 (10.8)	14 (14.7)	2 (2.3)
Headache	32 (34.4)	38 (40.0)	34 (39.1)
Respiratory system			
Cough increased	5 (5.4)	3 (3.2)	6 (6.9)
Pharyngitis	5 (5.4)	12 (12.6)	8 (9.2)
Respiratory disorder	10 (10.8)	7 (7.4)	11 (12.6)
Rhinitis	7 (7.5)	3 (3.2)	5 (5.7)
Sinusitis	6 (6.5)	2 (2.1)	7 (8.0)
Other			
Sweating	1 (1.1)	6 (6.3)	1 (1.1)
Abnormal vision	1 (1.1)	7 (7.4)	2 (2.3)
Asthenia	10 (10.8)	7 (7.4)	10 (11.5)
Back pain	4 (4.3)	2 (2.1)	10 (11.5)
Infection	10 (10.8)	5 (5.3)	9 (10.3)
Trauma	2 (2.2)	3 (3.2)	6 (6.9)

Note: Values represent no. (%).

increases or decreases in body weight were not observed among any of the three treatment arms of this study.

Serious adverse effects occurred in 11 patients in the paroxetine group, 5 in the imipramine group, and 2 in the placebo group. An event was defined as serious if it resulted in hospitalization, was associated with suicidal gestures, or was described by the treating physician as serious. The serious adverse effects in the paroxetine group consisted of headache during discontinuation taper (1 patient) and various psychiatric events (10 patients): worsening depression (2); emotional lability (e.g., suicidal ideation/gestures [5]); conduct problems or hostility (e.g., aggressiveness, behavioral disturbance in school [2]); and euphoria/expansive mood (1). Seven patients were hospitalized: 2 with worsening depression, 2 with emotional lability, 2 with conduct problems, and 1 with euphoria. Of the 11 patients, only headache (1 patient) was considered by the treating investigator to be related to paroxetine treatment.

The 5 serious adverse effects in the imipramine group consisted of maculopapular rash (1 patient), dyspnea/chest pain (1), hostility (1), emotional lability (1), and visual hallucinations/abnormal dreams (1). Two of the adverse effects (i.e., hallucinations, rash) were considered related to imipramine. All 5 patients were withdrawn from the study, and the patients with hostility or emotional lability were hospitalized. In the placebo group, emotional lability (1 patient) and worsening depression (1) were considered serious. The placebo-treated patient with emotional lability, which was considered to be related to placebo, was withdrawn from the study.

Of subjects in the imipramine group who stopped therapy because of adverse effects, nearly one third (13.7%) did so because of cardiovascular effects, including tachycardia, postural hypotension, and prolonged QT interval. Mean standing heart rate increased by 17 bpm over baseline among subjects treated with imipramine. Neither paroxetine nor placebo was associated with changes in heart rate.

DISCUSSION

This is the first study to compare efficacy of an SSRI and a tricyclic antidepressant with placebo in the treatment of major depression in adolescents. Paroxetine was significantly more effective than placebo with regard to achievement of both HAM-D total score ≤8, CGI score of 1 (very much improved) or 2 (much improved), and improvements in the depressed mood items of the HAM-D and the K-SADS-L. Paroxetine did not separate statistically from placebo for K-SADS-L depression subscore, mean CGI score, or HAM-D total score.

The demonstration of efficacy for paroxetine in this study is in accordance with findings of open-label studies of SSRIs (Ambrosini et al., 1999; Apter et al., 1994; Masi et al., 1997; McConville et al., 1996; Rey-Sanchez and Gutierrez-Casares, 1997; Rodriguez-Ramos et al., 1996; Simeon et al., 1998) and results from placebo-controlled (Emslie et al., 1997) and historical case-control (Strober et al., 1999) studies. These findings of efficacy for paroxetine and other SSRIs are notable in that randomized, double-blind, placebo-controlled trials (Geller et al., 1990; Hughes et al., 1990; Kashani et al., 1984; Klein et al., 1998; Kramer and Feiguine, 1981; Kutcher et al., 1994; Kye et al., 1996; Petti and Law, 1982; Preskorn et al., 1987) and one meta-analysis (Hazell et al., 1995) have not shown efficacy for the tricyclic antidepressants in the treatment of adolescent depression. Because efficacy has not been demonstrated for the tricyclic antidepressants and because these agents are associated with an unacceptably high risk of cardiotoxicity, especially in children, further controlled studies are not likely to be conducted. As such, future research involving bupropion or noradrenergic antidepressants not yet clinically available will be required to address more fully the question of preferential efficacy of the SSRIs in this age group.

Our study used a flexible-dose design in which doses could be adjusted on the basis of clinical response and tolerability. Roughly half of subjects were maintained at the paroxetine starting dose of 20 mg. The mean daily dose of paroxetine in this study, 28 mg, is comparable with that reported in flexible-dose trials in adults (Claghorn, 1992; Cohn and Wilcox, 1992; Dunbar et al., 1991; Fabre, 1992; Feighner and Boyer, 1992; Shrivastava et al., 1992; Smith and Glaudin, 1992).

The adverse-effect profile of paroxetine in this adolescent population was concordant with that reported in studies of adult patients with depression (Claghorn, 1992; Cohn and Wilcox, 1992; Dunbar et al., 1991; Fabre, 1992; Feighner and Boyer, 1992; Shrivastava et al., 1992; Smith and Glaudin, 1992). Serious adverse effects were reported during treatment with paroxetine (11 patients), imipramine (5), and placebo (2). Because these serious adverse effects were judged by the investigator to be related to treatment in only 4 patients (paroxetine, 1; imipramine, 2; placebo, 1), causality cannot be determined conclusively. Adverse cardiovascular effects were not

observed in subjects treated with paroxetine. In contrast, tachycardia, postural hypotension, and prolongation of QT intervals during imipramine therapy resulted in treatment discontinuation in one third of the 31.5% of subjects who stopped treatment prematurely with the tricyclic antidepressant.

Limitations

A high placebo response rate was observed in this study, which is not unusual for clinical trials of major depression in either pediatric or adult populations. In studies of pediatric patients with major depression, placebo response rates range from 20% to 80% (Birmaher et al., 1998; Emslie et al., 1997; Geller et al., 1992; Jensen et al., 1992; Kowatch et al., 1999). Placebo response also is high in adults with major depression as demonstrated by mean placebo response rates of approximately 30% to 40% in short-term studies (Brown, 1994; Schatzberg and Kraemer, 2000; Trivedi and Rush, 1994).

Several factors possibly contributed to the observed placebo response rate. A probable contributing factor was the weekly supportive case management sessions, which may have contributed to clinical improvement for patients in the placebo and active-treatment groups. In addition, the lack of a placebo run-in before randomization may have contributed to a higher placebo response. Inclusion of patients with externalizing disorders (e.g., conduct disorder, oppositional defiant disorder) also could be argued to have increased the placebo response rate. A post hoc analysis was conducted to assess this issue. However, the separate analysis of our database revealed that response rates to paroxetine, imipramine, and placebo among patients with attention-deficit/hyperactivity disorder (ADHD) were significantly lower than in patients without ADHD, regardless of treatment group assignment, including placebo (Birmaher et al., 2000).

The mean HAM-D total score from our sample at baseline in all three groups was 18 (±0.43), possibly accounting for the high placebo response. In fact, there appears to be an inverse relationship between placebo response in adults and clinical severity of depression. Adults with less severe depression exhibit greater placebo response rates than more seriously ill patients. Mild to moderate depression (i.e., HAM-D total score <19 in one study [Stewart et al., 1983], <13 in another [Paykel et al., 1988]) was associated with no drug–placebo difference in tricyclic antidepressant treatment studies of adult outpatients. Moreover, in contrast with our study, the mean baseline HAM-D total scores in short-term adult SSRI studies range from 23 to 28 (Cohn and Wilcox, 1985; Dunbar et al., 1991; Feighner and Overø, 1999; Reimherr et al., 1990; Stark and Hardison, 1985). It is important to emphasize, however, that comparisons in HAM-D scores between adults and adolescents may not be valid because of possible age-related variability in HAM-D.

Another methodological limitation must be acknowledged: the study was not designed to directly compare paroxetine with imipramine. The objective of the study was to determine the efficacy of two antidepressants with different mechanisms of action. To conduct a traditional three-arm comparative trial, this study would require testing at p values of .0167 rather than .05. To power a study at this level, it would have been necessary to enroll a greater number of patients, thus exposing more adolescents to the potential risks of clinical research.

Clinical Implications

Major depression in adolescents is an increasingly recognized clinical problem that is remarkably understudied. The majority of treatment studies involve the tricyclic antidepressants. Because these agents are associated with poor efficacy and cardiovascular adverse effects, their use is not recommended. In contrast, there are few large, well-controlled studies of SSRIs in adolescents. Our findings are therefore relevant to clinicians who are faced with treatment decisions for depressed adolescents and a relative paucity of data guiding therapeutic choice. Despite some methodological limitations, resulting in a high placebo response rate (outlined above), our study demonstrates that treatment with paroxetine results in clinically relevant improvement in depression scores. The SSRIs are the medications of choice for the treatment of major depression in adolescents because they are the only agents that have been shown to be efficacious in this population; they have a safer side-effect profile than other antidepressants, particularly in overdose; and they can be administered once daily. Clinicians should be aware that 8 weeks of treatment may not be sufficient to achieve a full clinical response, that some patients may benefit from higher doses, and that some as-yet unidentified groups of patients (e.g., more severely depressed; non-ADHD) may exhibit more robust responses to SSRI therapy.

Conclusion

The findings of this study provide evidence of the efficacy and safety of the SSRI, paroxetine, in the treat-

ment of adolescent depression. Additional studies are called for to define the optimal length of therapy and dose of SSRIs in this population.

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18

Review of Citalopram and Escitalopram Pediatric Safety Data

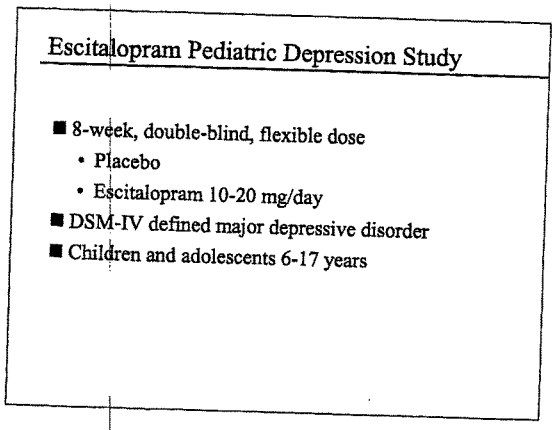
Jeffrey Jonas, MD
Vice President, CNS Therapeutic Area
Forest Laboratories, Inc.

General intro
Focus on Safety
Comment on Hx of Psychopham safety

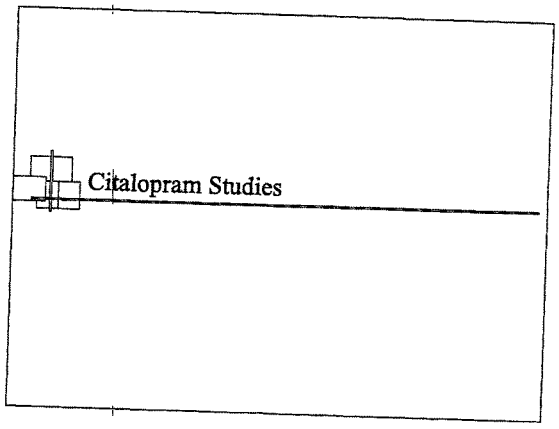
List of Controlled Studies

- 2 completed citalopram (Celexa™) studies in MDD
  - Citalopram vs. placebo
    - US Study (children and adolescents)
    - EU Study (adolescents only)
- 1 ongoing escitalopram (Lexapro™) study in MDD
  - Escitalopram vs. placebo
    - US Study (children and adolescents)

1. Comment that US study was positive
2. Commet that EU study was negative
3. Comment on risk-benefit assessment thinking



In this double-blind, placebo-controlled, flexible-dose study (MD-15), 264 children and adolescents (aged 6-17 years) with major depressive disorder will be randomized to receive either placebo or escitalopram 10-20 mg/day. After a 1-week single-blind placebo lead-in period, patients will receive 8 weeks of double-blind treatment. The primary efficacy measure will be change from baseline on the CDRS-R.


Citalopram Studies

Study Designs

US Study

- 8-week double-blind
- Children (7-11 years) and adolescents (12-17 years)
- Outpatients only
- DSM-IV criteria for MDD
- CDRS-R ≥40 at baseline
- Patients at high risk for suicide excluded
- Primary Efficacy: CDRS-R

EU Study

- 12-week double-blind
- Adolescents (13-18 years)
- Outpatients and inpatients
- DSM-IV criteria for MDD
- BDI ≥21(girls), ≥16 (boys)
- GAF ≤60
- Patients with prior suicide history were enrolled
- Primary Efficacy: K-SADS

1. Review slides
2. Note again efficacy findings for US and EU study
3. Note differences in design
4. Comment on issues regardining post-hoc analyses

Demographics

US Study

	Placebo	Citalopram
Safety Population	85	89
Children/Adolescents	38/47	45/44
Completed (%)	79%	80%
Mean Age (years)	12.1	12.1
Sex (% female)	54%	53%
Duration of MDD (years)	2.2	2.3

Demographics

EU Study

	Placebo	Citalopram
Safety Population	112	121
Completed (%)	66%	65%
Mean Age (years)	16	16
Sex (% female)	74%	74%
Inpatients (%)	12%	16%

Major Risk Factors at Baseline

EU Study

	Citalopram (N=121)		Placebo (N=112)		
	n	%	n	%	p-value*
Patients with past suicide attempts	37	31	34	30	1.00
Patients with past psych hospitalization	28	23	18	16	0.19
Inpatient at study start	19	16	13	12	0.45
Total risk events	84		65		NA
Patients with any risk event	51	42	42	38	0.51

* Fisher's Exact Test, two-sided

Note last line is also a non-duplicative patient number

Note comments on what are known RF's for swx

Note no systematic pre-hoc stratification

Review of Safety Data

- Prospectively defined analysis plan
- 3 independent, blinded reviews of AEs with verbatim terms containing:

"suic"	"overdos"	"attempt"	"cut"	"gas"
"hang"	"hung"	"jump"	"mutilat"	"selfharm"
"self inflict"	"self injur"	"shoot"	"slash"	

- Assessment of "hard" endpoints of behavioral deterioration: hospitalization and/or exacerbation of depression
- Reviewers meet to reconcile differences in blinded assessments
- Review of SAEs, AE discontinuation reports, and listings to identify additional cases
- Item analysis for CDRS-R and KSADS for changes in suicidality
- Analyses of "AE's of interest"

Note FDA hx

Categorization of Suicide Related Events

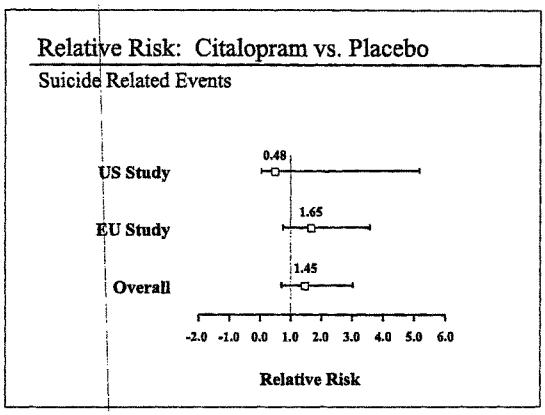
- Suicide Attempts (SA)
  - Any form of self-harm, regardless of stated suicidal intentions
  - Any event reported with the verbatim term or coded with the preferred term "suicide attempt"
- Suicide Related Events (SRE)
  - SA + suicidal ideation
- Worsening of Depression (WD) + SRE
  - Exacerbation of depression leading to hospitalization or premature discontinuation + SRE

Risk Ratios

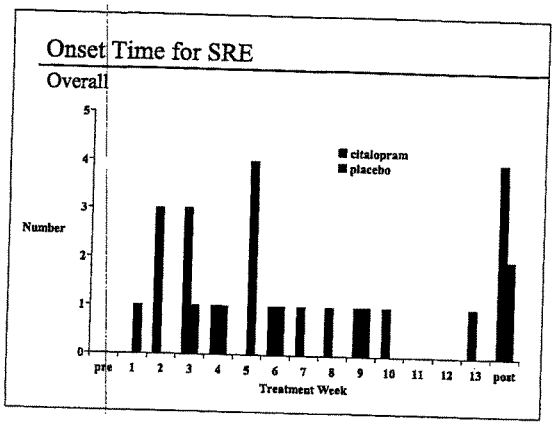
- Risk
  - # of patients with at least one event / # of treated patients
  - Type of event (SA, SRE, WD)
  - Age group (child vs. adolescent)
  - Temporal relationship (on-therapy vs. on-therapy + 30 days)

Risk Ratios of SRE by Study

Study	Treatment	Patients w/ Event	Safety Population	Person-Time Exposure (years)	Risk
US	PLA	2	85	12.0	0.02
	CIT	1	89	12.8	0.01
EU	PLA	9	112	21.3	0.08
	CIT	16	121	23.5	0.13
Overall	PLA	11	197	33.3	0.06
	CIT	17	210	36.3	0.08

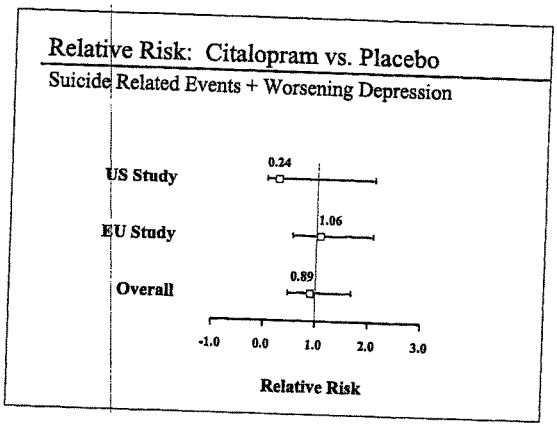


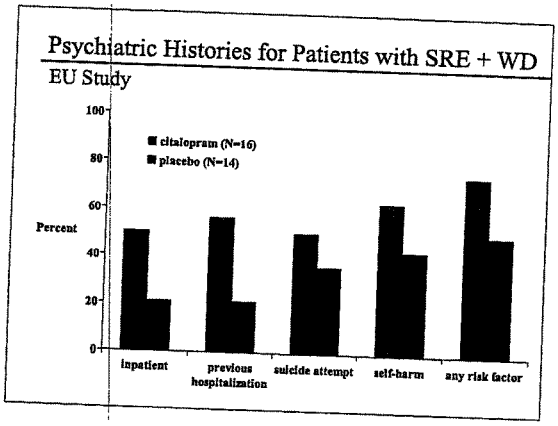
Describe format, meaning of RR in this context

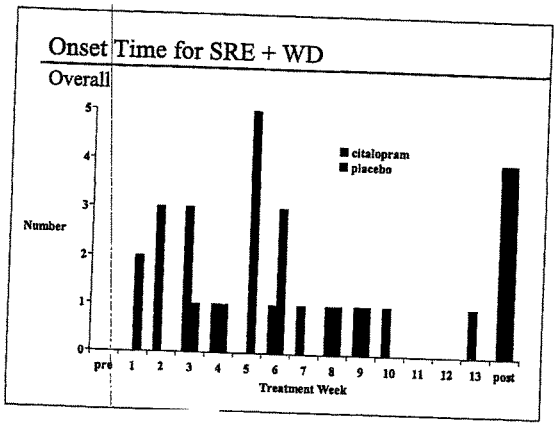

Onset Time for SRE
Overall
citalopram
placebo
Number
0
1
2
3
4
5
pre
1
2
3
4
5
6
7
8
9
10
11
12
13
post
Treatment Week

Risk Ratios of SRE + WD by Study

Study	Treatment	Patients w/ ≥ 1 Event	Safety Population	Person-Time Exposure (years)	Risk
US	PLA	4	85	12.0	0.05
	CIT	1	89	12.8	0.01
EU	PLA	14	112	21.3	0.13
	CIT	16	121	23.5	0.13
Overall	PLA	18	197	33.3	0.09
	CIT	17	210	36.3	0.08


Relative Risk: Citalopram vs. Placebo
Suicide Related Events + Worsening Depression
US Study
EU Study
Overall
0.24
1.06
0.89
-1.0
0.0
1.0
2.0
3.0
Relative Risk


Psychiatric Histories for Patients with SRE + WD
EU Study
citalopram (N=16)
placebo (N=14)
Percent
100
80
60
40
20
0
inpatient
previous hospitalization
suicide attempt
self-harm
any risk factor

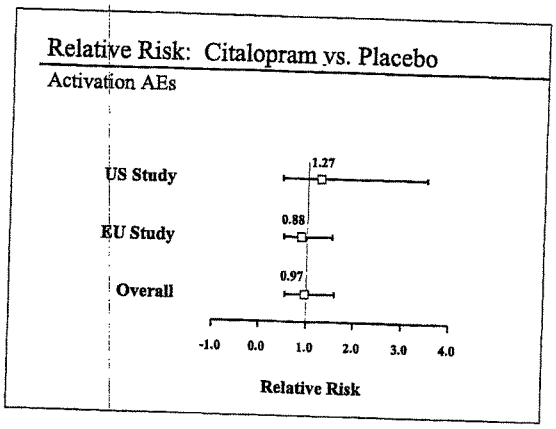

Onset Time for SRE + WD
Overall
citalopram
placebo
Number
0
1
2
3
4
5
pre
1
2
3
4
5
6
7
8
9
10
11
12
13
post
Treatment Week

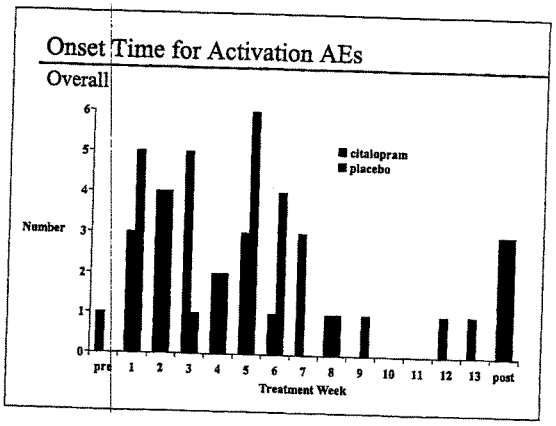
Adverse Events by Study

Activation AEs

Study	Treatment	Patients w/ AE	Treated Patients	Incidence %
US	PLA	6	85	7.0%
	CIT	8	89	9.0%
EU	PLA	21	112	18.8%
	CIT	20	121	16.5%
Overall	PLA	27	197	13.7%
	CIT	28	210	13.3%

AE cluster includes agitation, akathisia, anxiety, depression, depression aggravated, emotional lability, hyperkinesia, hypomania, impulsive behavior, irritability, manic reaction, nervousness, personality disorder, suicidal tendency, suicide attempt


Relative Risk: Citalopram vs. Placebo
Activation AEs
US Study
EU Study
Overall
1.27
0.88
0.97
-1.0
0.0
1.0
2.0
3.0
4.0
Relative Risk



Note historical hypotheses
No secular trend

Suicidal Item Analysis: CDRS-R

US Study

- Suicidal ideation assessed using CDRS-R item 13
  - Emergence of suicidal ideation
    - Baseline score of 1 or 2 and increase to 5 anytime during treatment
  - Worsening of suicidal ideation
    - Baseline score of 1 or 2 and increase to 3 or 4
    - Baseline score of 3 or 4 and increase to 5
  - Improvement of suicidal ideation
    - Baseline score of 5 and decrease to ≤ 4
    - Baseline score of 3 or 4 and decrease to 1 or 2

Beasley et al., *BMJ*, 1991; Jonas, *J Clin Psychiatry*, 1996.

Suicidal Ideation: Relative Risk Ratios for Emergence, Worsening, and Improvement

US Study

	Emergence		Worsening		Improvement	
Treatment Group	n/N (%)	CIT/PLA Relative Risk (p-value)	n/N (%)	CIT/PLA Relative Risk (p-value)	n/N (%)	CIT/PLA Relative Risk (p-value)
PLA	2/67 (3.0%)	0.44 (0.60)	12/82 (14.6%)	0.39 (0.073)	7/18 (38.9%)	1.98 (0.067)
CIT	1/76 (1.3%)		5/87 (5.8%)		10/13 (76.9%)	

Suicidal Item Analysis: KSADS

EU Study

- Suicidal ideation assessed using KSADS item 9
  - Emergence of suicidal ideation
    - Baseline score of 1 or 2 and increase to 5, 6, or 7 anytime during treatment
  - Worsening of suicidal ideation
    - Baseline score of 1 or 2 and increase to 3 or 4
    - Baseline score of 3 or 4 and increase to 5, 6, or 7
  - Improvement of suicidal ideation
    - Baseline score of 5, 6 or 7 and decrease to ≤ 4
    - Baseline score of 3 or 4 and decrease to 1 or 2

Suicidal Ideation: Relative Risk Ratios for Emergence, Worsening, and Improvement

EU Study

	Emergence		Worsening		Improvement	
Treatment Group	n/N (%)	CIT/PLA Relative Risk (p-value)	n/N (%)	CIT/PLA Relative Risk (p-value)	n/N (%)	CIT/PLA Relative Risk (p-value)
PLA	1/47 (2.1%)	1.02 (1.00)	17/95 (17.9%)	0.43 (0.052)	47/58 (81.0%)	1.01 (1.00)
CIT	1/46 (2.2%)		8/103 (7.8%)		55/67 (82.1%)	

Summary and Conclusions

- Overall rates for SRE, SA, and behavioral deterioration similar between citalopram and placebo
- EU study had baseline imbalances with respect to number of inpatients in each treatment arm
  - Many patients with SRE and SA treated successfully with CIT after discontinuation
- Analysis of AEs shows no evidence of activation, and no overt onset in early stages of therapy
- Item analyses of structured clinical scales show no evidence for systematic exacerbation of suicidality associated with treatment, and trend towards amelioration of suicidality associated with treatment

Studier af SSRI- og andre, nyere præparater
Selvom der endnu er et begrænset antal undersøgelser af deprimerede børn og unge, er der stigende sikkerhed for, at SSRI-præparater er effektive til behandling af depression i denne aldersgruppe med en effektivitet, som meget ligner den, der ses hos voksne patienter. Det ser ud til, at medikamenterne er sikre at bruge, i hvert fald på kort sigt, selvom der fortsat mangler yderligere forskning til belysning af effekten af langtidsbehandling af børn og unge.

Studier af SSRI-stoffer
Af tabel 2 fremgår undersøgelserne af SSRI-præparater.

Tabel 2

Undersøgelse	N	Dosis	Effekt
Simeon et al., 1990	40	Fluoxetin, 20 mg	Fluoxetin = placebo
Emslie et al., 1997	96	Fluoxetin, 20 mg	Fluoxetin > placebo
Mandoki et al., 1997	33	Venlafaxin (SNRI), 37,5-75 mg	Venlafaxin = placebo
Keller et al., 2001	275	Paroxetin, 20-40 mg	Paroxetin > placebo Paroxetin > Imipramin
Emslie et al., 2002	219	Fluoxetin, 20 mg	Fluoxetin > placebo
Wagner et al., 2003	376	Sertralin, 50-200 mg	Sertralin > placebo
von Knorring et al., ikke publiceret	260	Citalopram, 20-40 mg	Citalopram = placebo
Wagner og Ambrosini, ikke publiceret	174	Citalopram, 20-40 mg	Citalopram > placebo

To studier på fluoxetin (Fontex) har beskrevet virkningen i aldersgruppen 7-17 år (Emslie et al., 1997; Simeon et al., 1990). Resultaterne fra den ene af undersøgelserne viste, at 56% af patienterne på præparatet Fontex havde virkning af medicinen sammenlignet med 33% af de patienter, som fik

placebo. Det ene af studierne viste effekt hos unge (Emslie et al., 1997), det andet gjorde ikke (Simeon et al., 1990). I en ny stor undersøgelse af 122 børn og 97 unge behandlede man med 20 mg Fontex i 8 uger (Emslie et al., 2002). Studiet viste effekt af Fontex, uafhængigt af køn og alder, på de fleste af de anvendte skalaer. Paroxetin (Seroxat) blev på lignende måde undersøgt på 275 unge i alderen 12-19 år, med nogenlunde samme resultater (Keller et al., 2001). Helt nye undersøgelser af såvel citalopram (Cipramil) som sertralin (Zoloft) viser, at begge disse præparater er mere effektive end placebo i behandlingen af depression hos såvel børn som unge (Wagner og Ambrosini, endnu ikke publiceret; Wagner et al., 2003). Man har ikke systematisk undersøgt fluvoxamin (Fevarin), men et åbent studium, dvs. hvor såvel patient som behandler var klar over, at der blev givet aktiv medicin, viste, at ca. 66% af de behandlede unge i alderen 13-17 år havde effekt af den medikamentelle behandling (Findling et al., 1999).

Undersøgelser af andre nyere stoffer
Nefazodon: Der har ikke været udført kontrollerede undersøgelser på nefazodon til behandling af depression hos børn og unge. En lille, åben undersøgelse på 10 unge viste effekt hos ca. 70% i løbet af 8 uger (i doser på op til 400 mg/dag) (Wilens et al., 1997).

Venlafaxin: Der har været én kontrolleret undersøgelse af dette stof. I denne undersøgelse blev patienter i alderen 8-17 år behandlet over 8 uger. Man anvendte relativt lave doseringer (37,5 mg/dag for børn og 75 mg/dag for unge), og der blev givet samtidig psykoterapi. Man fandt en betydelig bedring, men man fandt dog ingen statistisk forskel mellem medicin- og placebogruppen. Dette kan forklares ved den lave dosering, det noget korte behandlingsforløb eller ved effekten af psykoterapi (Mandoki et al., 1997).

Reboxetin og Mirtazapin: Der har endnu ikke været studier på børn og unge af disse præparater.

Studies of SSRI and other, newer preparations

Although there have only been a limited number of studies to date on depressed children and adolescents, there is increasing proof that SSRI-preparations are effective in treating depression in this age group with an efficiency that very closely resembles that seen in adult patients. It appears that the drugs are safe to use, at least in the short term, although additional research is needed to provide information about the effect of the long-term treatment of children and adolescents.

Studies of SSRI-substances

Table 2 shows studies of SSRI-preparations

Table 2

Study	N	Dose	Effect
Simeon et al, 1990	40	Fluoxetine, 20 mg	Fluoxetine = placebo
Emslie et al., 1997	96	Fluoxetine, 20 mg	Fluoxetine > placebo
Mandoki et al.,1997	33	Venlafaxine (SNRI), 37.5-75 mg	Venlafaxine = placebo
Keller et al., 2001	275	Paroxetine, 20-40 mg	Paroxetine > placebo Paroxetine > Imipramine
Emslie et al, 2002	219	Fluoxetine, 20 mg	Fluoxetine > placebo
Wagner et al., 2003	376	Sertraline, 50-200 mg	Sertraline > placebo
van Knorring et al, not published	260	Citalopram, 20-40 mg	Citalopram = placebo
Wagner and Ambrosini, not published	174	Citalopram, 20-40 mg	Citalopram > placebo

Two studies of fluoxetine (Fontex) have described the effect on the seven to seventeen age group (Emslie et al., 1997; Simeon et al., 1990). The results of one of the studies demonstrated that out of the patients on the preparation Fontex, the medicine had an affect on 56% compared to 33% of the patients who were given the placebo. One of the studies showed the effect on adolescents (Emslie et al., 1997), the other one did not (Simeon et al., 1990). In a large new study 122 children and 97 adolescents were treated with 20 mg Fontex for eight weeks (Emslie et al., 2002). The study demonstrated the effect of Fontex regardless of sex and age on the majority of scales used. Paroxetine (Seroxat) was studied in a similar manner on 275 adolescents between twelve and nineteen years of age with somewhat similar results (Keller et al, 2001). Brand new studies of both citalopram (Cipramil) and sertraline (Zoloft) demonstrate that both of these preparations are more effective than the placebo in treating depression in both children and adolescents (Wagner and Ambrosini, not published yet; Wagner et al., 2003). Fluvoxamine (Fevarin) has not been systematically studied, but an open study where both the patients and the care giver knew that active medicine was being administered demonstrated that the drug therapy had an effect on about 66% of the treated adolescents between the ages of thirteen and seventeen (Findling et al., 1999).

Studies of other newer substances

Nefazodone: There have not been any controlled studies on nefazodone for treating depression in children and adolescents. A small, open study of ten adolescents demonstrated an effect on about 70% [of the patients] within eight weeks (in doses of up to 400 mg/day) (Wilens et al., 1997).

Venlafaxine: There has been one controlled study of this substance. In this study patients between the ages of eight and seventeen were treated for over eight weeks. Relatively low doses (37.5 mg/day for children and 75 mg/day for adolescents) and psychotherapy were administered at the same time. Significant improvement was found, but there was not statistical difference between the group treated with medicine and the group treated with the placebo. This may be explained by the low dose, the somewhat short period of therapy, or the effect of the psychotherapy (Mandoki et al., 1997).

Reboxetine and Mirtazapine: To date no studies of these preparations have been done on children and adolescents.

The "file drawer" phenomenon: suppressing clinical evidence

Accumulating evidence, including a report in this issue by Bhandari and colleagues, (see page 477) suggests that commercially sponsored clinical trials are biased toward obtaining positive results. Laurence Hirsch, vice-president of medical communications at Merck, argues in an accompanying commentary (see page 481) that while drug companies are likely to give "priority" to trials with the greatest likelihood of "positive return," the sources of bias in clinical trials of any funding stripe are difficult to tease out. But, clearly, a substantial proportion of clinical trial results is simply never reported in the public domain. Most go unreported because a treatment effect was not shown — the so-called "negative" study. But, in other cases, trial results are a commercial liability. The huge investment required to develop new drugs and devices and successfully carve out a share of the market for them puts pressure on companies to suppress results that might slow or extinguish sales. No surprise that selected clinical trial data are kept locked in the filing cabinet.

By concealing unfavourable evidence about efficacy and safety, pharmaceutical companies deceive physicians, their patients and, perhaps, shareholders. Worse, such concealment is a flagrant abuse of the trust freely offered to study investigators by research subjects. Nowhere is this more evident than in clinical trials of selective serotonin reuptake inhibitors (SSRIs) in children. Although depression is not an easy diagnosis to make in the often turbulent emotional life of children and adolescents, by age 18 about 20% of adolescents will have experienced an episode of major depressive disorder, lasting some months, and carrying the threat of recurrence. This large market of child and parent anguish has attracted pharmaceutical companies.

Jane Garland, a psychiatrist and clinical researcher, has been an investigator in a few trials of SSRIs in children (see page 489), not all of which have been published. To review product information before participating in one industry-sponsored trial she was obliged to sign a 10-year nondisclosure agreement. This embargoed information included a summary of negative data from previous unpublished trials that showed a lack of effectiveness for a drug already on the market. Garland has voiced to us and to others her resolve to "never do an industry-funded trial again unless the whole structure and management of these is drastically changed." She laments the fact that physician–researchers have not taken a collective stand on the disclosure of trial data.

Concealment occurs also at the level of government regulation. Given that companies seeking drug approval must report all trials to regulators, Health Canada cannot be oblivious to buried trials and conflicting evidence of efficacy and safety. Yet, constrained by laws with conflicting goals — to provide the public with safe and efficacious drugs and devices *and* to protect commercial interests — regulators are too often silent.

Other hidden evidence in the hands of regulators takes the form of adverse drug reaction reports. Andrew Herxheimer and Barbara Mintzes (see page 487) comment that, even in the United Kingdom, which has one of the best voluntary reporting systems in the world, the side-effects of drugs used to treat depression are underreported and hence underestimated.

The behaviour of industry, government and investigators must change. Investigators must demand access to all the data collected in clinical trials in which they participate[1] and to suitably anonymized aggregate information from adverse drug reaction reports. Investigators should be at liberty and even encouraged to provide alternate analyses and interpretations of clinical trial results and adverse event reporting and to publish these. Physicians, research subjects and the public should demand no less.

We are encouraged by Hirsch's announcement that "Merck has adopted guidelines in which we commit to publish the results of hypothesis-testing clinical trials regardless of outcome." Although some may find fault in the details, the new Merck guidelines are a bold step — one that should receive wide support and encouragement from the research community and physicians. Canada's Research-Based Pharmaceutical Companies should announce their full support for the Merck guidelines and make them part of the association's guidelines for all member companies.

We hope that with the proposed "renewal" of Canadian health protection legislation, our government will adhere to the stated values of "openness," "accountability" and the "primacy of health and safety."[2] In the regulation of clinical testing of drugs and devices, safety and efficacy must trump proprietary rights every time. — *CMAJ*

References

1. Davidoff F, DeAngelis CD, Drazen JM, Nicholls MG, Hoey J, Hojgaard L, et al. Sponsorship, authorship and accountability. *CMAJ* 2001;165(6):786-8.
2. *Health protection legislative renewal* [proposal]. Ottawa: Health Canada; 2003. Available: www2.hc-sc.gc.ca/HPCB/Policy/LegislativeRenewal.asp (accessed 2004 Jan 26).

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June 21, 2004

A Medical Journal Quandary: How to Report on Drug Trials

By BARRY MEIER

The issue of The American Journal of Psychiatry that hit the desks of its 37,000 readers this month reported test results for the antidepressant drug Celexa, indicating it could help children and teenagers.

Before publication, the article received the kind of scrutiny common among medical journals. The study's authors had been asked to divulge their financial ties, if any, to the drug's marketer, Forest Laboratories Inc., which sponsored the clinical trial. And the report was sent to reviewers who examined the trial methodology and checked to make sure that the article reflected other relevant research about the use of antidepressants in youngsters.

But neither the article nor the 27 scholarly footnotes that accompanied it mentioned another major drug-industry-sponsored trial completed in 2002, which found that Celexa did not help depressed adolescents any more than a placebo. Nor would the article's reviewers have been likely to find any clues of that trial's existence. The results of that trial were first noted last year on a single line of a chart that appeared on Page 96 of a textbook - one written in Danish.

Like most medical journals, The American Journal of Psychiatry does not require company sponsors of drug trials to divulge information about all relevant trials of a medication. But that may soon change, as some leading journal editors try to address what they see as shortcomings in the way clinical tests are designed and analyzed by the drug industry, and how test results are disclosed.

"There is so much sophistication, that if the journals are not careful they could end up being part of the drug industry's marketing arm," said Dr. Richard Smith, the editor of The British Medical Journal.

In written responses to inquiries from The New York Times, Forest stated that the negative Celexa test, sponsored by a related company, was not mentioned in the recent article because "there was no citable public reference for the authors to examine."

But drug makers often announce trials with positive results without waiting for the results to be published. Forest, for example, issued a news release three years ago that highlighted the outcome of the positive Celexa trial. That was shortly after the test's completion, when the findings were first presented at a medical conference, but before the study was even submitted to The American Journal of Psychiatry for consideration. Three of the authors of the Celexa drug article in this month's issue are Forest employees.

Dr. Smith and other editors say the challenges they face are not limited to the tendency by companies and academic researchers to showcase positive tests results while playing down trials with negative or inconclusive findings. Editors say they must also be vigilant against companies' cherry-picking favorable but limited data from a trial that had originally set out to test other aspects of a drug's

performance.

Some companies, several editors said, have also apparently milked tests for maximum publicity by submitting different parts of them under different authors' names to different medical journals.

A group of 12 medical journals worldwide including The Journal of the American Medical Association, The New England Journal of Medicine, The Lancet and The Annals of Internal Medicine are weighing a proposal that would require a drug trial to be listed at its start in a public database or registry as a prerequisite to its results being considered for publication. The British Medical Journal is not part of that group, which is known as the International Committee of Medical Journal Editors, but Dr. Smith said he also supported the initiative.

Editors say that a database could offer several benefits. Assigning a test a unique number could allow it to be tracked from start to finish. The results, be they positive or negative, could then be put into context with other relevant trials of the same drug. Moreover, journal editors say that if a trial's objectives were listed at the outset, they would know how to better assess an article that presented its results.

"It would be useful for us from an editorial perspective if trials were registered, so we could see what was on the mind of investigators when they started," said Dr. Jeffrey M. Drazen, the editor of The New England Journal of Medicine.

Some critics, however, have argued that medical journals themselves have been a part of the problem. A growing number of studies in recent years have shown that journals publish more trials with positive results than those with negative or inconclusive ones. And critics say the journals have moved too slowly to address such issues.

Dr. Catherine D. DeAngelis, the editor of The Journal of the American Medical Association, said the idea of requiring trial registration had been kicking around among editors for about a decade. She said the issue came up again during a discussion at a meeting earlier this month of the International Committee of Medical Journal Editors, partly out of frustration.

"We have tried editorials," said Dr. DeAngelis. "We tried getting the pharmaceutical companies to do it. We tried talking to leaders in government. But it hasn't happened."

While Dr. Drazen and Dr. DeAngelis said their group was likely to decide over the coming months what course to follow, it is not clear how the drug industry will react. Last week, Merck said it would support the idea of a government-run test registry. And GlaxoSmithKline said it would soon begin posting on its company Web site the trial results of all its drugs on the market, including tests for potential new uses of them.

Some other companies and the drug industry's trade group, the Pharmaceutical Research and Manufacturers Association of America, said last week that they could not comment because they had not seen specific registry proposals. But one official of the trade group raised concerns that registries could release company trade secrets or present data in ways confusing to doctors and the public.

Whatever the case, the example of the little-known test of Celexa in adolescents shows how medical journals can now miss information about a major trial of a drug that is the subject of an article.

Dr. Nancy C. Andreasen, the editor of The American Journal of Psychiatry, which is the flagship

publication of American Psychiatric Association, said it was the responsibility of a study's authors to provide a scholarly overview of the published articles discussed in their paper. She said that her publication did not specifically ask authors or companies that sponsor trials about unpublished studies.

"We didn't have a checklist that includes that question," Dr. Andreasen said. She added, though, that the publication regularly reviews its policies.

The Celexa trial in question was run in Europe from 1996 to 2002 and was sponsored by H. Lundbeck, the Danish company that developed the drug.

Forest Laboratories sells the drug, which is generically known as citalopram, in this country under a license with Lundbeck.

A spokesman for Lundbeck said the company reported the trial results to Forest, although he could not say when. Forest executives did not respond to written inquiries from The Times seeking that information.

But Forest executives apparently had an opportunity to know about the European test before the publication of the positive trial's results this month in The American Journal of Psychiatry. Forest executives said they presented safety data concerning potential suicide risk from both the positive study and the European trial last fall at a medical conference. It was around that time that regulators in Britain and this country expressed concerns that several antidepressants might cause some depressed teenagers to consider suicide; the issue is still under study.

The Lundbeck spokesman said that an abstract about the European trial had been presented in April at a Swedish medical meeting, and both companies said that an article about that trial was being prepared for publication. Both companies also said that they did not promote the drug's use in children because regulators had not approved it for pediatric use. (Doctors can legally prescribe a drug for any use, once it has been approved for at least one purpose.)

Dr. Andreasen and other journal editors interviewed said that a single failed trial of a drug did not mean that the treatment was ineffective, because the study's design might have been flawed. By the same token, of course, a single positive test of a drug does not necessarily mean that it works.

In a Lancet article in April, British researchers sought to compare the benefits and risks that widely used antidepressants pose for children and adolescents, based on published and unpublished data. They reported that their analysis of the pooled results from two unpublished Celexa trials - the one since published in The American Journal of Psychiatry and the European study cited in the Danish textbook - suggested that citalopram was unlikely to produce a "clinically important reduction in depressive symptoms."

"With no good evidence for efficacy and the potential for increasing the risk for suicide, the risk-benefit balance is unfavorable," the researchers reported.

Dr. Karen Dineen Wagner of the University of Texas Medical Branch in Galveston, who was the lead outside investigator on the study published in The American Journal of Psychiatry, did not respond to interview requests through a hospital spokeswoman. The two other outside researchers involved, however, both said that Celexa worked well in their test and that the young patients did not experience increased suicidal thoughts.

"I don't know what the raw data looks like from the European study," said one of them, Dr. Adelaide S. Robb of the Children's National Medical Center in Washington.

She said that she was informed by Forest executives in 1999 that the European study was under way but that she was never told that it had been completed.

The New York Times
nytimes.com

June 26, 2004

Drug Maker Acknowledges Some Negative Test Results

By BARRY MEIER

Forest Laboratories has said a recently concluded test found that its antidepressant Lexapro did not help depressed children and adolescents, an announcement that comes amid the growing controversy over clinical drug tests.

The company's announcement is significant because Lexapro contains essentially the same active ingredient as another Forest antidepressant, Celexa, which is widely prescribed for pediatric use.

The company made its announcement late Thursday, when it also released a second statement addressing how it had handled its disclosure of results from two trials of Celexa in depressed children.

The New York Times reported Monday that Forest officials had not told a medical journal about a failed unpublished study in 2002 of Celexa use in children and adolescents, before the journal published an article this month about a separate test indicating the drug could help young people. Some of the recent article's authors were Forest employees.

In recent weeks, pharmaceutical companies have faced growing pressure on the issue of selective disclosure of drug test results. The American Medical Association has called on the federal government to create a database in which trials can be tracked from start to finish. And several medical journals are considering a proposal that would require trials to be registered at the outset as a prerequisite to the results' eventual publication.

Forest's disclosure on Thursday about the negative Lexapro test came before the initial results were presented at a medical meeting or published in a journal. Forest had said earlier that it did not point to the negative Celexa test because there was no published reference to cite.

Forest said that the pediatric test of the drug had been recently completed and that the company had issued a safety report to the Food and Drug Administration indicating that Lexapro did not cause an increase in the test patients' suicidal thinking. Regulators are concerned that several widely used antidepressants like Celexa might cause children and adolescents to harm themselves or consider suicide.

In the separate announcement addressing Forest's handling of the two Celexa tests in depressed young people, the company said, "Given the current increased interest in industry publication practices as well as outstanding questions about the role of antidepressants in the pediatric populations, questions about the availability of these reports have been raised."

The study with positive findings, which was conducted in this country, was published in this month's issue of The American Journal of Psychiatry. The findings of the negative study, which was conducted in Europe from 1996 to 2002, have never been published nor were they referred to in the recent journal

article.

In Thursday's release, Forest said that the company had discussed both the "topline efficacy results" as well as safety findings from the failed European study at a meeting of the American Academy of Child and Adolescent Psychiatry in October 2003. The company did not elaborate about that presentation, and a Forest official said in an e-mail message that the company could not respond to questions about its statement until early next week.

In previous responses to inquiries from The Times, however, Forest stated that it presented safety data at that meeting, rather than both safety and efficacy findings. Two outside researchers involved in the positive Celexa study, also said in recent interviews that Forest did not tell them about the efficacy findings of the European study and that they were not independently aware of them.

In October 2003, the finding of the European study that Celexa showed no effects greater than a placebo was noted in a chart published in a medical textbook written in Danish. The European study was sponsored by H. Lundbeck, the Danish company that developed citalopram, which Forest markets in this country as Celexa.

Forest officials, who said that they did nothing wrong, also stated in Thursday's announcement that the European study involved some hospitalized patients, while the tests in this country involved only patients treated in clinics or doctor's offices. Both Celexa studies were reported to regulators, the company said.

The company is not currently permitted to promote either Lexapro or Celaxa as a treatment for depression in young people, although doctors are free to prescribe the drugs for any purpose. Celexa is the fourth-leading drug prescribed for pediatric depression.

Because Celexa's patent is about to expire, Forest has been aggressively marketing Lexapro as a treatment for adult depression. The company said in its statement that it intended to discuss with federal regulators its plan to start additional pediatric tests of Lexapro in the hope of eventually winning approval for such uses.

Although Forest's stock fell in after-hours trading Thursday following the company's announcements, and briefly plunged when the market opened yesterday, the shares recovered by the end of yesterday's trading session. They closed at 58.46, up 91 cents. That is still below their 52-week high of nearly $79 in early March.

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Forest Laboratories, Inc.
909 Third Avenue
New York, New York 10022

STUDY Report for
Protocol No. CIT-MD-18

Title: A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression

Abbreviated Title: Citalopram Pediatric Depression

Name of Study Drug: Citalopram
Indication: Major Depressive Disorder
Study Phase: III
Initiation Date: 31 Jan 2000
Completion Date: 10 Apr 2001

The study was carried out in compliance with the International Conference on Harmonization (ICH)-E6 Good Clinical Practice Guideline.

Report Date: April 8, 2002

SYNOPSIS

Name of sponsor/company: Forest Laboratories, Inc.	
Title of study: A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression	
Protocol No.: CIT-MD-18	
Study period: 31 Jan 2000 (Date of first enrollment) 10 Apr 2001 (Date of last completion)	**Development Phase:** III
Objectives: The objective of this study was to evaluate the safety and efficacy of citalopram (20–40 mg/day) compared with placebo in children (7-11 years) and adolescent (12-17 years) outpatients with major depressive disorder (MDD).	
Study design: Randomized, double-blind, placebo-controlled, multicenter, parallel-group, 2-arm, flexible dose study consisting of a 1-week single-blind placebo lead-in and an 8-week double-blind treatment phase in pediatric outpatients diagnosed with MDD (DSM-IV criteria).	
Number of patients: One hundred seventy-four (174) patients received at least one dose of double-blind study medication (safety population).	
Study centers: 21 US centers.	
List of investigators: A list of investigators is presented in Appendix II.	
Diagnosis and main criteria for inclusion: Male or female children (7 to 11 years) and adolescent (12 to 17 years) outpatients, who met DSM-IV criteria for MDD.	
Study drug and dosage strength: Citalopram - 20 mg tablets and placebo tablets. **Dosage groups:** Citalopram 20 mg/day or citalopram 40 mg/day; placebo. **Mode of administration:** All study drugs were administered orally. **Lot numbers:** Citalopram - lot nos. P01102, P01165, P02161; placebo - lot no. P01164.	
Duration of treatment: One week of single-blind placebo treatment and 8 weeks of double-blind treatment.	
Criteria for evaluation: **Efficacy: Primary –** Children's Depression Rating Scale - Revised (CDRS-R). **Secondary –** Clinical Global Impression – Severity (CGI-S); Clinical Global Impression – Improvement (CGI-I); Children's Global Assessment Scale (CGAS); Kiddie Schedule for Affective Disorders and Schizophrenia – Present (depression module) (K-SADS –P depression module). **Safety:** Recording of adverse events (AEs), standard laboratory measurements, physical examination, vital signs evaluation, and electrocardiograms (ECGs).	
Statistical methods: Patient disposition, demographics, and safety analyses were based on the safety population, which included all patients who received double-blind treatment. Efficacy analyses were based on the ITT population, which included all patients in the safety population who had at least one post-baseline efficacy assessment on the CDRS-R. All tests were two-sided with a 5% significance level for main effects and a 10% significance level for interaction terms. The primary efficacy parameter was the change from baseline in CDRS-R score at Week 8. Comparisons of citalopram and placebo were performed using an analysis of covariance (ANCOVA) additive model with treatment, study center, and age group as factors and baseline score as covariate. The primary efficacy analysis used the last observation carried forward (LOCF) approach.	

All secondary efficacy parameters except the CGI-I score were analyzed using the same ANCOVA model as for the primary efficacy parameter. A three-way analysis of variance (ANOVA) model was used for the CGI-I score, since this parameter records improvement relative to baseline and baseline score is not applicable. Additional by visit analyses were carried out for all effiacacy parameters, using both the LOCF and observed cases (OC) approach.

Summary – Conclusions:

Patient Disposition:

A total of 174 patients entered the double-blind treatment period and received study drug, 89 in the citalopram group and 85 in the placebo group. These patients were included in all safety and efficacy analyses. Thus, the safety population and the efficacy population were identical (N=174). A total of 138 (79%) patients completed the study, 80% of patients in the citalopram group and 79% of patients in the placebo group.

Demography:

Demographic characteristics were similar between the treatment groups. In the placebo group, 38 patients were 7-11 years of age and 47 patients were 12-17 years of age. In the citalopram group, 45 patients were 7-11 years of age and 44 patients were 12-17 years of age. Mean age in both treatment groups was 12 years. The majority of subjects in both treatment groups were female (53% for citalopram and 54% for placebo) and Caucasian (81% and 73%, respectively).

Efficacy results:

On the primary efficacy parameter, the change from baseline in CDRS-R at Week 8, citalopram produced significantly greater improvement than placebo.

Change from Baseline to Week 8 in CDRS-R [Mean ± SEM]

	Placebo (N=85)	*Citalopram (N=89)*	*p-value*
Mean ± SEM	-16.5 ± 1.6	-21.7 ± 1.6	0.038

The citalopram group exhibited significantly greater improvement than the placebo group beginning at Week 1 and at all subsequent clinic visits. Analysis of the response rate on the CDRS-R also revealed a significantly higher percentage of responders (CDRS-R ≤ 28 at study endpoint) in the citalopram group (36.0%) as compared to the placebo group (23.5%) (p=0.041).

Significant differences ($p<0.05$) indicative of greater improvement in citalopram patients than placebo patients were also observed on the CGI-I, CGI-S, and CGAS. Numerically greater improvement was observed on the K-SADS-P. Statistically significant effects were not found as consistently across study timepoints for the secondary efficacy parameters as for the primary efficacy parameter, but numerically greater improvement in the citalopram group was observed on every efficacy instrument at every clinic visit in both the LOCF and OC analyses. Results from the LOCF and OC analyses were similar.

No treatment-by-age group interaction was observed, indicating that the magnitude of the treatment effect was similar in the child and adolescent subgroups.

No treatment-by-baseline score interaction was observed, indicating that the magnitude of the treatment effect was not related to the patients' baseline symptom severity.

Pharmacokinetic results:
Citalopram concentrations in plasma samples obtained at the final study visit were approximately 13% higher in children as compared to adolescents. However, there was no significant correlation between plasma concentrations of citalopram and patient age, body weight, or improvement on the CDRS-R.

Safety results:
No deaths occurred during the conduct of the study. There was one serious adverse event, in a placebo treated patient, and one clinically significant ECG abnormality, also in a placebo treated patient. The rate of discontinuation for adverse events was 5.6% in the citalopram group and 5.9% in the placebo group. Treatment emergent adverse events with a higher incidence in the citalopram group than the placebo group were typically either gastrointestinal symptoms (nausea and diarrhea) or respiratory disorders. Few psychiatric adverse events were reported, with little sign of CNS stimulation or depression. More than 98% of adverse events in each treatment group were mild or moderate in intensity. Citalopram's adverse event profile was generally similar in child and adolescent patients and in male and female patients. Analysis of laboratory, vital sign, body weight, and ECG parameters revealed a low incidence of PCS values in both treatment groups; the mean changes from baseline were clinically unremarkable.

Conclusion:
The results of this study support the conclusion that citalopram, 20–40 mg/day, is safe and efficacious in the treatment of major depressive disorder in children and adolescents.

Date of the report: April 8, 2002

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Integrated Clinical Study Report

A double-blind study comparing citalopram tablets (Lu 10-171, 10-40 mg per day) and placebo in the treatment of major depression in adolescents

Investigational Product: Citalopram

Clinical study ID:	94404
Phase of development:	Phase III
Indication:	Major depression
First patient first visit:	19 November 1996
Last patient last visit:	23 April 2001
Investigators:	31 recruiting investigators in 7 countries *Signatory Investigator*: Professor Anne-Liis von Knorring, M.D., Uppsala, Sweden
Study centres:	31 recruiting centres in 7 countries: 3 in Denmark, 2 in Estonia, 12 in Finland, 2 in Germany, 3 in Norway, 7 in Sweden, and 2 in Switzerland
Sponsor:	International Clinical Research H.Lundbeck A/S DK-2500 Copenhagen-Valby, Denmark
Study director:	Karoline Als, M.Sc. Pharm., H.Lundbeck A/S
Report No. and date:	236/311, 2001, 21 March 2002

This study was conducted in compliance with the principles of Good Clinical Practice.

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Synopsis

Title of Study
A double-blind study comparing citalopram tablets (Lu 10-171, 10-40 mg per day) and placebo in the treatment of major depression in adolescents

Investigators
31 recruiting investigators in 7 countries
Signatory investigator Professor Anne-Liis von Knorring, M.D., Uppsala, Sweden

Study Centres
31 recruiting centres in 7 countries: 3 in Denmark, 2 in Estonia, 12 in Finland, 2 in Germany, 3 in Norway, 7 in Sweden, and 2 in Switzerland

Publications
None

Study Period
First patient first visit – 19 November 1996
Last patient last visit – 23 April 2001

Phase of Development
Phase III

Objectives
- *Primary objective* – to study the efficacy and tolerability of citalopram compared to placebo in adolescent patients suffering from major depression
- *Secondary objective* – to investigate the Expressed Emotions (EE)

Methodology
- Multicentre, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study in adolescents with major depression
- At screening, patients were randomly assigned to 12 weeks of double-blind treatment with either citalopram 10mg daily or placebo. Based on the investigator's clinical evaluation, there was a possibility of a 10mg dose increase for patients in the citalopram group at the end of Week 1 (to a maximum of 20mg), Week 2 (to a maximum of 30mg), Week 5 (to a maximum of 40mg), or Week 9 (to a maximum of 40mg).

Number of Patients Planned and Analysed
- A total of 220 patients were planned (110 patients in each treatment arm).
- Patient disposition is tabulated below.

	Placebo N (%)	Citalopram N (%)	All N (%)
Patients randomised	120	124	244
Patients treated	112	121	233
Patients completed	74 (66%)	79 (65%)	153 (66%)
Patients withdrawn from APTS	38 (34%)	42 (35%)	80 (34%)
Primary reason for withdrawal:			
Adverse Event(s)	9 (8%)	13 (11%)	22 (9%)
Lack of efficacy	18 (16%)	11 (9%)	29 (12%)
Patient data sets:			
All Patients Treated Set (APTS)	112	121	233
Full Analysis Set (FAS)	108	115	223

Diagnosis and Main Inclusion Criteria Inpatients or outpatients who fulfilled the criteria for major depression according to DSM-IV, who had a Beck's Depression Inventory (BDI) score ≥21 (girls) or ≥16 (boys) and a Global Assessment of Functioning (GAF) score ≤60 for any of the four items assessed, who were 13-18 years of age (extremes included), and whose puberty had commenced (Tanner Stage III). The duration of the current depressive episode was at least 4 weeks and up to one year.
Investigational Product, Dose and Mode of Administration, Batch Number *Citalopram (Lu 10-171)* – 10, 20, 30, or 40mg once daily; tablets, orally Batch Nos: 10mg – B 868, B 994, PD 1226; 20mg – 201, 203, PD 1227; 30mg – B 863, 702, PD 1228; and 40mg – 019, PD 1229
Duration of Treatment 12 weeks of double-blind treatment
Reference Therapy, Dose and Mode of Administration, Batch Number *Placebo* – once daily; tablets, orally; Batch Nos. 001, PD 1214, and PD 1215
Criteria for Evaluation – Serum Concentrations/Pharmacodynamics Serum concentrations of citalopram and it's metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT); correlation between serum concentrations and response on primary efficacy variable
Criteria for Evaluation – Efficacy • *Primary efficacy endpoint* - change from baseline in the Schedule for Affective Disorders and Schizophrenia for School Aged Children (Kiddie-SADS-P) total score over time • *Secondary efficacy endpoints* - change from baseline to each visit and to final assessment in Kiddie-SADS-P total score - response on the Kiddie-SADS-P scale (items "depression" and "anhedonia" score ≤2) at each visit and at final assessment - change from baseline in MADRS total score over time - change from baseline to each visit and to final assessment in MADRS total score - MADRS remission (total score ≤12) at each visit and at final assessment - MADRS response (at least a 50% reduction of the baseline MADRS total score) at each visit and at final assessment - analyses of scores on the Kiddie-SADS-P single items, BDI, GAF, and Life Event Scales
Criteria for Evaluation – Safety Adverse events (AEs), Utvalg for Kliniske Undersøgelser (UKU) symptom checklist, clinical laboratory tests, electrocardiograms (ECGs), weight, vital signs, and physical examination
Criteria for evaluation – Expressed emotions Five Minute Speech Samples

Statistical Methods

- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all patients randomised in the study
  - *all-patients-treated set* (APTS) – all randomised patients who took at least one dose of double-blind study product
  - *full-analysis set* (FAS) – all randomised patients who took at least one dose of double-blind study product and who had at least one post-baseline assessment of the Kiddie-SADS-P total score
- All efficacy analyses were conducted for the FAS. All safety analyses were conducted for the APTS.
- The primary efficacy endpoint was analysed using the principle of observed cases (OC) for each visit. The primary efficacy analysis was based on a repeated measures analysis using an unstructured variance covariance matrix and with factors for: treatment, centre, time, time squared, treatment by time, treatment by centre, and treatment by time by centre.
- The secondary efficacy endpoints were analysed using the principle of OC, and for analysis of final assessment data the principle of last observation carried forward (LOCF) at Week 12 was used. The secondary efficacy analyses were based on repeated measures analysis, ANCOVA, and Fisher's exact test.
- The distribution of the FMSS scores (high or low) were tabulated. The FMSS score was included as an additional explanatory variable in the primary efficacy analysis.
- Withdrawals were compared between treatment groups using a χ^2 test.
- The incidences of all treatment-emergent adverse events (TEAEs) were tabulated by system organ class and preferred term for each treatment group.
- For each of the TEAEs with a frequency ≥5% in either treatment group, the incidence in the citalopram group *versus* that in the placebo group was tested using Fisher's exact test.
- Absolute values and changes in clinical laboratory tests, ECG parameters, vital signs, and weight/BMI were summarised using descriptive techniques. The QT_c values were categorised in accordance with the CPMP recommendations. Values outside normal range and potentially clinically significant (PCS) values were flagged and tabulated. Treatment differences in baseline adjusted changes in ECG parameters were analysed by ANCOVA.

Demography of Study Population

- The treatment groups were comparable with respect to age, sex, race, BMI, and baseline efficacy parameters.
- There was a 3 to 1 ratio of females to males and almost all patients were Caucasian.
- At baseline, the mean Kiddie-SADS-P and MADRS total scores were 32 and 30, respectively.

Pharmacokinetic/Efficacy Results

- The mean citalopram serum concentrations at Week 12 were 130, 217, and 288nmol/L after treatment with 20, 30, or 40mg,, respectively. No consistent pattern in serum levels in males as compared to females was observed.
- The primary analysis of efficacy could not detect a statistically significantly different response profile on the Kiddie-SADS-P scale over time between placebo and citalopram treatment. In both treatment groups, the mean Kiddie-SADS-P total score decreased as a function of time. In the citalopram group, the adjusted mean reduction in Kiddie-SADS-P total score from baseline to Week 12 (OC) was 12.4 points, a reduction that was not statistically significantly different from that observed in the placebo group (12.7 points).
- The proportion of responders on the Kiddie-SADS-P scale, defined as patients with score ≤2 on the "depression" and "anhedonia" items, increased during the study. A remarkably high placebo response was observed (61% at Week 12) and the response rate in the citalopram group was similar.

Pharmacokinetic/Efficacy Results – continued

- The analyses of scores on the MADRS scale showed similar results. The response profile over time did not differ between treatment groups. The adjusted mean reduction in MADRS total score from baseline to Week 12 (OC) was 16 points in both treatment groups.
- The proportion of responders on the MADRS scale, defined as patients with at least a 50% reduction from baseline, increased during the study period. At Week 12, 59% and 61% of the patients treated with placebo and citalopram, respectively, were responders. With respect to frequency of remission, defined as MADRS total score ≤12, no difference between treatments was detected.
- The results of the analyses of the BDI and GAF scales did not reveal any additional information regarding the therapeutic effect of citalopram *versus* placebo.
- The baseline Kiddie-SADS-P and MADRS total scores had a statistically significant impact on the response profiles over time. This means that patients with higher baseline scores were likely to show a greater improvement than patients with lower scores.
- Expressed emotions did not have a statistically significant impact on the response profile over time.
- An apparent relationship between the citalopram serum concentrations and response at last assessment on the Kiddie-SADS-P scale was not detected.
- Overall, the proportion of patients withdrawn from the study did not differ between treatment groups. Approximately one-third of the patients withdrew from the study. However, withdrawals due to lack of efficacy were more frequent in the placebo group than in the citalopram group (16% *versus* 9%), whereas withdrawals due to adverse events were slightly more common in the citalopram group (8% in the placebo group and 11% in the citalopram group). The differences were not statistically significant.

Safety Results

- The AE incidence is summarised below:

	Placebo N (%)	Citalopram N (%)
Patients with serious AEs	16 (16%)	18 (15%)
Patients with treatment-emergent AEs	79 (71%)	91 (75%)
Total number of treatment-emergent AEs	275	344

N = number of patients; % = percentage of patients within treatment group

- Citalopram was safe and well tolerated. No deaths occurred during the study. After start of double-blind treatment, SAEs were reported by 16 patients in the placebo group and by 18 patients in the citalopram group. The majority of the patients with SAEs reported hospitalisations due to psychiatric disorders (9 patients in the placebo group and 14 patients in the citalopram group). In the placebo group, the other SAEs were surgical interventions (3 patients), epileptic fit, head trauma, medication error, and hospitalisation for social reasons. In the citalopram group, the other SAEs were dyspnoea, non-suicidal overdose, hospitalisation for social reasons, and abortion.
- Withdrawal due to AEs occurred for 9% of the patients and were similarly distributed among treatment groups.
- Treatment emergent adverse events (TEAEs) were reported by 71% of patients in the placebo group and 75% of patients in the citalopram group. The majority of the TEAEs were considered by the investigator to be mild or moderate for both treatment groups.

Safety Results – continued • The TEAEs that occurred in ≥5% of patients and were more common in the citalopram group than in the placebo group were (in descending order): headache, nausea, insomnia, suicide attempt, rhinitis, abdominal pain, dizziness, pharyngitis, diarrhoea, fatigue, and influenza-like symptoms. Fatigue was the only TEAE that was statistically significantly more common in citalopram-treated patients (6%) than in placebo-treated patients (1%). • There were no discernible trends within treatment groups or between treatment groups with regard to laboratory tests, vital signs, weight changes, or ECGs.
Conclusions • In this 12-week study, a better therapeutic effect of citalopram in the treatment of adolescent depression as compared to placebo could not be established. The patients showed improvement on the efficacy scales as a function of time, but the placebo response was high and not different from that of citalopram. • No impact of expressed emotions on the outcome was identified. • Treatment with citalopram was safe and well tolerated. • Safety findings, that were not expected from the safety profile known from adults, were not observed.
Report Date 21 March 2002
This study was conducted in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the study and the principles of Good Clinical Practice.

FOREST LABORATORIES, INC.

Investor Relations

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Forest Announces Results of Recently Completed Lexapro(R) Pediatric Depression Clinical Trial

Forest Laboratories, Inc.

FOREST LABORATORIES LOGO
Forest Laboratories Inc. logo. (PRNewsFoto)[AG JL]
NEW YORK, NY USA 10/11/2000

NEW YORK, June 24 /PRNewswire-FirstCall/ -- Forest Laboratories, Inc. (NYSE: FRX) announced today the results of a recently completed placebo-controlled study of Lexapro(R) (escitalopram oxalate) in children and adolescents. Patients receiving Lexapro did not demonstrate statistically significant separation from placebo in the primary efficacy measure, the mean change from baseline in the Children's Depression Rating Scale-Revised (CDRS-R) score.

(Logo: http://www.newscom.com/cgi-bin/prnh/20001011/FORESTLOGO)

The study was just completed and the safety data reported to the U.S. Food and Drug Administration (FDA). While data from the study are still being analyzed, initial results are being disclosed in this release.

The study found that Lexapro was well tolerated in both children and adolescents with no significant difference in withdrawal rates due to adverse events with Lexapro as compared to placebo. A separate analysis evaluating the frequency of suicide-related events and worsening of depression found that two placebo-treated patients reported suicide-related events and one placebo patient reported worsening of depression, whereas only one Lexapro-treated patient reported a suicide-related event and no Lexapro-treated patient reported worsening of depression. Forest believes the results of this trial

in addition to the pediatric depression trials of citalopram (marketed as Celexa(R) in the U.S.) show that there is no added risk of suicidality or worsening of depression due to the use of these products in pediatric patients. There have been no suicides observed in the pediatric placebo-controlled clinical trial experience with either citalopram or Lexapro.

These initial analyses revealed positive trends in some of the secondary efficacy measures for the group of patients treated with Lexapro as compared to the placebo group.

Escitalopram is the single S-enantiomer form and therapeutically active component of the drug citalopram. There have been two pediatric, placebo-controlled clinical trials involving citalopram; one European trial in both hospitalized and outpatient adolescents, and one U.S. trial in child and adolescent outpatients.

In the European trial, citalopram did not show any improvement of depressive symptoms versus placebo. In contrast, the U.S. pediatric depression trial of citalopram showed a reduction of symptoms of depression to a significantly greater extent than placebo.

"It is important to better define the role antidepressants can play in treating this population," said Lawrence S. Olanoff, M.D., Ph.D., Executive Vice President and Chief Scientific Officer, Forest Laboratories, Inc. "The two U.S. studies are comparable in design and studied similar patient populations. We recognize that the European study is limited in its comparability to the U.S. experience due to its unique design and patient population -- which included both hospitalized patients and outpatients, many of whom had a history of more complicated depressive disorders. We believe that the aggregate safety and efficacy experience with Celexa and Lexapro in pediatric patients remains encouraging and that further study is warranted."

Forest plans to discuss with the FDA the initiation of new pediatric studies with Lexapro in the U.S. with the goal of ultimately achieving approval of its use in pediatric patients with major depressive disorder.

Lexapro Pediatric Study Details

Two hundred and sixty four patients, ages 6 to 17 with major depressive disorder and a CDRS-R score of 40 or greater, participated in the randomized, double-blind, multicenter, flexible dose study. Patients received either Lexapro (10-20 mg/day) or placebo treatment for up to 8 weeks. The primary

efficacy measure was the mean change from baseline to week eight on the CDRS-R score. Secondary efficacy measures included the Clinical Global Impressions - Improvement (CGI-I) Scale, the Clinical Global Impressions - Severity (CGI-S) Scale, and the Children's Global Assessment Scale (CGAS). The initial results of the trial indicated that the change from baseline for the CGAS and the CGI-S scores appeared greater for the Lexapro treated group compared to the placebo group, however the differences did not quite achieve statistical significance ($p = 0.07$ and 0.06, respectively). When these same efficacy measures were analyzed for those subjects who remained in the study through the eight week assessment, statistically significant ($p < 0.05$) improvements were seen in the Lexapro group for both these assessments by comparison to the placebo group.

Lexapro was well tolerated in both pediatric and adolescent groups as compared to placebo treatment. No significant difference in drop-out rates due to adverse events compared to placebo was observed (1.5 % for both Lexapro-treated patients and placebo-treated patients). The incidence of patients with adverse events, including activation side effects, was similar between the Lexapro and placebo groups. Adverse events occurring at an incidence of >= 10% in patients treated with Lexapro or placebo respectively, included headache (22.9% and 21.8%), abdominal pain (10.7% and 5.3%), and menstrual cramps (4.4% and 10.1%).

About Lexapro

Lexapro is the newest and fastest-growing selective serotonin reuptake inhibitor (SSRI) and has been prescribed for more than 5 million patients in the U.S.

Lexapro was approved by the U.S. Food and Drug Administration in August 2002 for both the initial and maintenance treatment of major depressive disorder in adults and in December 2003 for the treatment of generalized anxiety disorder in adults.

The most common adverse events reported with Lexapro (reported at rates of approximately 5% or greater and 2 times or more the incidence seen in the placebo group) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia. Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients with a hypersensitivity to escitalopram oxalate or any of the

ingredients in Lexapro.

As with other SSRIs, caution is indicated in the co administration of tricyclic antidepressants (TCAs) with Lexapro. As with other psychotropic drugs that interfere with serotonin reuptake, patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation.

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although no causal role for antidepressants in inducing such behaviors has been established, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.

Forest Laboratories licenses Lexapro from H. Lundbeck A/S, the Danish pharmaceutical firm that developed escitalopram and citalopram.

About Forest Laboratories and Its Products

Forest Laboratories' growing line of products includes: Lexapro(R), an SSRI antidepressant indicated for the initial and maintenance treatment of major depressive disorder and for generalized anxiety disorder; Celexa(R), an antidepressant; Namenda(R), an N-methyl-D-aspartate (NMDA)-receptor antagonist indicated for the treatment of moderate to severe Alzheimer's disease; Tiazac(R), a once-daily diltiazem, indicated for the treatment of angina and hypertension; Benicar(R),* an angiotensin receptor blocker indicated for the treatment of hypertension; Benicar HCT(TM), an angiotensin receptor blocker and diuretic combination product indicated for the second-line treatment of hypertension; and Aerobid(R), an inhaled steroid indicated for the treatment of asthma.

*Benicar(R) is a registered trademark of Sankyo Pharma, Inc.

Except for the historical information contained herein, this release contains "forward-looking statements" within the meaning of the Private Securities Reform Act of 1995. These statements are subject to risks and

uncertainties that affect our business, including risk factors listed from time to time in the Company's SEC reports, including the Company's Annual Report on Form 10-K for the fiscal year ended March 31, 2004. Actual results may differ materially from those projected.

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Forest Laboratories, Inc.

Press release

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Forest Discusses Disclosure of Citalopram Clinical Trial Data in Children and Adolescents

NEW YORK, Jun 24, 2004 /PRNewswire-FirstCall via COMTEX/ -- Forest Laboratories, Inc. (NYSE: FRX) wishes to provide additional information regarding the dissemination of the clinical trial results of two studies of its antidepressant Celexa(R) (citalopram HBr) in the treatment of children and adolescents. Citalopram is not approved for use in children or adolescents and has not been promoted by Forest for use in these populations.

There are two placebo-controlled studies of citalopram in the treatment of pediatric and/or adolescent depression. These studies include a European trial in both hospitalized and outpatient adolescents conducted by H. Lundbeck A/S (the Danish company that developed citalopram), which did not show efficacy versus placebo, and a U.S. trial in child and adolescent outpatients, conducted by Forest, the results of which showed efficacy versus placebo. The U.S. study was published in June 2004 in the American Journal of Psychiatry.

Although no published peer-reviewed reference of the European citalopram pediatric study is currently available, the results of this study were disclosed on several occasions to the scientific community in various formats prior to the June 2004 publication of the U.S. study(1). These disclosures included information from submissions by Forest or Lundbeck to the U.S. and United Kingdom (U.K.) regulatory authorities, both of which posted summary results on the Internet. H. Lundbeck A/S also has advised Forest that the principal investigator of the European study is preparing a report for publication.

Given the current increased interest in industry publication practices as well as outstanding questions about the role of antidepressants in the pediatric populations, questions about the availability of these results have been raised. It is crucial in this context to point out that results of the European study were not hidden but were disclosed and available. In addition, the results may not be comparable to the U.S. study because of contrasting trial designs and patient populations.

Modern depression trials typically utilize a study design and patient selection criteria that will most objectively define the effect of a medication. Greater accuracy is accomplished by studying patients under conditions in which many of the known social and medical factors that can affect patients' response can be prospectively identified and controlled for, so as to separate those factors from the determination of the actual drug effect. Carefully balancing the patient groups is important to obtain a proper interpretation of the results.

This approach is commonly used in today's antidepressant trials and was used in the U.S. citalopram trial. However, in the European trial, both hospitalized patients and outpatients were allowed to enroll, many of whom had a history of more complicated depressive disorders. The trial analysis could not be adjusted for such differences in the patients

between the drug treated or placebo groups, which makes it more difficult to evaluate the drug's effect as well as to establish comparability of the results of this study to those of the U.S. trial.

With respect to safety, Forest believes that its overall analysis of the clinical trial data, including both the placebo-controlled pediatric citalopram studies, shows that there is no increased risk of suicidality or worsening of depression associated with citalopram therapy. In addition, there were no suicides in these studies. The FDA is actively reviewing the data it has for pediatric studies involving a number of different antidepressants and in the interim, and in accordance with the FDA's request of all anti-depressant manufacturers, Forest has included in its labeling for Celexa additional information regarding suicidality(2).

Forest believes there was nothing unusual or incorrect about the disclosure of the results of the two studies. We recognize the complexity involved in determining the role of antidepressants in the treatment of pediatric depression especially given the difficulty of diagnosing and evaluating response in this group of patients. We are also aware of interest in augmenting the exchange of scientific information. Therefore, today, Forest has issued a press release with respect to a pediatric study just completed on the safety and efficacy of our antidepressant Lexapro(R) (escitalopram oxalate) based upon initial analyses of that study.

Forest will work with the government, the scientific community and the industry to evolve generally accepted standards and practices supporting the scientific exchange of information, particularly with regard to the treatment of children and adolescents suffering from depression.

About Forest Laboratories and Its Products

Forest Laboratories' growing line of products includes: Lexapro(R), an SSRI antidepressant indicated for the initial and maintenance treatment of major depressive disorder and for generalized anxiety disorder; Celexa(R), an antidepressant; Namenda(R), an N-methyl-D-aspartate (NMDA)-receptor antagonist indicated for the treatment of moderate to severe Alzheimer's disease; Tiazac(R), a once-daily diltiazem, indicated for the treatment of angina and hypertension; Benicar(R),* an angiotensin receptor blocker indicated for the treatment of hypertension; Benicar HCT(TM), an angiotensin receptor blocker and diuretic combination product indicated for the second-line treatment of hypertension; and Aerobid (R), an inhaled steroid indicated for the treatment of asthma.

*Benicar(R) is a registered trademark of Sankyo Pharma, Inc.

Except for the historical information contained herein, this release contains "forward-looking statements" within the meaning of the Private Securities Reform Act of 1995. These statements are subject to risks and uncertainties that affect our business, including risk factors listed from time to time in the Company's SEC reports, including the Company's Annual Report on Form 10-K for the fiscal year ended March 31, 2004. Actual results may differ materially from those projected.

(1) Following is a detailed account of the prior disclosure of the European pediatric results:

* October 16, 2003 -- Forest Laboratories discusses topline efficacy results and presents a detailed safety analysis of both the U.S. and European citalopram pediatric depression trials at the annual meeting of the American Academy of Child and Adolescent Psychiatry.

* October 30, 2003 -- Medical textbook in Danish titled, "Children and Adolescents with Depression" that referenced the efficacy results of both citalopram studies.

* December 10, 2003 -- Study results from both citalopram pediatric depression trials, that were previously submitted by H. Lundbeck A/S to The Medicines and Healthcare Products Regulatory Agency in the U.K., were posted on their website: http://medicines.mhra.gov.uk/.

* January 3, 2004 -- The British Medical Journal published an editorial titled, "Treatment of Major Depressive Disorder in Children and Adolescents." The editorial discussed the United Kingdom's Committee of Safety in Medicines evaluation of these studies.

* January 13, 2004 -- The U.S. Food and Drug Administration (FDA) posted on its public website a summary of their evaluation of these trials for inclusion in the February 2, 2004, meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee.

* April 22, 2004 -- The European study's principle investigator of the trial presented information about the European citalopram pediatric depression trial during the annual meeting of the Scandinavian College of Neuropsychopharmacology.

* April 24, 2004 -- The Lancet published an article titled, "Selective Serotonin Reuptake Inhibitors in Childhood Depression: systematic review of published versus unpublished data," which included a review of both citalopram pediatric depression studies.

(2) Celexa Labeling: Patients with major depressive disorder, both adult and pediatric, can experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although no causal role for antidepressants in inducing such behaviors has been established, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.

Source: Forest Laboratories, Inc.
Web Site: http://www.frx.com
Photo Notes: http://www.newscom.com/cgi-bin/prnh/20001011/FORESTLOGO

Contact: Charles E. Triano
Vice President - Investor Relations of Forest Laboratories, Inc.
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Assurance of Discontinuance Between Forest Laboratories and the Attorney General of the State of New York

WHEREAS, pursuant to N.Y. Executive Law § 63(12), Eliot Spitzer, the Attorney General of the State of New York, opened an inquiry into whether pharmaceutical companies, including Forest Laboratories, Inc. ("Forest"), disclosed the results of clinical studies of their drugs; and

WHEREAS, Forest cooperated with the Office of the Attorney General ("OAG") in this inquiry by producing certain documents on or about August 20, 2004. Before the OAG completed its review of these documents, Forest informed the OAG that it intended to create a Clinical Trial Registry ("CTR") that will provide physicians and patients with information regarding its Clinical Studies, and after discussions, the parties agreed that Forest's CTR will be implemented in accordance with the standards for disclosure of Clinical Studies (which is attached hereto as Appendix A), and the templates for the Summaries of Clinical Study Reports which will appear in the CTR (which are attached hereto as Appendices B & C); and

WHEREAS, Forest asserts that its past disclosures of Clinical Studies have fully complied with all laws of the State of New York, and all other laws or regulations, but has decided to provide broader disclosure of the results of its Clinical Studies of Forest Drugs; and

WHEREAS, the OAG has reviewed the standards and templates and finds that the information to be provided on Forest's proposed CTR would disclose useful information to the medical community;

IT IS HEREBY AGREED by Forest, its agents, employees, and subsidiaries, that:

DEFINITIONS

1. The following definitions apply to the following terms as used throughout this Assurance, including in any Appendices. Any terms which are not defined in this section shall be interpreted to have the same meaning as they have in ICH's *Guidelines for Industry: Structure and Content of Clinical Study Reports* (July 1996):

a. "Adverse Events" are unfavorable and undesired effects observed in patients during a Clinical Study. "Serious" Adverse Events are those that, at any dose, are fatal, life-threatening, disabling or incapacitating; result in hospitalization; prolong a hospital stay; or are associated with congenital abnormality, cancer or overdose (whether accidental or intentional). In addition, any event not meeting the above criteria may still be deemed Serious by the Investigator if such an event jeopardizes the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

b. "Assurance Date" means the date on which the parties sign this Assurance.

c. "Clinical Study" means a research investigation on human subjects to answer specific questions about a Forest drug. The term "Clinical Study" is not limited to a research study that is randomized, controlled or blinded.

d. "Clinical Study Report" means a report describing (i) the investigational plan and Protocol used to conduct the Clinical Study, (ii) all the data developed during the Study, and (iii) the clinically relevant conclusions drawn from the data, including the answers to the questions posed at the outset of the Study and the results of the Protocol-defined outcomes.

e. "Forest Drug" is a prescription pharmaceutical product that Forest is selling for human consumption in the United States following FDA approval (including a Forest investigational product once it receives FDA approval and is sold by Forest), for which Forest has both the clinical development responsibility and the legal right to use or disclose such product's Clinical Study data.

f. "Forest-Sponsored Clinical Studies" means Clinical Studies of a Forest Drug where Forest is ultimately responsible for regulatory approvals, site selection, Protocol development, initiation, monitoring, safety reporting, and data analysis, even if some or all of these activities are transferred to another party (*e.g.*, Clinical Research Organization). "Forest-Sponsored Clinical Studies" excludes studies initiated by a third party for which Forest provides some support, for example, by way of grant or supply of

medication, but with sponsor responsibilities for study initiation and management agreed in writing to reside with the third party.

g. "Forest Web Site" refers only to Forest's main corporate Internet site, currently www.frx.com, or any sites which one can access though a link from that site.

h. "Off-Label Use" means the use of a Forest Drug to treat a condition, disease or population not listed as an indication on the U.S. Prescribing Information (labeling) for the Forest Drug.

i. "On-Label Use" means the use of a Forest Drug to treat a condition, disease or population listed as an indication on the U.S. Prescribing Information (labeling) for the Forest Drug.

j. "Peer Reviewed Journal" refers to a professional periodical that, before accepting an original article for publication, has it reviewed, at a minimum for scientific merit, by relevant experts selected by the journal. A "Peer Reviewed Journal" does not include a supplement of a professional periodical that is sponsored or supported in any way by or on behalf of Forest or any other manufacturer, seller or promoter of prescription pharmaceutical products.

k. "Post" means to provide access to information on an Internet site that provides no-cost and unrestricted access to both the site and the information Forest has provided through the site. Forest does not fulfill a requirement to Post information under this Assurance if it does so on an Internet site, other than the Forest Web Site, that

contains any advertising by any pharmaceutical company or for any pharmaceutical product.

l. "Protocol" means the investigational plan used to conduct the Clinical Study.

m. "Study Completion Date" is the date on which the last observation is made either of the last patient who remains enrolled in the Clinical Study or following a decision to terminate the Clinical Study early, whichever happens first.

n. "Summary of Clinical Study Report" refers to the brief presentations of Clinical Study Reports that are required by this Assurance and that provide the information pursuant to the templates set forth in Appendix B or Appendix C, whichever is applicable.

FOREST'S CLINICAL TRIAL REGISTRY

2. Forest shall Post on the CTR Summaries of Clinical Study Reports for Forest-Sponsored Clinical Studies involving Forest Drugs in accordance with Appendix A. The Summaries shall conform to the ICH E3 principles articulated in ICH's *Guidelines for Industry: Structure and Content of Clinical Study Reports* (July 1996) and to the templates set forth in Appendix B or Appendix C, whichever is applicable.

3. For (i) studies in which Forest had significant participation but did not sponsor which are initiated after the Assurance Date, or (ii) studies conducted by Forest's licensing partners which are initiated after the Assurance Date, Forest will also make reasonable efforts to encourage the publication of, or in the alternative, secure the right to publish on the CTR. Forest will use reasonable efforts to exclude from future contracts or licensing agreements any provisions limiting the publication of Summaries of Clinical Study Reports for all future Clinical Studies of Forest Drugs.

4. Forest will Post on the CTR Summaries of Clinical Study Reports for Clinical Studies of the use of Celexa and Lexapro in the pediatric population, including the Clinical Study conducted by its licensor.

The Summaries of Clinical Study Reports that Forest Posts on the CTR shall accurately reflect the methodology used to conduct the Clinical Study and the data obtained during the Clinical Study.

6. Forest shall clearly and conspicuously state the location of the CTR (URL, and where relevant, a link) on the Home Page of the Forest Web Site.

OTHER PROVISIONS

7. This Assurance shall constitute a full resolution of any claims that the Attorney General could assert relating to the past disclosure of Clinical Studies of the use of Celexa and Lexapro in the pediatric population.

8. Nothing in this Assurance shall in any way limit the right of the Attorney General to request information from Forest regarding any matter relating to Clinical Studies, and subject to a reasonable confidentiality agreement, Forest shall cooperatively respond to such requests.

9. Nothing contained in this Assurance shall in any way limit the Attorney General's right to obtain, by subpoena or any other means permitted by law, documents, testimony or other information.

10. Nothing contained in this Assurance shall be construed to deprive any individual of any private right of action under the law.

11. This Assurance shall not be admissible in any other case for any purpose.

12. The execution of this Assurance by the Attorney General shall not be deemed or construed as an approval by the Attorney General of any of Forest's actions, and Forest shall not make any representation to the contrary.

13. The execution of this Assurance by Forest shall not be deemed or construed to be an admission of liability by Forest or a waiver of any defense which Forest has or may have in any dispute with the OAG or any other person or entity, including but not limited to, the defense of federal preemption.

14. This Assurance shall not be construed to preclude Forest from complying with any Federal legal or regulatory requirement to which Forest is, or in the future will be, subject. Any Federal legal or regulatory requirement which conflicts with the provisions of this Assurance shall supercede the provision of this Assurance with which it conflicts, but only if the conflict is such that compliance with the Federal legal or regulatory requirement could not be achieved without modification of a provision of this Assurance.

15. Forest may make changes to the standards for disclosure, as set forth in Appendix A, and its templates, as set forth in Appendix B and Appendix C, so long as such changes would not diminish the data Posted pursuant to the terms of this Assurance. Further, other than the changes covered by the preceding sentence (*i.e.*, changes that would not diminish the data Posted pursuant to the terms of this Assurance) or covered by paragraph 14 above, if Forest believes that any material modifications to Appendix A Appendix B, or Appendix C, or any modification of any other term of this Assurance, are necessary in light of changed circumstances, including changes in the environment in which Forest operates, Forest may request that the OAG modify Forest's obligations

under this Assurance, and the OAG shall promptly respond reasonably to any such requests, giving due consideration to such changes.

16. This Assurance shall remain in effect for seven years following the Assurance Date.

17. Forest will, in its sole discretion, make Clinical Study Reports and related data available to bona fide researchers who are preparing scholarly work for publication in Peer Reviewed Journals.

WHEREFORE, the following signatures are affixed hereto on the specified dates:

AGREED TO by the parties:

Dated: New York, New York
September 7, 2004

ELIOT SPITZER
Attorney General of the
State of New York

By:

BUREAU OF CONSUMER
FRAUDS AND PROTECTION

Thomas G. Conway
Assistant Attorney General in Charge

HEALTH CARE BUREAU

Joseph Baker, III
Assistant Attorney General in Charge

Rose E. Firestein
Assistant Attorney General

Shirley Stark
Assistant Attorney General

Dated: New York, New York
September 7, 2004

FOREST LABORATORIES, INC.

DEBEVOISE & PLIMPTON LLP

By:

Mary Jo White, Esq.

APPENDIX A TO ASSURANCE BETWEEN THE OAG AND FOREST

Standards For Disclosures of Clinical Studies

I. Ongoing Studies. When Forest initiates a phase III or phase IV Forest-Sponsored Clinical Study, the unique study number, study title, study start date and key objectives will be Posted to an online Clinical Trials Registry ("CTR") to be maintained by Forest and located on Forest's Web Site. In addition, Forest will Post the same information for phase III studies conducted on Forest investigational products for which Forest is planning on seeking FDA approval.

II. Studies Concluded After the Assurance Date. For all Forest-Sponsored Clinical Studies of Forest Drugs completed after the Assurance Date, Forest will Post Summaries of Clinical Study Reports (regardless of outcome) to the CTR according to the following time schedule:

a) Phase III Studies. Summaries of Clinical Study Reports of Forest-Sponsored phase III Clinical Studies shall be Posted when a Forest investigational product first becomes commercially available following FDA approval (identified by the study numbers assigned previously when listed as ongoing trials). The Summaries of these phase III Clinical Study Reports will include the data set forth in the template attached as Appendix B.

b) Phase IV Studies. Summaries of Clinical Study Reports of Forest-Sponsored phase IV Clinical Studies shall be Posted within one year of their Study Completion Date (identified by the study numbers assigned

previously when listed as ongoing trials). All Summaries of these phase IV Clinical Study Reports covered by this paragraph will include the data set forth in the template attached as Appendix B.

c) Phase I and II Studies. Summaries of safety data from Clinical Study Reports of Forest-Sponsored phase I and phase II Clinical Studies shall be Posted within one year of their Study Completion Date (but in no event shall Forest be required to Post such Clinical Studies before a Forest investigational product first becomes commercially available following FDA approval) if those safety results are material to the clinical use of these drugs or the care of patients. The Summaries of these phase I and phase II Clinical Study Reports will include the data set forth in the template attached as Appendix C.

d) All Studies. When the results of a Forest-Sponsored Clinical Study are submitted to a Peer Reviewed Journal whose editorial policy prohibits any prior disclosure of study results, the results will be Posted to the CTR at the time of publication. Similarly, in some instances, there may be a delay in Posting to the CTR because Forest must seek intellectual-property protection. In such instances, Forest shall make reasonable efforts to seek intellectual property protection as quickly as practicable.

III. Studies Concluded Between January 1, 2000 and the Assurance Date: For all Forest-Sponsored Clinical Studies of Forest Drugs completed after January 1, 2000 and before the Assurance Date, Forest will Post to the CTR Summaries of Clinical Study Reports

according to the same standards (other than the timing provisions) for each of the different phases of Clinical Studies set forth in Section II. All of these Summaries of Clinical Study Reports shall be Posted by December 31, 2005.

IV. Studies Concluded Prior to January 1, 2000: For all Forest-Sponsored Clinical Studies of Forest Drugs which are actively promoted by Forest completed before January 1, 2000, Summaries of Clinical Study Reports shall be Posted in accordance with the following terms:

a) Clinical Studies of On-Label Uses: Summaries of safety data from Clinical Study Reports of Forest-Sponsored phase I, II, III and IV Clinical Studies for an On-Label Use shall be Posted by December 31, 2005 if those safety results are material to the clinical use of the drugs or the care of patients. The Summaries of these Clinical Study Reports will include the data set forth in the template attached as Appendix C.

b) Phase I and Phase II Clinical Studies of Off-Label Uses: Summaries of safety data from Clinical Study Reports of Forest-Sponsored phase I and phase II Clinical Studies for an Off-Label Use shall be Posted in accordance with the standards and time periods set forth in subparagraph IV(a) above.

c) Phase III and Phase IV Clinical Studies of Off-Label Uses: Summaries of Clinical Study Reports of Forest-Sponsored phase III and phase IV Clinical Studies for an Off-Label Use shall be Posted by December 31 2005 if those safety or efficacy results are material to the clinical use of

the drugs or the care of patients. The Summaries of these phase III and phase IV Clinical Study Reports shall include the data set forth in the template attached as Appendix B, which contains both safety and efficacy data.

V. All information provided to the CTR will comply with all relevant FDA regulations.

APPENDIX B

Study No.: As on the report cover		
Title: As on the report cover. Trade name may be used if was included in the report title. All other sections of the CTR summary MUST use the generic name (not the trade name).		
Rationale: From synopsis OR extracted from introduction of report. Do not include information about mode of action. Do not use any trade name(s).		
Phase: As in the synopsis		
Study Period: As in the synopsis		
Study Design: List of descriptive terms taken from appropriate section of synopsis		
Centres: Summarised by region/county		
Indication: As agreed by MDC		
Treatment: # Denotes treatment regimens approved in the US and at least one country in the European Union. Summarised from synopsis (exclude batch numbers) using generic name		
Objectives: Primary objective as written in synopsis		
Primary Outcome/Efficacy Variable: Either from synopsis or body of report		
Secondary Outcome/Efficacy Variable(s): From the body of the report. List only the variables that were prospectively defined in the report not any post hoc analysis. Exclude pharmacoeconomics variables (may need to be taken out of secondary objectives list)		
Statistical Methods: As in the study synopsis. .Add definitions of the populations included in the CTR summary for the assessment of efficacy and safety if not included in the synopsis stats section. Make it clear if the populations for efficacy and safety are not the same.		
Study Population: Extracted from synopsis using key inclusion exclusion criteria		
	A	**B**
Number of Subjects: Adjust layout according to study design		
Planned, N	From body of report	
Randomised, N Note: for non-randomised studies, substitute the number of subjects entered into the study and replace the heading with "Entered, N"	From synopsis	
Completed, n (%)	ditto	
Total Number Subjects Withdrawn, N (%)	ditto	
Withdrawn due to Adverse Events n (%)	From synopsis or body of the report	
Withdrawn due to Lack of Efficacy n (%)	ditto	
Withdrawn for other reasons n (%)	Add-up ALL other reasons for withdrawal	
Demographics	**A**	**B**
N (ITT)	From synopsis	
Females: Males If only one gender was studies, just give information for the one gender and modify the heading accordingly.	ditto	
Mean Age, years (SD)	ditto	
Race, n (%) Substitute the name of the predominant race(s) studied for the word "Race"	ditto	
Include any other relevant demographic criteria, e.g., Children:adolescents	ditto	

Primary Efficacy Results:
Primary outcome variable(s) with statistical annotation must be presented in tabular format. Include p-values, if available. Format and presentation will be indication/study dependent. **No text or contextual statements are to be included.** An example is shown in the instruction text below.

	A	B
Mean Baseline (SE)	From synopsis or report	
Difference between treatments (as appropriate to endpoint)		
95% Confidence Interval		
p-value		

Secondary Outcome Variable(s):

Summarise all variables in **tabular format.** Group similar variables. Use 95% CI when appropriate. **Do not include p-values for secondary endpoints.** The analyses presented should be on the primary of population of interest, as presented in the CSR (for example, ITT or ITT LOCF). Quality of life and population pK endpoints should also be added when included in secondary endpoints. **Do not summarise Pharmacoeconomics or tertiary endpoints.** . No text or contextual statements are to be included.

	A	B
Secondary endpoint	From synopsis or report	
Difference between treatments (as appropriate to endpoint)		
95% CI (if appropriate)		

Safety Results: Define the period for the collection of 'on therapy' AEs and SAEs as given in the methodology section of the report e.g ., An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.

Summarise Adverse events as follows:

30 patients or less /treatment group: any AE that occurs in more than one patient in any group

More than 30 patients per treatment group and <= 3 groups: the most frequent 10 events in each group

More than 30 patients/treatment group and > 3 groups: the most frequent 5 events in each treatment group

The Numerator, denominator and the % will all be given

	A	B
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)		
List specific AEs according to guidance above		

Serious Adverse Events - On-Therapy

n (%) [n considered by the investigator to be related to study medication] Information on **all** on-therapy SAEs by preferred term will be provided. Format will vary, depending on how non-fatal and fatal SAEs were tabulated in the CSR. The table will indicate the number of subjects with specific SAEs, the percentage, and the number considered by the investigator to be related/possibly related/probably related to study medication.

Format of presentation of individual SAEs by preferred term is: n, (%) [n considered "related"]

If the report presents SAEs as "non-fatal SAEs" and "fatal SAEs" (or "deaths") separately, the CTR summary first presents the tabulations of "non-fatal" SAEs and then presents the tabulations of "fatal" SAEs.

If the report presents an all-inclusive SAE (both non-fatal and fatal), then the CTR summary first presents a tabulation of SAEs and then presents a tabulation of fatal SAEs. The heading for the "all SAEs" table should read:

Subjects with any SAEs, n (%)
-Includes both fatal and non-fatal events

	A	B
Subjects with non-fatal SAEs, n (%)		
	n (%) [related]	**n (%) [related]**
Present a table of all on-therapy SAEs using this format: Event A, n (%) [number of subjects who had "related" events]		
Subjects with fatal SAEs, n (%)		
	n (%) [related]	**n (%) [related]**
Event 1, n (%) [number of subjects who had events considered "related"]		

Conclusion:
Within 1 year after study completion this section will either refer you to a publication or contain text interpreting the trial results.

Publications: Add citations

APPENDIX C

Use subject not patient throughout (except for the title which should be verbatim from the report)

Study No: study number as in report		
Title : Enter title as in report		
Rationale: Not always available in report. May have to be extracted from introduction		
Phase: Enter phase as in the synopsis of the report		
Study Period: As in the synopsis		
Study design: Enter list of descriptive terms		
Centres: Summarised by region/county		
Indication: Enter indication as in the synopsis of the report, enter none if its not applicable.		
Treatment: # Denotes treatment regimens approved in the US and at least one country in the European Union. Summarised from synopsis		
Objectives: Objectives as written in synopsis/report		
Statistical Methods: : As in the study synopsis. .Add definitions of the populations included in the CTR summary for the assessment of efficacy and safety if not included in the synopsis stats section. Make it clear if the populations for efficacy and safety are not the same		
Study Population: Extracted from synopsis.		
Number of Subjects: Adjust according to study	**Group A**	**Group B**
Planned N	From synopsis or body of the report	
Dosed N		
Completed n (%)		
Total Number Subjects Withdrawn N (%)		
Withdrawn due to Adverse Events n (%)		
Withdrawn for Other Reasons n (%)	Add-up ALL other reasons for withdrawal	
Demographics	**Group A**	**Group B**
N (ITT)	From synopsis	
Females: Males		
Mean Age in Years (sd)		
Mean Weight in Kg (sd)		
Race, n (%) Substitute the name of the predominant race(s) studied for the word "Race"		

Safety results:
Define the period for the collection of 'on therapy' AEs and SAEs as given in the methodology section of the report e.g ., An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.

Summarise Adverse events as follows:

30 subjects or less /treatment group: any AE that occurs in more than one patient in any group

More than 30 subjects per treatment group and<= 3 groups: the most frequent 10 events in each group

More than 30 subjects/treatment group and > 3 groups: the most frequent 5 events in each treatment group

The Numerator, denominator and the % will all be given

Adverse Events:	Group A	Group B
N (ITT)		
No. subjects with AEs n (%)		
Most Frequent AEs		

Serious Adverse Events, n (%) [# considered by the investigator to be related, possibly related, or probably related to study medication]:
Summarise SAEs. Table preferred (if available), otherwise use text/list. In square brackets, indicate the number of specific SAEs considered by the investigator to be related/possibly related/probably related.

Format of presentation is: n (%) [n (%)]

Publications: Add citations

NCDEU Poster Abstracts

Session II - 64

Efficacy and Safety of Nefazadone in the Treatment of Adolescents with Major Depressive Disorder

Graham J. Emslie[1]
Robert L. Findling[2]
Moira A. Rynn[3]
Ronald N. Marcus[4]
Lori A. Fernandes[4]
M. Frances D'Amico[4]
Sterling A. Hardy[4]

[1]UT Southwestern Medical Center, Dept of Psychiatry, 5323 Harry Hines Blvd, Dallas, TX 75235
[2]University Hospitals of Cleveland
[3]University of Pennsylvania, Mood and Disorders Section
[4]Bristol-Myers Squibb Co., Pharmaceutical Research Institute

Objective: To determine the efficacy and safety of nefazodone vs. placebo in the treatment of adolescents with Major Depressive Disorder (MDD).

Methods: After a 2-4 week baseline phase, 195 adolescents (aged 12-17) meeting *DSM-IV* criteria for MDD with a Childhood Depression Rating Scale-Revised (CDRS-R) score $\geq$ 45 were randomized to receive 8 weeks of nefazodone (n=99) or placebo (n=96) at 15 sites. Adolescents randomized to nefazodone initially received 100 mg daily in equally divided doses BID and were titrated by 100 mg/week to targeted total daily doses of 300-400 mg based on clinical response and tolerability. Efficacy and safety were evaluated weekly. The primary efficacy measure was the nefazodone to placebo comparison in mean CDRS-R score from baseline to week 8 (LOCF).

Results: A longitudinal analysis which compares the change in CDRS-R over the 8 weeks was significant in favor of nefazodone (p=0.03). There was a significant difference in the CDRS-R score favoring nefazodone at week 7 (-26.7 vs. -21.3, p=0.006) and a 4.0 point improvement in CDRS-R score at week 8 which narrowly missed statistical significance (-26.5 vs. -22.5, p=0.055). The nefazodone group was superior to placebo at week 8 on CGI response rate (62% vs. 42%, p=0.005), CGI Improvement (2.3 vs. 2.8, p=0.012), CGI Severity (-1.7 vs. -1.3, p=0.022), HAM-D (-10.0 vs. -8.2, p=0.023) and CGAS (17.2 vs. 13.0, p=0.020). Nefazodone was well tolerated with a rate of discontinuation for AEs equal to placebo (3.0%).

Conclusions: In this study nefazodone was shown to be safe and effective in the acute treatment of adolescents with MDD.

Source of Funding: This research was funded by Bristol-Myers Squibb Company.

For more information about this site or NCDEU, please contact us at:
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The following information concerns a use that has not been approved by the U.S. Food and Drug Administration.

ABSTRACT

OBJECTIVE:
To determine the efficacy and safety of nefazodone vs. placebo in adolescents with Major Depressive Disorder (MDD)

METHODS:
After a 2-4 week baseline phase, 195 adolescents (aged 12-17) meeting DSM-IV criteria for MDD with a Childhood Depression Rating Scale-Revised (CDRS-R) score ≥ 45 were randomized to receive 8 weeks of nefazodone (n=99) or placebo (n=96) at 15 sites. Adolescents randomized to nefazodone initially received 100 mg daily in equally divided doses BID and were titrated by 100 mg/week to targeted total daily doses of 300-400 mg based on clinical response and tolerability. Efficacy and safety were evaluated weekly. The primary efficacy measure was the nefazodone to placebo comparison in mean CDRS-R score from baseline to Week 8 (LOCF).

RESULTS:
A longitudinal analysis which compares the change in CDRS-R over the 8 weeks was significant in favor of nefazodone (p=0.03). There was a significant difference in the CDRS-R score favoring nefazodone at Week 7 (-26.7 vs. -21.3, p=0.006) and a 4.0 point improvement in CDRS-R score at week 8 which narrowly missed statistical significance (-26.5 vs. -22.5, p=0.055). The nefazodone group was superior to placebo at week 8 on CGI response rate (65% vs. 46%, p=0.005), CGI Improvement (2.3 vs. 2.8, p=0.012), CGI Severity (-1.7 vs. –1.3, p=0.022), HAM-D (-10.0 vs. –8.2, p=0.023) and CGAS (17.2 vs. 13.0, p=0.020). Nefazodone was well tolerated with a rate of discontinuation for AEs equal to placebo (3.0%).

CONCLUSION:
In this study nefazodone was shown to be safe and effective in the acute treatment of adolescents with MDD.

INTRODUCTION

PRECLINICAL PROFILE OF NEFAZODONE:

- **$5HT_2$ Antagonist**
- **5HT Reuptake Blocker**
- **NE Reuptake Blocker**
- **Minimal anticholinergic and antihistaminic effects**

CLINICAL PROFILE OF NEFAZODONE:

- **Effective in the treatment of moderately to severely ill depressed adult outpatients and inpatients**
  - **Early relief of depression-related anxiety and insomnia**
  - **Unique beneficial effects on sleep quality**
- **Long-term antidepressant efficacy has been demonstrated in adults**
- **Tolerability profile well-suited for long-term treatment in adults**
  - **Preserves sexual function**
  - **Weight neutral**
- **Pharmacokinetics (PK) in adolescents were similar to that in adults**

STUDY DESIGN

- **Double-blind, randomized, multicenter, parallel group, placebo-controlled**
- **Outpatient adolescents with MDD**
- **Two- to four-week Baseline Phase**
- **Eight-week Acute Phase; optional 26-week Double-blind Extension Phase**
- **Eligible patients received nefazodone (titrated between 100 and 600 mg/day) or placebo**
- **Starting dose - 100 mg/day; Target dose - 300 to 400 mg/day based on PK and tolerability in prior trial**

KEY INCLUSION CRITERIA:

- **Physically healthy adolescents, male or female, aged 12-17**
- **Primary diagnosis (DSM-IV) of Major Depressive Episode**
- **CDRS-R Total Score of ≥ 45 at the end of baseline**

KEY EXCLUSION CRITERIA:

- **Concurrent Axis I diagnosis in the following categories: cognitive disorders, psychotic disorders, Bipolar Disorder, eating disorders, Obsessive Compulsive Disorder, Conduct Disorder, Pervasive Developmental Disorder**
- **Met DSM-IV criteria for any significant Psychoactive or Substance Use Disorder within the 6 months prior to the start of the Baseline Phase**
- **Represented a significant risk of committing suicide, based on history or mental status examination**
- **Refractory to two or more courses of antidepressant medication when treated for an adequate period with a therapeutic dose**

DEMOGRAPHIC AND PSYCHIATRIC HISTORY

195 Patients at 15 study centers (US) were randomized. Treatment groups were comparable for age, sex, race, and psychiatric history

- **Mean age was 14.7 years (SE = 0.1); range was 12-17 years**
- **59% girls and 41% boys**
- **78% White, 9% Black, 9% Hispanic/Latino, 4% Other**

Characteristics	Placebo N=96	Nefazodone N=99
Mean Age at First Onset of MDD (years)	12.1 (±0.3)	12.7 (±0.3)
Single/Recurrent Episode		
Single	72 (75%)	70 (71%)
Recurrent	24 (25%)	29 (29%)
Number of Prior Episodes	2.5 (±0.4)	2.2 (±0.3)
Weeks Since Present Episode	80.1 (±9.5)	66.9 (±8.6)
Baseline CDRS-R Total Score	61.3	60.2
Baseline HAM-D Score	16.8	16.7

PATIENT STATUS AT END OF THE TRIAL

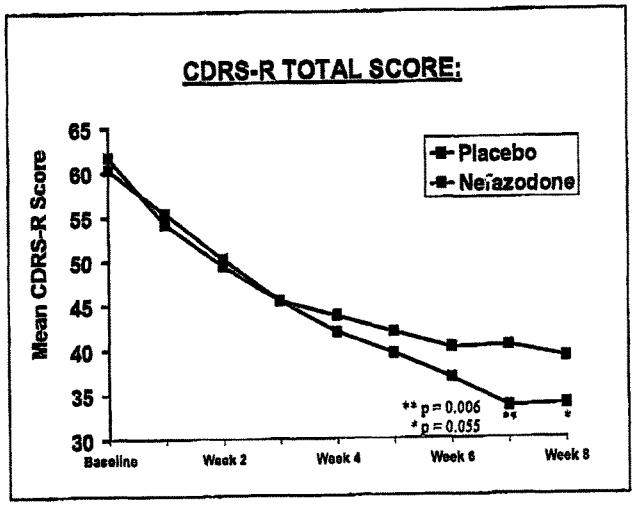
Randomized Sample	Placebo N=96 (%)	Nefazodone N=99 (%)
Completed Study	57 (59)	72 (73)
Total Discontinuations	39 (41)	27 (27)
Adverse Event	3 (3)	3 (3)
Lost to Follow-Up	3 (3)	7 (7)
Patient Withdrew Consent	9 (9)	3 (3)
Lack of Efficacy	15 (16)	9 (9)
Other Known Cause	10 (10)	4 (4)
Mean Dose at Week 8[a]	4.8 tablets	444.0 mg

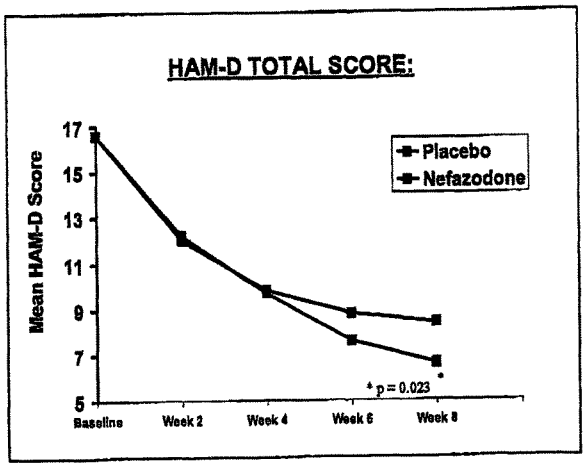
[a] Observed Cases (placebo N=59; nefazodone N=74)

SUMMARY OF EFFICACY RESULTS AT ENDPOINT
Last Observation Carried Forward, Week 8

Efficacy Sample	Placebo N = 92	Nefazodone N = 95	P-Value
CDRS-R Total Score			
Mean Change from Baseline[a,b]	-22.5	-26.5	0.055
Rate of Change/Week[a,c]	-2.78	-3.45	0.025
HAM-D Total Score			
Mean Change from Baseline[a,b]	-8.2	-10.0	0.023
Mean CGI Improvement Score[d]	2.8	2.3	0.012
% of Patients with CGI Response[d,e]	46	65	0.005
CGI Severity Score			
Mean Change from Baseline[a,b]	-1.3	-1.7	0.022
CGAS[b,f]	13.0	17.2	0.020

[a] Negative values indicate improvement.
[b] ANCOVA analysis with model terms for treatment group, study center and baseline score.
[c] Random effects longitudinal model fit to the actual scores at each week.
[d] CMH analysis stratified by study center.
[e] CGI Response = Very much or much improved.
[f] Positive values indicate improvement.


CDRS-R TOTAL SCORE:
Mean CDRS-R Score
65
60
55
50
45
40
35
30
Placebo
Nefazodone
** p = 0.006
* p = 0.055
Baseline
Week 2
Week 4
Week 6
Week 8


HAM-D TOTAL SCORE:
Mean HAM-D Score
17
15
13
11
9
7
5
Placebo
Nefazodone
* p = 0.023
Baseline
Week 2
Week 4
Week 6
Week 8

ADVERSE EVENTS 10% INCIDENCE*

Safety Sample	Placebo N = 95 (%)	Nefazodone N = 95 (%)
Body as a Whole		
Headache	45 (47.4)	53 (55.8)
Abdominal Pain	15 (15.8)	26 (27.4)
Digestive System		
Nausea	8 (8.4)	28 (29.5)
Vomiting	8 (8.4)	10 (10.5)
Nervous System		
Somnolence	14 (14.7)	24 (25.3)
Dizziness	3 (3.1)	19 (20.0)

[a] Nefazodone incidence greater than placebo.

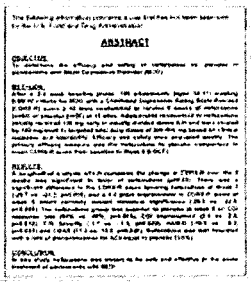
CONCLUSIONS

- **At Week 8, nefazodone showed greater improvement compared with placebo in the treatment of adolescents with a major depressive episode.**
  - **This improvement approached statistical significance for the Primary Efficacy Measure, the change from baseline in the CDRS-R Total Score.**
  - **For all other efficacy measures, including the HAM-D Score, the CGI responder analysis, the CGI Improvement Score, the CGI Severity Score, and the CGAS, nefazodone was demonstrated to be statistically more effective than placebo.**
- **Nefazodone was safe and well tolerated in this trial.**
  - **The rate of discontinuation for AEs was similar between the treatment groups.**
  - **No patients who received nefazodone experienced an SAE.**
  - **No clinically important cardiac risks or laboratory abnormalities were identified.**
- **In a second depression trial in pediatric patients (aged 7-17), nefazodone did not differentiate from placebo.**

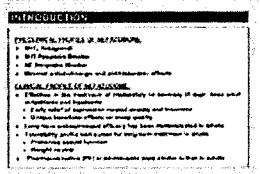
Efficacy and Safety of Nefazodone in the Treatment of Adolescents with Major Depressive Disorder

Graham J. Emslie[1], Robert L. Findling[2], Moira A. Rynn[3], Ronald N. Marcus[4], Lori A. Fernandes[4], M. Frances D'Amico[4], Sterling A. Hardy[4]

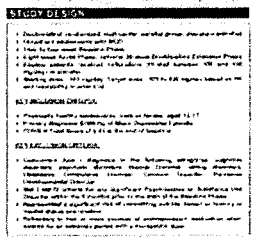
[1]UT Southwestern Medical Center, Dept of Psychiatry, 5323 Harry Hines Blvd, Dallas, TX 75235; [2]University Hospitals of Cleveland, 11100 Euclid Ave, Cleveland, OH 44106; [3]University of Pennsylvania Mood & Disorders Section, 3535 Market Street, Philadelphia, PA 19104; [4]Bristol-Myers Squibb Co., Pharmaceutical Research Institute, 5 Research Pkwy, Wallingford, CT 06492



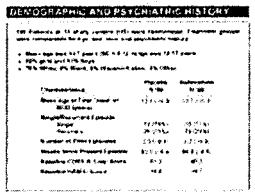
ABSTRACT



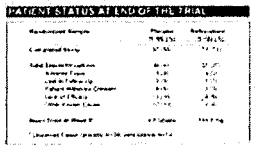
INTRODUCTION



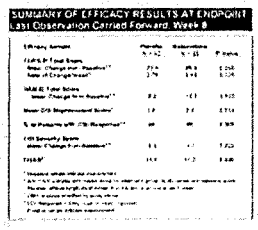
STUDY DESIGN



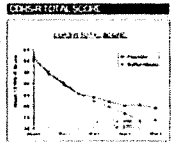
DEMOGRAPHIC AND PSYCHIATRIC HISTORY



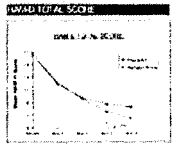
PATIENT STATUS AT END OF THE TRIAL



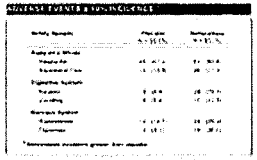
SUMMARY OF EFFICACY RESULTS AT ENDPOINT
Last Observation Carried Forward, Week 8



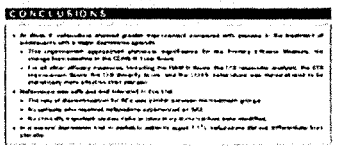
CGI-I TOTAL SCORE



HAM-D TOTAL SCORE



ADVERSE EVENTS & DISCONTINUATION



CONCLUSIONS

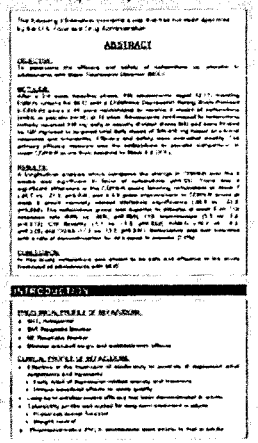
Supported by funding from Bristol-Myers Squibb Company

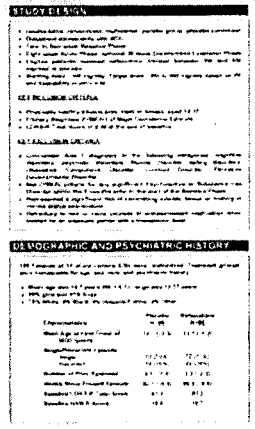
NR: 98

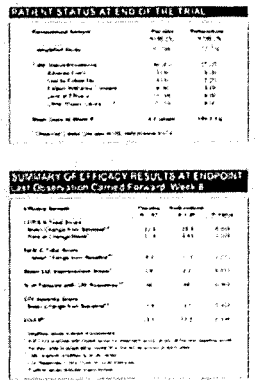
Efficacy and Safety of Nefazodone in Adolescents with MDD

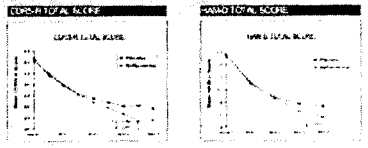
Moira A. Rynn[1], Robert L. Findling[2], Graham J. Emslie[3], Ronald N. Marcus[4], Lori A. Fernandes[4], M. Frances D'Amico[4], Sterling A. Hardy[4]

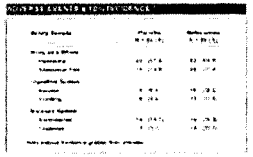
[1]University of Pennsylvania, Mood & Disorders Section, 3535 Market Street, Philadelphia, PA 19104; [2]University Hospitals of Cleveland, 11100 Euclid Ave, Cleveland, OH 44106; [3]UT Southwestern Medical Center, Dept of Psychiatry, 5323 Harry Hines Blvd, Dallas, TX 75235; [4]Bristol-Myers Squibb Co., Pharmaceutical Research Institute, 5 Research Pkwy, Wallingford, CT 06492

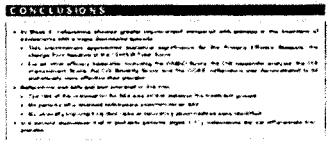












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Nefazodone Pharmacokinetics in Depressed Children and Adolescents

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ABSTRACT

Objective: To describe the pharmacokinetics and safety of nefazodone (NFZ) in depressed children and adolescents. **Method:** Depressed youths aged 7 to 17 years were eligible to participate. Intensive sampling for pharmacokinetic analyses of NFZ and 3 of its active metabolites was performed after single and multiple dose administration. Treatment was continued for 6 more weeks and titrated to maximize clinical response. **Results:** Twenty-eight patients were enrolled. Systemic exposure to NFZ and 3 metabolites was generally higher in children than adolescents. NFZ and metabolite disposition profiles showed high intra- and interpatient variability. Compared to published data in adults, the half-life of NFZ and 2 of its metabolites appears shorter in children and adolescents. *Meta*-chlorphenylpiperazine pharmacokinetic parameters were different in 5 patients determined to be poor metabolizers of cytochrome P450 2D6 (CYP2D6). NFZ was well tolerated, and administration was associated with significant reductions ($p < .001$) in depressive symptoms. **Conclusions:** The pharmacokinetics of NFZ in pediatric patients is highly variable. NFZ appears to be safe in this small, short-term study. Pediatric patients who are poor metabolizers of CYP2D6 do not appear to be at increased risk for NFZ-associated adverse events. Open-label treatment of NFZ is associated with reductions in depressive symptoms. *J. Am. Acad. Child Adolesc. Psychiatry,* 2000, 39(8):1008–1016.

Key Words: depression, nefazodone, pharmacokinetics.

Depression is a common disorder during childhood and adolescence. Youths with depression often have significant interpersonal, intrafamilial, and academic difficulties. Probably of greatest concern is that major depression is a significant risk factor for suicide (Birmaher et al., 1996). Unfortunately, definitive therapeutic approaches for the management of these pediatric patients are yet to be established. Clearly, effective treatments for depressed youths are needed.

The tricyclic antidepressants are the standards to which pharmacological treatments of depressed adults are often compared. Nevertheless, results from controlled trials of these drugs in children and adolescents have failed to demonstrate that any of these agents are superior to placebo (Findling et al., 1999). In hopes of identifying a pharmacological treatment for major depression in children and adolescents, investigators have begun to examine whether newer antidepressants can provide safe, effective therapy for these patients.

Nefazodone (NFZ) is an effective and well-tolerated treatment for depressed adults. The drug is extensively metabolized to at least 3 pharmacologically active metabolites, hydroxynefazodone (OH-NFZ), a triazoledione (dione), and *meta*-chlorphenylpiperazine (mCPP) (Fig. 1). NFZ acts presynaptically as a serotonin reuptake inhibitor and also as a postsynaptic serotonin receptor antagonist. The presence of this postsynaptic serotonin receptor antagonism distinguishes NFZ from the serotonin-specific reuptake inhibitors (see review by Davis et al., 1997; Eison et al., 1990; Taylor et al., 1995).

The primary goal of this study was to describe the safety of NFZ and the pharmacokinetics of NFZ and 3 of its

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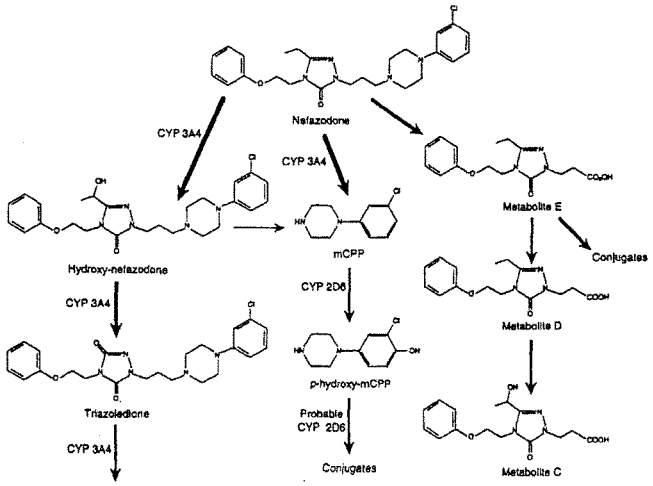

Fig. 1 Proposed metabolic scheme for nefazodone in humans. Specific cytochrome P450 (CYP) isozymes responsible for metabolism of individual compounds (where not known, proposed) are denoted. Apparent primary metabolic pathways are shown with boldface arrows. Scheme adapted from Greene and Barbhaiya (1997). mCPP = *meta*-chlorphenylpiperazine.

metabolites (OH-NFZ, mCPP, and dione) in depressed children and adolescents. Inasmuch as mCPP formation is catalyzed by cytochrome P450 2D6 (CYP2D6) (Fig. 1) (Barbhaiya et al., 1996a) and the activity of this CYP isozyme may be important to overall NFZ pharmacological activity, we determined the CYP2D6 phenotype of our study subjects. A secondary goal of our study was to examine whether open-label, flexible-dose treatment with NFZ would produce reductions in depressive symptoms in depressed youths.

METHOD

Study Design

This was an 8-week, open-label trial of NFZ in depressed children and adolescents. Prior to medication administration, each subject underwent a 1- to 4-week baseline assessment period. During the course of the 8-week trial, intensive blood sampling occurred over 3 separate 12-hour periods for pharmacokinetic analyses.

All procedures were approved by the 2 participating centers' institutional review boards for human investigation prior to initiation of this study. All subjects' parents/guardians provided written consent, and all subjects provided written assent for participation in this trial.

Subjects

Eligible subjects were children between 7 and 12 years of age (inclusive) whose Tanner Rating Scale score was <3 or adolescents between the ages of 12 and 17 years (inclusive) scoring ≥3 on the Tanner Rating Scale (Kulin, 1996) and who met at least 3 of 9 "A" criteria for a *DSM-IV* major depressive episode. Otherwise, subjects met all other symptom criteria for a major depressive episode (American Psychiatric Association, 1994) at both the beginning and end of the 1- to 4-week baseline observation period. Entry criteria did not stipulate that youths meet full symptom criteria for a major depressive episode, in order to permit youths who might benefit from pharmacotherapy to enroll into this trial. Current and past psychiatric diagnoses were determined on the basis of the results of a semistructured interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (Orvaschel, 1994) and were confirmed by a physician's clinical interview. Patients were excluded from enrollment if (1) there was any evidence of significant past or current medical conditions, (2) there was significant psychiatric comorbidity, (3) they had received other psychotropic medications within 2 weeks of enrollment (6 weeks for fluoxetine), or (4) they had a known first-degree relative with bipolar disorder.

Medication Dosage

Treatment was initiated at a dose of 50 mg of NFZ administered orally, twice daily (morning and evening) for 8 days. On the ninth day,

the dose was increased to 100 mg b.i.d. After the 16th day, doses could be adjusted on the basis of clinical response. For children, dosing increments were no larger than 50 mg/week, with a maximum daily dose of 150 mg b.i.d. This dose ceiling was selected as representing half the recommended maximum total daily dose for adults (Davis et al., 1997). For adolescents, 50- to 100-mg/week increments were permissible, with a maximum daily dose being 300 mg b.i.d. Doses of medication could be decreased as needed.

Pharmacokinetic Sampling and Analysis

Blood samples for the determination of NEF and its metabolites in plasma were obtained before the drug was taken and at 0.5, 1, 2, 4, 6, 8, and 12 hours after the first 50-mg oral dose; again after 1 week of 50 mg administered b.i.d. (dose day 7 or 8); and, finally, after subjects had received 100 mg administered b.i.d. for 1 week (dose day 14 or 15). Each blood sample was centrifuged within 1 hour of collection at 1,000 × *g* for 15 minutes at 5°C. Plasma was then harvested and placed in a capped polyethylene vial, which was stored at −20°C until it was shipped for analysis. All samples were shipped on dry ice to Bristol-Myers Squibb for analysis.

The quantitation of NFZ and 3 of its primary metabolites, OH-NFZ, mCPP, and dione (Fig. 1), in plasma was performed using high-pressure liquid chromatography with ultraviolet detection (HPLC-UV). With this validated method (Franc et al., 1991) and 1-mL plasma samples for analysis, the lower limit of quantitation was 10 ng/mL for NFZ and the dione, 5 ng/mL for OH-NFZ, and 2.5 ng/mL for mCPP. Peak height ratios of the study samples were used for calculating concentrations from the regression equation derived from the standard curve. Under these analytic conditions the overall between- and within-day coefficients of variation for the quality control samples were <7% for the dione, <5% for NFZ and mCPP, and <4% for OH-NFZ.

Pharmacokinetic Analysis

The disposition characteristics of NFZ, OH-NFZ, dione, and mCPP were characterized using noncompartmental pharmacokinetic techniques (Gibaldi and Perrier, 1982). Plasma concentrations of each component were plotted against time on a semilogarithmic scale. The maximal plasma concentration of parent NFZ or metabolite was identified (C_{max}) and the time to C_{max} (T_{max}) recorded for each study subject. The terminal portion of the log-linear plasma concentration–time curve was identified and elimination half-life ($t_{1/2}$) determined. The area under the plasma drug concentration–time curve (AUC) was determined using a combination of the linear and log-linear trapezoidal rules. The linear trapezoidal rule was used in the portion of the curve prior to the log-linear phase, at which time the log-linear rule was applied. The AUC for each compound was determined to the final measured plasma concentration exceeding the assay's lower limit of quantitation for the respective compound and extrapolated to infinity after the first dose administration (SAS/STAT version 6.07). If the drug/metabolite concentration at 12 hours postdose was below its limit of quantitation during the multiple-dose phase of the study, concentrations were estimated on the basis of the determined drug/metabolite $t_{1/2}$ and the predicted concentration used in the calculation of the AUC zero to the end of the dosing interval, tau. When a $t_{1/2}$ could not be estimated, the AUC zero to last quantifiable time point was used.

Medical/Psychiatric Monitoring

All subjects had a physical examination at the beginning of the baseline period and at the end of the 8-week trial. Vital signs were measured at the beginning and end of baseline and at the end of weeks 1, 2, 3, 4, 6, and 8. A standard electrocardiogram (ECG) with a 30-second lead-II rhythm strip, supine and standing blood pressure, and pulse measurements were obtained before and at 2, 4, and 8 hours after the dose of NFZ was administered on each of the 3 pharmacokinetic sampling periods. Clinical laboratory tests including a chemistry profile, a complete blood cell count, platelet count, and urinalysis were conducted at the beginning of the baseline period and at the end of the study. A urine pregnancy test at the end of baseline, at the end of week 4, and at the end of the study was obtained in postmenarchal females. A urine drug screen was obtained at the beginning and end of the baseline period and at the end of weeks 1 and 2 in all subjects. Subjects and their families were queried about adverse events at each study visit. The severity of possible NFZ-associated side effects were to be rated as "mild," "moderate," "severe," or "very severe" based on a priori criteria. Medication compliance was assessed by pill count at each study visit.

Depressive symptoms were assessed during the study using the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1985), the Clinical Global Impressions Scale (CGI) (National Institute of Mental Health, 1985), and the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1985).

Determination of CYP2D6 Phenotype

The phenotype of CYP2D6 was determined in each subject before NFZ therapy. Subjects received a single oral dose of the CYP2D6 probe compound, dextromethorphan. All urine excreted over the next 8 hours was collected for quantitation of urinary dextromethorphan and its O-demethylated metabolite dextrorphan, using HPLC-UV methodology. Patients with a dextromethorphan-dextrorphan ratio >0.1 were considered "poor metabolizers." This ratio conforms with the overall NFZ study program and permitted identification of a larger cohort of patients who might be at risk for accumulation of its mCPP metabolite (Fig. 1).

Statistical Analyses

Descriptive statistics including mean, median, standard deviation, and standard error were used for both the pharmacokinetic and psychometric data. Data are presented as means (SD) unless otherwise noted. Psychometric results were evaluated using an intent-to-treat last observation carried forward data set. The a priori criterion to distinguish "responders" from "nonresponders" was a CGI-Improvement score at the end of study participation indicative of being "much" or "very much" improved. Numbers of responders and nonresponders were compared between children and adolescents using the Fisher exact test. Baseline psychometric scores were compared with those at week 8 using a paired *t* test. Only psychometric data from subjects completing the entire first week of the study were analyzed. Results of analyses were considered to be statistically significant if $p < .05$.

RESULTS

A total of 28 subjects were enrolled into this study. There were 15 children (7 males) with a mean age of 10 years (range 7–12) and a mean weight of 45.1 kg. Of the 13 adolescents (5 males) who participated in this protocol, the mean age was 14.2 years (range 13–16) with a mean weight of 55.7 kg. Twenty-three patients, 11 children and 12 adolescents, completed the 8-week trial. Four children were dropped from the study: one was withdrawn because

of lack of efficacy, one developed a rash during the first week of therapy and was withdrawn, one withdrew assent to participate during the baseline evaluation, and one was withdrawn because of questionable medication compliance. Of the 15 enrolled children, 13 underwent complete blood sampling for pharmacokinetic analysis at each of the 3 scheduled sampling times (first dose and at the end of weeks 1 and 2). One adolescent was withdrawn from the study because of lack of efficacy. All adolescents completed the blood sampling for pharmacokinetic analysis at the 3 sampling times.

Pharmacokinetic Characteristics of Nefazodone and Its Metabolites

The overall mean plasma concentration–time curves for parent NFZ and the 3 studied metabolites in the children and adolescents are shown in Figure 2. Substantial variation was observed in the number of patients with quantifiable plasma NFZ and metabolite concentrations at each sampling time (see below). For the vast majority of sampling times, plasma NFZ concentrations were higher in children compared with adolescents (Fig. 2). This difference is most pronounced with the final 100-mg b.i.d. dose, wherein plasma NFZ concentrations in children were more than twice that observed in adolescents for up to 6 hours after dosing and then approaching similar values for the 2 age groups by 8 hours. Similar increases in the magnitude of the plasma concentration for OH-NFZ in children were observed, and less dramatic increases were observed for the mCPP and dione metabolites. As such, plasma C_{max} concentrations were always higher in children than in adolescents (Fig. 2 and Table 1). These differences appear to be at least partially due to differences in administered NFZ dose per kilogram of body weight.

Nefazodone

After administration of the first dose, the determination of C_{max} for NFZ was possible in nearly all of the children studied whereas C_{max} could be identified in only 7 of 13 adolescents (Table 1). The median T_{max} was relatively rapid, ranging from 0.5 to 1 hour. NFZ pharmacokinetic parameter estimates are shown in Table 1. The NFZ $t_{1/2}$ and AUC were highly variable, increasing disproportionately with repeated doses and dose escalation to 100 mg b.i.d. (Table 1). The observed $t_{1/2}$ averaged 1.9 hours after the first dose, increasing to 2.7 hours after 1 week of b.i.d. dosing and increasing further to 4.1 hours after approximately 7 days of an increased NFZ dose of 100 mg b.i.d. These increases in $t_{1/2}$ and AUC with repeated dosing appear to reflect differences in the activity and/or saturation of specific CYP isozyme activity (Fig. 1) relative to achieved concentrations of NFZ and its metabolites with repeated dosing.

Nefazodone Metabolites

After administration of the first dose, the number of patients with quantifiable metabolite concentrations and the resultant, apparent parameter estimates were highly variable (data not shown). With repeated dosing, both the number of evaluable subjects and the absolute values of $t_{1/2}$ and AUC determinations increased for OH-NFZ and were highly variable for the mCPP metabolite; only the AUC could be estimated for the dione metabolite (data not shown). The apparent pharmacokinetic characteristics of the 3 studied NFZ metabolites on study days 14 and 15 after 1 week of 100 mg b.i.d. dosing are shown in Table 2. Similar to that observed for NFZ (Table 1), substantial variability was observed in the number of patients with quantifiable plasma concentrations and in calculated parameter estimates (Tables 1 and 2). The median T_{max} for OH-NFZ, mCPP, and dione metabolites ranged from 0.5 to 2 hours, 1.5 to 2 hours, and 1 to 2 hours, respectively. In contrast to OH-NFZ and mCPP, a determination of the dione $t_{1/2}$ was not possible because of the slow decline in plasma concentration over the 12-hour sampling period (Fig. 2).

CYP2D6 Phenotype

Two children and 3 adolescents were determined to be poor metabolizers of CYP2D6. Comparison of mCPP $t_{1/2}$ and AUC determinations after 1 week of NFZ 100 mg b.i.d. in poor and extensive metabolizers is shown in Table 3. Substantial differences are observed in the parameter estimates between these 2 groups. Using a dextromethorphan-dextrorphan ratio of >0.3, 3 of these 5 study subjects would have been identified as poor metabolizers of CYP2D6.

Open-Label Treatment: Clinical Response

The baseline CGI symptom severity score for children and adolescents averaged 3.85 (SE = 0.15) and 4.15 (SE = 0.15), respectively. By the end of week 8, the CGI-Severity score averaged 1.85 for both children (SE = 0.36) and adolescents (SE = 0.40). The improvements reflected by both of these changes in the CGI score were statistically significant ($p < .001$) when compared with baseline. By the

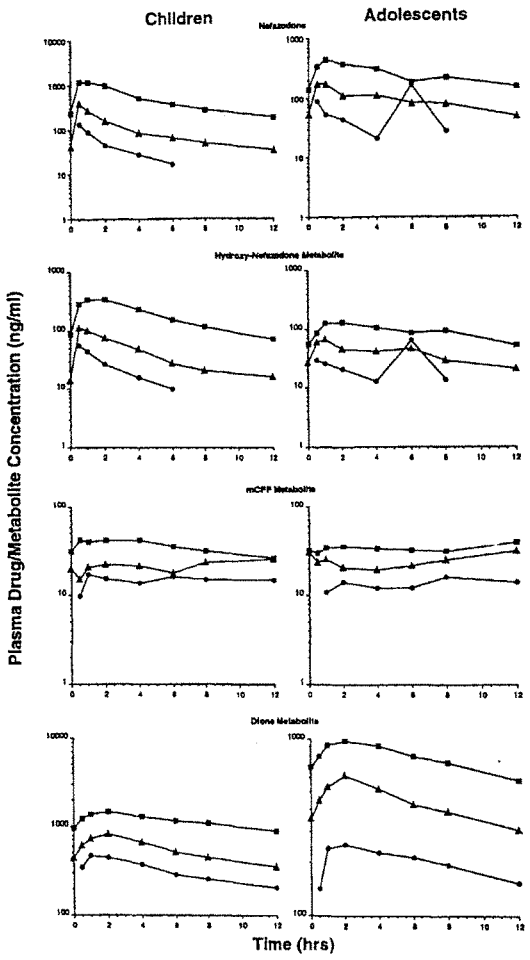

Fig. 2 Mean plasma concentration–time curve for nefazodone and its metabolites hydroxynefazodone, *meta*-chlorphenylpiperazine (mCPP), and triazoledione after 3 different dose regimens: 50 mg single dose (●), 50 mg b.i.d. (▲), and 100 mg b.i.d. (■). The number of study subjects with quantifiable plasma drug/metabolite concentrations was highly variable. See text for details.

TABLE 1
Pharmacokinetics of Nefazodone in Children and Adolescents

	Study Day 1[a] (50 mg)			Study Day 7–8[a] (50 mg b.i.d.)			Study Day 14–15[a] (100 mg b.i.d.)		
	n[b]	Mean	(SD)	n[b]	Mean	(SD)	n[b]	Mean	(SD)
Children (n = 13)									
C_{max} (ng/mL)	13	127	(127)	13	430	(322)	13	1,546	(948)
$t_{1/2}$ (hr)	7	1.9	(1.6)	12	2.7	(1.7)	13	4.1	(3.1)
AUC (ng·hr/mL)	7	321	(165)	12	1,023	(729)	13	5,839	(3,724)
Adolescents (n = 13)									
C_{max} (ng/mL)	7	99.3	(65)	13	222	(185)	13	537	(373)
$t_{1/2}$ (hr)	1	0.74		7	2.7	(1.8)	13	3.9	(3.7)
AUC (ng·hr/mL)	1	185		7	984	(795)	13	2,554	(2,657)
Adult volunteers (n = 12)[c]									
C_{max} (ng/mL)								880	(417)
$t_{1/2}$ (hr)								7	(5.8)
AUC (ng·hr/mL)								3,213	(2,705)

Note: C_{max} = maximal plasma drug concentration; $t_{1/2}$ = elimination half-life; AUC = area under the plasma drug concentration–time curve.

[a] Dosing sequence: see "Method" section for details.

[b] n = number of patients with sufficient measurable plasma concentrations to permit determination of specific parameter estimate.

[c] Data obtained from Barbhaiya et al. (1995) after 100 mg of nefazodone twice daily for 10 days.

end of study week 8, the average daily NFZ dose was 233 mg (range 150–300 mg) for children and 342 mg (range 200–500 mg) for adolescents.

Using the a priori criteria for response, 86% of children and 69% of adolescents were considered responders. This difference in response rate was not different between the 2 groups (Fisher exact test p = .39).

When compared with baseline values, statistically significant differences were noted on the CDRS-R by week 1 and the CGI-Severity score by week 2 ($p < .05$). Sta-

TABLE 2
Disposition Characteristics of Nefazodone Metabolites After Multiple Dosing in a Group of Children and Adolescents

	Nefazodone Metabolites								
	OH-NEF			mCPP			Dione		
	n[a]	Mean	(SD)	n[a]	Mean	(SD)	n[a]	Mean	(SD)
Children (n = 13)									
C_{max} (ng/mL)	13	392	(218)	13	51	(45)	13	1,644	(553)
$t_{1/2}$ (hr)	13	3.5	(3.1)	12	6.4	(4.8)	—	—	—[b]
AUC (ng·hr/mL)	13	2,016	(1,192)	12	411	(484)	13	14,045	(4,778)
Adolescents (n = 13)									
C_{max} (ng/mL)	13	158	(96.1)	13	39	(40)	13	1067	(345)
$t_{1/2}$ (hr)	12	3.3	(2.3)	11	4.8	(2.2)	—	—	—[b]
AUC (ng·hr/mL)	12	920	(821)	12	345	(437)	13	9,458	(3,127)
Adult volunteers (n = 12)									
C_{max} (ng/mL)	12	265	(112)		20	(4.9)		1,080	(303)
$t_{1/2}$ (hr)	12	4	(1.7)		8.3	(4.6)		—	—
AUC (ng·hr/mL)	12	1,297	(990)		130	(37)		8,610	(2,910)

Note: All study subjects received nefazodone 100 mg orally twice daily for at least 7 days (see "Method" section for complete description of nefazodone dosing sequence). OH-NEF = hydroxynefazodone; mCCP = *meta*-chlorphenylpiperazine; dione = triazoledione metabolite; C_{max} = maximal plasma drug concentration; $t_{1/2}$ = elimination half-life; AUC = area under the plasma drug concentration–time curve.

[a] n = number of patients with sufficient measurable plasma concentrations to permit determination of specific parameter estimate.

[b] Not able to be determined. See text for details.

TABLE 3
Elimination Half-Life and Area Under the Plasma Concentration–Time Curve for mCPP in Poor and Extensive Cytochrome P450 2D6 Metabolizers

	Study Day 14 (Nefazodone 100 mg b.i.d.)			
	$t_{1/2}$ (hr)		AUC (ng·hr/mL)	
Age Group	P	E	P	E
Children	9.2 (4.9)	5.9 (4.9)	1,249 (719.1)	243 (203)
Adolescents	8.2 (2.7)	4.0 (1.3)	995.2 (437.0)	128 (53.5)

Note: Values presented as mean (±SD). P = poor and E = extensive cytochrome P450 2D6 metabolizer phenotype as determined by dextromethorphan (see text for details). $t_{1/2}$ = elimination half-life; AUC = area under the plasma drug concentration–time curve; mCPP = *meta*-chlorphenylpiperazine.

tistically significant reductions ($p < .0001$) for CGAS and CDRS-R ($p < .0008$) scores were identified for both children and adolescents when week 8 scores were compared with baseline. For children, the mean CGAS score increased from 49.82 (SE = 4.06) to 80.73 (SE = 2.33) and the mean CDRS-R score decreased from 47.83 (SE = 2.67) to 26.83 (SE = 3.33). In adolescents, the mean CGAS score increased from 52.23 (SE = 2.98) to 74.54 (SE = 3.07) and the mean CDRS-R score decreased from 52.92 (SE = 3.67) to 32.46 (SE = 4.62).

Safety

No clinically significant changes in laboratory measures, ECG tracings, or vital signs were found to be associated with NFZ treatment. Overall, NFZ was well tolerated. One subject was withdrawn after an adverse event. This patient, an extensive metabolizer, developed a generalized rash after 5 days of NFZ. The child recovered without sequelae.

All subjects except one reported at least one adverse event during the course of the study. Most side effects reported in children (56%) and adolescents (55%) were considered mild. Of all the side effects reported, 53% of these were reported in children and 47% described in adolescents. The most common side effects reported in children were headache ($n = 6$), nausea ($n = 6$), vomiting ($n = 5$), and anorexia ($n = 4$). The most common side effects reported in adolescents were headache ($n = 6$), asthenia ($n = 4$), and sedation ($n = 2$).

DISCUSSION

The focus of this study was to describe the safety and pharmacokinetics of NFZ in depressed pediatric patients. The drug was relatively well tolerated by our study subjects. The incidence and magnitude of NFZ-associated side effects was modest, necessitating discontinuation of drug therapy in only one patient who developed a skin rash. Moreover, NFZ administration was associated with a marked reduction in depressive symptoms.

The pharmacokinetic data generated in this study are consistent with previous findings in both adult volunteers and patients (Barbhaiya et al. 1995, 1996b; Greene and Barbhaiya, 1997; Kaul et al., 1995), reflecting the complexity (Fig. 1) and marked degree of inter- and intraindividual variability (Fig. 2; Tables 1–3) in NFZ's disposition characteristics. After drug administration, substantial variability was observed in the number of subjects with sufficient measurable plasma NFZ concentrations. The number of subjects with measurable plasma concentrations increased with repeated and long-term medication use (Table 1). Furthermore, the NFZ C_{max} and AUC were much higher in children than in adolescents, whereas the NFZ $t_{1/2}$ was very similar for the 2 age groups. The reason(s) for these differences in plasma drug concentrations and AUC with no appreciable change in $t_{1/2}$ between children and adolescents is unknown. A portion of these differences in C_{max} and AUC appear to be due to the difference in dose per kilogram of body weight administered to our study subjects. The average body weight was 44.7 (±12.7) kg in our study children and 68.5 (±25.9) kg in our study adolescents, representing a 53% greater body mass in our adolescent subjects. Additional factors that may influence NFZ disposition, partially accounting for these differences, include developmental changes in hepatic P450 metabolism, potential differences in drug bioavailability, and differences in drug distribution characteristics coincident with puberty (Kaul et al., 1995; Rodman, 1994; Sjoqvist, 1989). Unfortunately, the lack of an intravenous drug formulation precludes us from a critical assessment of possible differences in drug bioavailability, distribution, or clearance mechanisms.

Barbhaiya and colleagues (1996b) were able to assess the absolute bioavailability of NFZ using ^{14}C-labeled NFZ in a group of 9 healthy adult volunteers. Each subject received 5 mg of NEF intravenously, followed by groups of 3 volunteers receiving single oral solution doses of 50, 100, or 200 mg NFZ 7 days later. After each dose subjects underwent comprehensive blood, urine, and feces sampling for 7 days. These investigators found that the overall bioavailability of NFZ is very low and highly variable and that it increases with increasing dose. The average (±SD)

bioavailability of NFZ was 15% (±7), 18% (±7), and 23% (±7) after the 50-, 100-, and 200-mg doses, respectively. Thus, the increases in NFZ plasma concentrations and AUC observed in our study patients appears consistent with the increased bioavailability observed with increasing dose as well as probable influences of systemic accumulation due to possible saturation of metabolic pathways (Tables 1 and 2; Fig. 1).

Comparison of our NFZ pharmacokinetic data with data reported for healthy adult volunteers receiving the same daily dose (100 mg b.i.d.) reveals important differences (Table 1). As expected based on body size, the NFZ AUC is much higher in children than adults whereas the NFZ AUC is similar for adolescents and adults. In contrast, the NFZ $t_{1/2}$ is much more rapid in both children (3.5 hours) and adolescents (3.9 hours), compared with 7 hours reported in adults. The reason(s) for this potential difference in $t_{1/2}$ is unknown but may reflect potential age-related differences in the affinity or specificity of these compounds for specific CYP isozymes important in NFZ metabolism (Fig. 1) (Kaul et al., 1995; Sjoqvist, 1989). It is also possible that the proposed metabolic scheme for NFZ in adults shown in Figure 1 is different in children and adolescents.

The apparent disposition characteristics of the 3 NFZ metabolites in our study subjects after multiple 100-mg doses are shown in Table 2. Similar to parent NFZ, substantial intraindividual variability was observed in the pharmacokinetic parameter estimates determined. In addition, similar differences in metabolite C_{max} and AUC were observed between children and adults, with no appreciable difference in $t_{1/2}$. Comparison of these results with data reported in adults reveals differences similar to those observed with parent NFZ described above.

Five of our study patients were identified to be poor CYP2D6 metabolizers as determined by dextromethorphan-dextrorphan ratio, a probe reflecting CYP2D6 isozyme activity. Substantial differences in the important pharmacokinetic parameter estimates $t_{1/2}$ and AUC were observed between poor and extensive metabolizers for mCPP. These findings are comparable with similar differences described in mCPP disposition in poor and extensive metabolizers in adults (Barbhaiya et al., 1996a; Greene and Barbhaiya, 1997). The differences in mCPP disposition in poor metabolizers in our 5 study patients were not associated with any differences in NFZ safety or clinical effects. This observation of a lack of exaggerated effects from greater mCPP exposure in poor metabolizers is consistent with the findings in adults (Barbhaiya et al., 1996a), reflecting the apparent safety of this metabolite and NFZ.

NFZ and its metabolites OH-NFZ, mCPP, and dione all modulate serotonin activity within the CNS (Davis et al., 1997; Taylor et al., 1995). Thus, the combined effects of all 4 moieties appear responsible for the overall antidepressant effects produced with NFZ administration. This interplay of 4 compounds, each with different disposition characteristics (Tables 1 and 2), underscores the importance of slow dose titration of NFZ when initiating therapy. The optimal duration of an adequate therapeutic trial before upward dose titration remains to be defined. Nevertheless, from the pharmacokinetic data generated in this study, it appears prudent to assess patient response after a minimum of 1 to 2 weeks after the child has received a constant dose regimen. A 2-week period should permit clinical assessment when steady-state conditions have been achieved for each compound, including the dione metabolite.

Although assessment of NFZ's antidepressant efficacy was not a primary focus of our study, the drug was found to be effective in most study patients. In a case series, Wilens et al. (1997) also described effective antidepressant activity of NFZ in young patients. Because of the open-label design of our study, specific conclusions about the antidepressant efficacy of NFZ cannot be drawn. Furthermore, the high degree of inter- and intraindividual variation in plasma NFZ and metabolite concentrations and pharmacokinetic estimates precludes an integrated assessment of our pharmacokinetic data with pharmacodynamic observations as well as any attempt to identify a relationship between specific plasma concentration and clinical effect. Similar attempts in adults have been unsuccessful in identifying any specific plasma concentration or dose effect relationship for NFZ in depressed patients.

In summary, this study provides evidence that similarities and differences exist in the pharmacokinetics of NFZ in children, adolescents, and adults. Substantial intersubject variation was observed in plasma concentrations and pharmacokinetic characteristics of NFZ and metabolites in children and adolescents. The observed data suggest possible differences in bioavailability and/or metabolism of NFZ between children and adolescents and among children, adolescents, and adults. Only after more critical, age-controlled metabolic studies are conducted will a greater understanding of these probable differences be possible, permitting an integration of the drug's pharma-

cokinetic and pharmacodynamic profiles. As in adults, NFZ appears to be safe and well tolerated in pediatric patients. Questions about whether NFZ would be well tolerated in poor metabolizers with respect to CYP2D6 were raised before we conducted our study. Despite pharmacokinetic differences between extensive and poor metabolizers with respect to mCPP, our results in 5 pediatric subjects who were poor metabolizers (Table 3) indicate that poor CYP2D6 metabolizers tolerate treatment with NFZ as well as do extensive metabolizers. At the doses of NFZ used in this study, significant reductions in depressive symptoms were also noted.

Clinical Implications

NFZ appears to be safe and relatively well tolerated when given to depressed pediatric patients. This implication must be considered within the context of our study design, which involved a small number of subjects evaluated over a short, 8-week period. In addition, open-label treatment with NFZ is associated with reductions in depressive symptoms. For these reasons, blinded, placebo-controlled studies with NFZ should be undertaken.

Limitations of Study

The substantial inter- and intrasubject variability observed in NFZ and metabolite disposition characteristics as well as the flexible-dose design and short study duration precludes any integration of the compound's pharmacokinetics with pharmacodynamic actions. Although our data suggest that NFZ might have antidepressant efficacy in pediatric patients, the drug's true efficacy must be ascertained in a randomized, double-blind, controlled evaluation. Moreover, owing to the brevity of the trial, conclusions about the long-term safety of NFZ cannot be made on the basis of these data. Because of the small number of subjects studied, the effects of gender and Tanner stage were not considered. Finally, CYP3A4 activity was not assessed in our study patients.

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NEFAZODONE

Indication:	Depression
Protocol No.:	CN104141
Phase:	III
Study Initiation Date:	29-Oct-1998
Study Completion Date:	19-Sep-2001
Report Date:	27-Feb-2002

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A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF NEFAZODONE IN DEPRESSED ADOLESCENTS

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CLINICAL REPORT SYNOPSIS

TITLE OF STUDY: A Multicenter, Double-Blind, Placebo-Controlled Trial of Nefazodone in Depressed Adolescents

INVESTIGATORS AND STUDY CENTERS: Fifteen investigators at 15 centers in the United States participated in the conduct of the study. Investigator information is provided in Table 4.

PUBLICATIONS: None

STUDY PERIOD: Date first patient enrolled: 29-Oct-1998

Date last patient completed: 19-Sep-2001

CLINICAL PHASE: III

OBJECTIVES: The objective of this study was to evaluate the safety and efficacy of nefazodone in adolescents with a major depressive episode.

METHODOLOGY: This was a double-blind, multicenter study of nefazodone in adolescent outpatients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for a Major Depressive Episode. This study was originally designed for 12- to 18-year-old patients; however, after the study had been initiated, the FDA requested that the study be conducted in 12- to 17-year-old patients and Amendment 2 (15 June 2000) was written.

After eligibility criteria had been met, patients began a 2- to 4-week baseline phase. Patients who continued to meet study criteria at the end of the baseline phase were randomized to either placebo or nefazodone (100 - 600 mg/day). Doses were administered twice daily (BID) starting at 50 mg, and were increased by 100 mg/week until the target dose of 300 - 400 mg/day had been reached. A dose range of 100 to 600 mg/day was allowed. The dose level could be reduced at any time if adverse events (AEs) occurred. Patients received 8 weeks of double-blind treatment.

At the conclusion of the 8-week short-term phase, patients who were at least minimally improved were given the option to continue on double-blind treatment for an additional 26 weeks. The results of the 26-week long-term phase will be presented in a separate report after the completion of that phase.

NUMBER OF PATIENTS: Two hundred eighty-two patients were enrolled in the study. Two hundred and six patients were randomized to treatment: 83 (40%) of the patients were boys and 123 (60%) were girls. One hundred ninety-five (95%) patients were between 12 and 17 years of age. Eleven (5%) 18-year old patients were treated prior to Amendment 2 (15 June 2000), which lowered the upper age limit from 18 to 17 years. Of the 206 patients randomized to treatment, 100 were randomized to the placebo group and 106 were randomized to the nefazodone group. Two hundred one patients were included in the Safety Sample, 198 patients were included in the Primary Efficacy Sample (12- to 18-years old), and 187 patients were included in the Secondary Efficacy Sample (12- to 17-years old).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Patients met DSM-IV criteria for a nonpsychotic Major Depressive Episode and had a Childhood Depression Rating Scale-Revised (CDRS-R) Total Score of ≥ 45 at the end of baseline.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Nefazodone 50-mg tablet, batch numbers C97392 and N95059; nefazodone 100-mg tablet, batch numbers M99042 and N95074. All doses were administered orally.

DURATION OF TREATMENT: Eight weeks of double-blind treatment.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Placebo tablet 50 mg, batch numbers N97037 and N95056; placebo tablet 100 mg, batch numbers N95048 and N98066. All doses were administered orally.

CRITERIA FOR EVALUATION:

Efficacy: Efficacy rating scales completed weekly during the study were the CDRS-R and the Clinical Global Impression (CGI). The Clinical Global Assessment Score (CGAS) and the 17-item Hamilton Depression Rating Scale (HAM-D) were completed every 2 weeks.

The primary efficacy measure was the mean change from baseline to endpoint in the CDRS-R Total Score. The secondary efficacy measure was the mean CGI Improvement Score. CGI response was defined as a score of 1 (very much improved) or 2 (much improved) on the CGI Improvement Scale.

Safety: Safety and tolerability evaluations included AE reports (both serious and nonserious), physical examinations, clinical laboratory results, electrocardiograms (ECGs), and vital signs data.

STATISTICAL METHODS: The planned sample size of 200 patients (100 per treatment group) was estimated to yield 92% power to detect a difference of 7 in the change from baseline to endpoint in the CDRS-R Total Score between placebo and nefazodone, assuming a standard deviation of 14.7 and an alpha level of 0.05.

The Safety Sample included those patients who received at least one dose of study medication as indicated on the dosing record. Safety was evaluated for all patients in the Safety Sample. The Primary Efficacy Sample included 12- to 18-year-old patients in the Safety Sample who had at least one postrandomization efficacy evaluation (ie, evaluable patients). The Secondary Efficacy Sample included 12- to 17-year-old patients in the Safety Sample who had at least one postrandomization efficacy evaluation. The last observation carried forward (LOCF) data set was used for analyses of drug efficacy. Analyses were also performed on the observed cases (OC) data set.

The mean CDRS-R Total Score was analyzed using analysis of variance (ANOVA) at baseline and analysis of covariance (ANCOVA) on the change from baseline, adjusted for the baseline score and study center, at each week. The CGI Improvement Score (full scale) was analyzed using the Cochran-Mantel-Haenszel (CMH) row mean score test, adjusting for study center. CGI response was analyzed by CMH analysis, adjusting for study center. The mean change from baseline in the HAM-D Total Score and CGAS were analyzed by ANCOVA, adjusting for baseline score and study center.

EXTENT OF EXPOSURE: At endpoint (Week 8), the mean daily dose of study medication was 4.8 tablets for the placebo group and 448 mg/day for the nefazodone group.

EFFICACY RESULTS: For the primary efficacy measure of CDRS-R, there was a greater mean change from baseline for the nefazodone group (-25.8) compared with the placebo group (-22.1) for the Primary Efficacy Sample (12- to 18-year olds); however, the difference between the groups was not statistically significant ($P = 0.077$). For the Secondary Efficacy Sample (12- to 17-year olds), the mean change from baseline was greater for the nefazodone group (-26.5) compared with the placebo group (-22.5), and the difference between the groups approached significance ($P = 0.055$). On the secondary efficacy measure of mean CGI Improvement Score, nefazodone showed statistically significantly greater improvement for both the Primary and Secondary Efficacy Samples. On all other efficacy measures, nefazodone was statistically significantly superior to placebo.

NEFAZODONE

Indication:	Depression
Protocol No.:	CN104187 **32**
Phase:	III
Study Initiation Date:	23-Oct-2000
Study Completion Date:	15-Nov-2001
Report Date:	26-Mar-2002

A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF TWO DOSE RANGES OF NEFAZODONE IN THE TREATMENT OF CHILDREN AND ADOLESCENTS WITH A MAJOR DEPRESSIVE EPISODE

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Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product:		
Name of Active Ingredient:		

SYNOPSIS

Clinical Report Synopsis for Protocol CN104187

TITLE OF STUDY: A Multicenter, Double-Blind, Placebo-Controlled Trial of Two Dose Ranges of Nefazodone in the Treatment of Children and Adolescents With a Major Depressive Episode

INVESTIGATORS AND STUDY CENTERS: Twenty-eight investigators at 28 centers in the United States of America participated in the conduct of the study. Investigator information is presented in Table 4.

PUBLICATIONS: None

STUDY PERIOD: Date first patient enrolled: 23-Oct-2000

Date last patient completed: 15-Nov-2001

PLANNED SAMPLE SIZES PER TREATMENT ARM:

CHILDREN: Low-dose nefazodone, 42 patients; high-dose nefazodone, 42 patients; placebo, 42 patients.

ADOLESCENTS: Low-dose nefazodone, 42 patients; high-dose nefazodone, 42 patients; placebo, 42 patients.

CLINICAL PHASE: III

OBJECTIVES: The objectives of this study were to demonstrate the efficacy and safety of nefazodone at two dose ranges compared with placebo in children and adolescents with a nonpsychotic major depressive episode.

METHODOLOGY: This was a multicenter, randomized, double-blind, placebo-controlled, outpatient study. Children and adolescents who met diagnostic criteria for a Major Depressive Episode, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), were to be enrolled into the study. Children were defined as patients 7 - 11 years of age and adolescents were defined as patients 12 - 17 years of age.

Enrolled patients entered a 2 - 4 week baseline phase, which required a minimum of three visits. Patients whose depressive symptoms had not significantly improved in the opinion of the investigator and who continued to meet eligibility criteria at the end of the baseline phase were stratified by age and randomized to one of three treatment groups in a 1:1:1 ratio. Approximately equal numbers of patients were randomized to each age strata within a low-dose nefazodone group (100 - 150 mg/day for children and 200 - 300 mg/day for adolescents), a high-dose nefazodone group (200 - 300 mg/day for children and 400 - 600 mg/day for adolescents), or a placebo group.

Patients who were unable to tolerate the minimum required number of tablets for their age group were discontinued from the study. Alternative treatment was available for patients who discontinued because of an AE or due to nonresponse to study medication.

Patients were treated for 8 weeks in the double-blind short-term phase. Patients who completed the short-term phase and were eligible could continue in a 26-week, open-label, long-term phase, if continued treatment was indicated.

This clinical study report presents the results of the 8-week short-term phase. The results of the 26-week long-term phase will be presented in a separate report after the completion of that phase.

NUMBER OF PATIENTS: Four hundred seventeen patients were enrolled in the study. Two hundred eighty-four patients were randomized to treatment: 143 (50%) of these patients were boys and 141 (50%) were girls. One hundred thirty-six (48%) patients were between 7 and 11 years of age and 148 (52) patients were between 12 and 17 years of age. Ninety-four (33%) patients were randomized to the placebo group, 95 (33.5%) were randomized to the low-dose nefazodone group, and 95 (33.5%) were randomized to the high-dose nefazodone group. Two hundred seventy-eight patients were included in the Safety Sample and 273 patients were included in the Efficacy Sample. Two hundred seventeen (76%) of the 284 randomized patients completed the 8-week short-term phase.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Patients met DSM-IV criteria for a nonpsychotic Major Depressive Episode and had a Childhood Depression Rating Scale - Revised (CDRS-R) Total Score of ≥ 45 at the end of baseline phase.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Nefazodone 50-mg tablet, batch number M99038; nefazodone 100-mg tablet, batch number C97393. All doses were administered orally.

DURATION OF TREATMENT: Eight weeks of double-blind treatment.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS: Placebo tablet 50 mg, batch number N98069; placebo tablet 100 mg, batch number N98066. All doses were administered orally.

CRITERIA FOR EVALUATION:

Efficacy: Efficacy rating scales completed during this study included the CDRS-R and the Clinical Global Impression (CGI).

Safety: Safety and tolerability evaluations included AE reports (both serious and nonserious), physical examinations, clinical laboratory results, electrocardiograms (ECGs), and vital signs data.

STATISTICAL METHODS: The primary measure of efficacy was the mean change in the CDRS-R Total Score (17 items) from baseline to endpoint (Week 8, last observation carried forward [LOCF]). The comparison of each nefazodone treatment group with placebo was of primary interest in this study. This study was not designed for comparisons between the nefazodone treatment groups. Testing was carried out using the closed testing procedure proposed by Tamhane, Hochberg and Dunnett, which assumed monotone increasing dose response. The high dose was tested first versus placebo at 0.05 level. If significant, then the low dose was tested versus placebo at 0.05 level. Results from a similarly designed study, where equal numbers of children and adolescents were randomized, gave CDRS-R mean change scores of -10.5 for placebo and -20.5 for fluoxetine with an estimated standard deviation of 14.7. Based on this information and with an alpha level set at 0.05, a sample size of 252 patients yields 87% power to detect a difference of 7 in the CDRS-R change from baseline scores between nefazodone and placebo, assuming a standard deviation of 14.7.

The mean CDRS-R Total Score was analyzed using analysis of covariance (ANCOVA) on the change from baseline, adjusted for the baseline score, study center, and age group at each week. The secondary efficacy measure, the CGI Improvement Score (full scale), was analyzed using the Cochran-Mantel-Haenszel (CMH) row mean score test, adjusting for age group. Other efficacy measures included CGI response and mean change from baseline on the CGI Severity Score. CGI response, defined as a score of 1 (very much improved) or 2 (much improved) on the CGI Improvement scale, was analyzed by CMH analysis, adjusting for age group. The CGI Severity Score was analyzed using ANCOVA on the change from baseline, adjusting for the baseline score, study center effect, and age group at each week. Confidence intervals for treatment differences were calculated.

Safety was evaluated for all patients in the Safety Sample (ie, all patients who received at least one dose of study medication as indicated on the dosing record). Efficacy was evaluated for all patients in the Efficacy Sample (ie, patients in the Safety Sample who had at least one postrandomization efficacy evaluation). The LOCF data set was used for primary analyses of drug efficacy. Analyses were also performed on the observed cases (OC) data set.

EXTENT OF EXPOSURE: For children aged 7 - 11 years, the mean daily dose of study medication at endpoint (Week 8) was 130 mg for the low-dose nefazodone group and 249 mg for the high-dose nefazodone group. The mean daily dose for adolescents aged 12 - 17 years was 266 mg for the low-dose nefazodone group and 556 mg for the high-dose nefazodone group.

EFFICACY RESULTS: At endpoint (Week 8, LOCF), there was 0.9 point less improvement in the mean CDRS-R Total Score in the high-dose nefazodone group compared with the placebo group. For the low-dose nefazodone group, there was a 1.7 point greater improvement compared with placebo. Neither difference was statistically significant. There were no significant differences between placebo and either of the nefazodone treatment groups in the mean CGI Improvement Score at endpoint, the CGI response rate at endpoint, or the mean change in CGI Severity Score from baseline to endpoint.

Efficacy and Safety of Nefazodone in Adolescents with MDD

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CN104-141 Study Presented At
American Psychiatric Association Annual Meeting
May 2002

The following information concerns a use that has not been approved by the U.S. Food and Drug Administration.

ABSTRACT

OBJECTIVE:
To determine the efficacy and safety of nefazodone vs. placebo in adolescents with Major Depressive Disorder (MDD)

METHODS:
After a 2-4 week baseline phase, 195 adolescents (aged 12-17) meeting DSM-IV criteria for MDD with a Childhood Depression Rating Scale-Revised (CDRS-R) score ≥ 45 were randomized to receive 8 weeks of nefazodone (n=99) or placebo (n=96) at 15 sites. Adolescents randomized to nefazodone initially received 100 mg daily in equally divided doses BID and were titrated by 100 mg/week to targeted total daily doses of 300-400 mg based on clinical response and tolerability. Efficacy and safety were evaluated weekly. The primary efficacy measure was the nefazodone to placebo comparison in mean CDRS-R score from baseline to Week 8 (LOCF).

RESULTS:
A longitudinal analysis which compares the change in CDRS-R over the 8 weeks was significant in favor of nefazodone (p=0.03). There was a significant difference in the CDRS-R score favoring nefazodone at Week 7 (-26.7 vs. -21.3, p=0.006) and a 4.0 point improvement in CDRS-R score at week 8 which narrowly missed statistical significance (-26.5 vs. -22.5, p=0.055). The nefazodone group was superior to placebo at week 8 on CGI response rate (65% vs. 46%, p=0.005), CGI Improvement (2.3 vs. 2.8, p=0.012), CGI Severity (-1.7 vs. –1.3, p=0.022), HAM-D (-10.0 vs. –8.2, p=0.023) and CGAS (17.2 vs. 13.0, p=0.020). Nefazodone was well tolerated with a rate of discontinuation for AEs equal to placebo (3.0%).

CONCLUSION:
In this study nefazodone was shown to be safe and effective in the acute treatment of adolescents with MDD.

INTRODUCTION

PRECLINICAL PROFILE OF NEFAZODONE:

- $5HT_2$ Antagonist
- 5HT Reuptake Blocker
- NE Reuptake Blocker
- Minimal anticholinergic and antihistaminic effects

CLINICAL PROFILE OF NEFAZODONE:

- Effective in the treatment of moderately to severely ill depressed adult outpatients and inpatients
  - Early relief of depression-related anxiety and insomnia
  - Unique beneficial effects on sleep quality
- Long-term antidepressant efficacy has been demonstrated in adults
- Tolerability profile well-suited for long-term treatment in adults
  - Preserves sexual function
  - Weight neutral
- Pharmacokinetics (PK) in adolescents were similar to that in adults

STUDY DESIGN

- Double-blind, randomized, multicenter, parallel group, placebo-controlled
- Outpatient adolescents with MDD
- Two- to four-week Baseline Phase
- Eight-week Acute Phase; optional 26-week Double-blind Extension Phase
- Eligible patients received nefazodone (titrated between 100 and 600 mg/day) or placebo
- Starting dose - 100 mg/day; Target dose - 300 to 400 mg/day based on PK and tolerability in prior trial

KEY INCLUSION CRITERIA:

- Physically healthy adolescents, male or female, aged 12-17
- Primary diagnosis (DSM-IV) of Major Depressive Episode
- CDRS-R Total Score of ≥ 45 at the end of baseline

KEY EXCLUSION CRITERIA:

- Concurrent Axis I diagnosis in the following categories: cognitive disorders, psychotic disorders, Bipolar Disorder, eating disorders, Obsessive Compulsive Disorder, Conduct Disorder, Pervasive Developmental Disorder
- Met DSM-IV criteria for any significant Psychoactive or Substance Use Disorder within the 6 months prior to the start of the Baseline Phase
- Represented a significant risk of committing suicide, based on history or mental status examination
- Refractory to two or more courses of antidepressant medication when treated for an adequate period with a therapeutic dose

DEMOGRAPHIC AND PSYCHIATRIC HISTORY

195 Patients at 15 study centers (US) were randomized. Treatment groups were comparable for age, sex, race, and psychiatric history

- **Mean age was 14.7 years (SE = 0.1); range was 12-17 years**
- **59% girls and 41% boys**
- **78% White, 9% Black, 9% Hispanic/Latino, 4% Other**

Characteristics	Placebo N=96	Nefazodone N=99
Mean Age at First Onset of MDD (years)	12.1 (±0.3)	12.7 (±0.3)
Single/Recurrent Episode		
Single	72 (75%)	70 (71%)
Recurrent	24 (25%)	29 (29%)
Number of Prior Episodes	2.5 (±0.4)	2.2 (±0.3)
Weeks Since Present Episode	80.1 (±9.5)	66.9 (±8.6)
Baseline CDRS-R Total Score	61.3	60.2
Baseline HAM-D Score	16.8	16.7

PATIENT STATUS AT END OF THE TRIAL

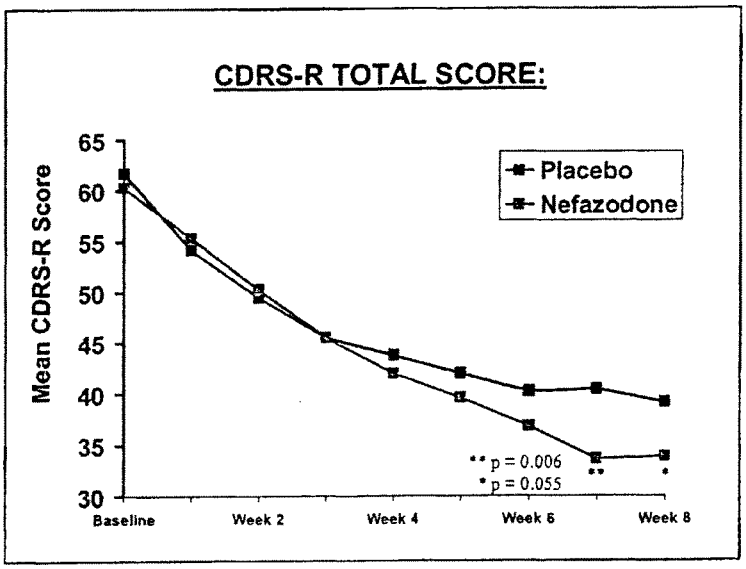
Randomized Sample	Placebo N=96 (%)	Nefazodone N=99 (%)
Completed Study	57 (59)	72 (73)
Total Discontinuations	39 (41)	27 (27)
Adverse Event	3 (3)	3 (3)
Lost to Follow-Up	3 (3)	7 (7)
Patient Withdrew Consent	9 (9)	3 (3)
Lack of Efficacy	15 (16)	9 (9)
Other Known Cause	10 (10)	4 (4)
Mean Dose at Week 8[a]	4.8 tablets	444.0 mg

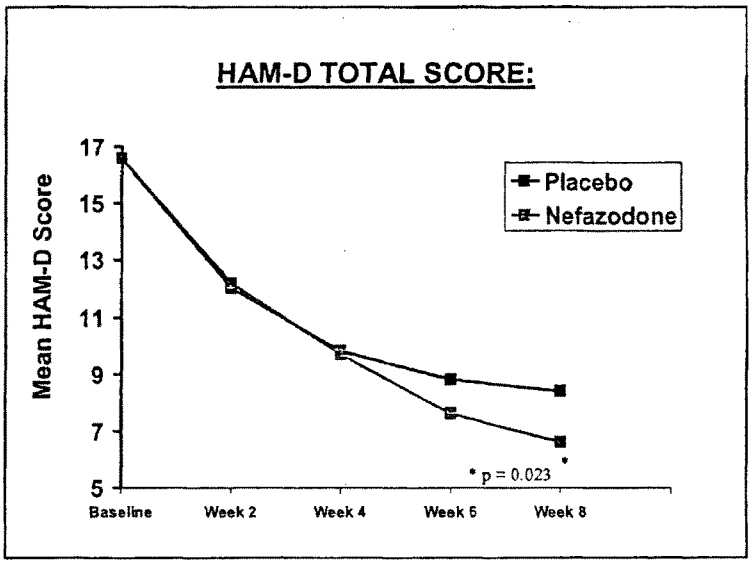
[a] Observed Cases (placebo N=59; nefazodone N=74)

SUMMARY OF EFFICACY RESULTS AT ENDPOINT
Last Observation Carried Forward, Week 8

Efficacy Sample	Placebo N = 92	Nefazodone N = 95	P-Value
CDRS-R Total Score			
Mean Change from Baseline[a,b]	-22.5	-26.5	0.055
Rate of Change/Week[a,c]	-2.78	-3.45	0.025
HAM-D Total Score			
Mean Change from Baseline[a,b]	-8.2	-10.0	0.023
Mean CGI Improvement Score[d]	2.8	2.3	0.012
% of Patients with CGI Response[d,e]	46	65	0.005
CGI Severity Score			
Mean Change from Baseline[a,b]	-1.3	-1.7	0.022
CGAS[b,f]	13.0	17.2	0.020

[a] Negative values indicate improvement.
[b] ANCOVA analysis with model terms for treatment group, study center and baseline score.
[c] Random effects longitudinal model fit to the actual scores at each week.
[d] CMH analysis stratified by study center.
[e] CGI Response = Very much or much improved.
[f] Positive values indicate improvement.


CDRS-R TOTAL SCORE:
Mean CDRS-R Score
65
60
55
50
45
40
35
30
Placebo
Nefazodone
** p = 0.006
* p = 0.055
Baseline
Week 2
Week 4
Week 6
Week 8


HAM-D TOTAL SCORE:
Mean HAM-D Score
17
15
13
11
9
7
5
Placebo
Nefazodone
* p = 0.023
Baseline
Week 2
Week 4
Week 6
Week 8

ADVERSE EVENTS ↓ 10% INCIDENCE*

Safety Sample	Placebo N = 95 (%)	Nefazodone N = 95 (%)
Body as a Whole		
Headache	45 (47.4)	53 (55.8)
Abdominal Pain	15 (15.8)	26 (27.4)
Digestive System		
Nausea	8 (8.4)	28 (29.5)
Vomiting	8 (8.4)	10 (10.5)
Nervous System		
Somnolence	14 (14.7)	24 (25.3)
Dizziness	3 (3.1)	19 (20.0)

[a] Nefazodone incidence greater than placebo.

CONCLUSIONS

- At Week 8, nefazodone showed greater improvement compared with placebo in the treatment of adolescents with a major depressive episode.
  - This improvement approached statistical significance for the Primary Efficacy Measure, the change from baseline in the CDRS-R Total Score.
  - For all other efficacy measures, including the HAM-D Score, the CGI responder analysis, the CGI Improvement Score, the CGI Severity Score, and the CGAS, nefazodone was demonstrated to be statistically more effective than placebo.
- Nefazodone was safe and well tolerated in this trial.
  - The rate of discontinuation for AEs was similar between the treatment groups.
  - No patients who received nefazodone experienced an SAE.
  - No clinically important cardiac risks or laboratory abnormalities were identified.
- In a second depression trial in pediatric patients (aged 7-17), nefazodone did not differentiate from placebo.

Efficacy and Safety of Venlafaxine ER in Children and Adolescents With Major Depressive Disorder

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ABSTRACT

Purpose: Venlafaxine extended release (ER) is an effective treatment for adults with major depressive disorder (MDD), but no controlled data are available in pediatric patients with MDD. The purpose of this research was to assess the efficacy and safety of venlafaxine ER in the treatment of children and adolescents with MDD

Methods: Results were combined from two, 8-week, multicenter, double-blind, flexible-dose studies in 137 children (age 7–11 years) and 197 adolescents (age 12–17 years) randomly assigned to receive venlafaxine ER (dosed by weight; n=169) or placebo (n=165). The primary efficacy variable was the Children's Depression Rating Scale-Revised (CDRS-R) total score; primary endpoint was the final on-therapy evaluation

Results: Venlafaxine-treated children had an adjusted mean decrease of -22.7 points on the primary efficacy variable versus -24.0 for the placebo group (P=0.53). Venlafaxine-treated adolescents had an adjusted mean decrease of -24.4 points on the primary efficacy variable versus -19.9 for the placebo group (P=0.022). The most common (at least 5% incidence at a rate twice placebo) adverse events were anorexia and abdominal pain. Hostility and suicide-related adverse events such as suicidal ideation and intentional injury occurred at a greater rate in the venlafaxine-treated group than in the placebo-treated group. There were no suicides in these studies

Conclusion: Venlafaxine ER may not be effective in depressed children, but may be effective in depressed adolescents. Prescribers should be alert to signs of suicidal ideation and hostility in pediatric patients taking venlafaxine

INTRODUCTION

- In children and adolescents, MDD is a common, chronic and recurrent condition that usually persists into adulthood. The prevalence of MDD is approximately 2% in children and 4% to 8% in adolescents.[1] These children and adolescents face a 2 to 4 greater risk of developing MDD as adults, and 4- to 5-fold higher lifetime risk of attempted suicide.[2,3] Treatment options include psychotherapy and psychopharmacological interventions. Venlafaxine ER, a serotonin-norepinephrine reuptake inhibitor, is an effective treatment for adults with MDD, generalized anxiety disorder, or social anxiety disorder. However, there is a lack of data regarding the safety and efficacy of venlafaxine ER in depressed pediatric patients

OBJECTIVE

- The primary objective of this research was to evaluate the safety and efficacy of venlafaxine ER treatment in child and adolescent outpatients with MDD

METHODS

Design

- Two, double-blind, placebo-controlled, randomized, parallel-group, flexible-dose studies were conducted in depressed children and adolescents who were outpatients at 52 sites

Supported by funding from Wyeth Research.

Presented at the American Psychiatric Association, New York, New York, May 1–6, 2004

This information contained in this poster concerns a use that has not been approved by the US Food and Drug Administration.

- After a single-blind, placebo run-in period (14-day duration in study 1 and 7-day duration in study 2), eligible patients (n=334) were randomly assigned to receive venlafaxine ER (n=169) or placebo (n=165)
- Study medication was administered once daily, and dosage was based on body weight (Table 1)
- Duration of treatment was up to 8 weeks, followed by ≤2-week tapered or blinded taper period

Inclusion Criteria

- Outpatients (7 to 17 years of age) with MDD diagnosis according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) and Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KIDDIE-SADS-PL) criteria at prestudy visit
- CDRS-R scores of >40 at prestudy and study day-1, and no greater than a 20% decrease in CDRS-R score between the prestudy screen and study day 1
- Clinical Global Impression–Severity of Illness (CGI-S) score >4 at study day 1
- Depressive symptoms for at least 1 month before entry into the studies

Exclusion Criteria

- No history of any psychotic disorder, bipolar disorder, MDD with psychotic features, anorexia or bulimia, conduct disorder, panic disorder or obsessive compulsive disorder; no first-degree relative with bipolar disorder, no recent drug or alcohol dependence or abuse, not acutely suicidal, and no serious medical problem or mental disorder due to general medical condition
- No use of venlafaxine within 6 months or fluoxetine within 21 days; no use of investigational drugs, antipsychotics, or electroconvulsive therapy within 30 days; no use of MAO inhibitors, triptans, or herbal products within 14 days; no use of any other antidepressants, anxiolytics, sedative-hypnotics, stimulants, other psychotropic drugs or substances or norpsychopharmacologic drugs with psychotropic effects (except if on stable dose for >1 month) within 14 days of start of on-therapy treatment period
- Lactating females or females of childbearing potential with a positive B-HCG test result during the prestudy evaluation

Efficacy Assessments

- CDRS-R at prestudy, baseline, and study days 4, 7, 14, 21, 28, 42, and 56
- 21-item HAM-D at prestudy, baseline, and study days 4, 7, 14, 21, 28, 42, and 56
- Montgomery-Asberg Depression Rating Scale (MADRS) total at prestudy, baseline, and study days 4, 7, 14, 21, 28, 42, and 56
- CGI at baseline (day 1, CGI-S only), and study days 4, 7, 14, 21, 28, 42, and 56

Safety Assessments

- Physical examination at prestudy and on study day 56
- Vital signs and weight at prestudy, baseline (day 1), on study days 4, 7, 14, 21, 28, 42, and 56, and at the poststudy visit
- Laboratory determinations (hematologic and blood chemistry tests, serum B-HCG pregnancy test and urinalysis) at prestudy and on study days 56
- Standard 12-lead ECG at prestudy, baseline (day 1), and study days 42 and 56

Statistical Analysis

- The primary efficacy variable was the CDRS-R total score based on the last-observation-carried-forward (LOCF) evaluation at week 8 visit
- The secondary efficacy variables were HAM-D total, HAM-D Depressed Mood item, MADRS total, and the CGI-S scores
- Primary and secondary efficacy scores were analyzed using ANCOVA with treatment and investigator as main effects and baseline scores as the covariate
- Patients whose CDRS-R total scores decreased by 35% or more from baseline were considered responders
- Patients whose HAM-D total scores decreased by 50% or more from baseline were considered responders
- Patients who achieved a score of 1 or 2 on the CGI-I scale were considered responders
- Patient responder status was analyzed using the Fisher exact test
- CGI-I scores were analyzed using a 2-way analysis of variance with treatment and investigator as factors
- An alpha level of 0.05 was considered significant. The primary population was the intent-to-treat population

Table 1. Daily Dosages of Venlafaxine (mg/day) by Patient Body Weight and Time Period

	Body Weight Range*		
Time Period	25–39 kg	40–49 kg	≥50 kg
Day 1–7	37.5	37.5	37.5
Day 8–14	37.5 or 75	75†	75†
Day 15–28	37.5 or 75	75 or 112.5	75 or 150
Day 29–56	37.5, 75, or 112.5	75, 112.5, or 150	75, 150, or 225

* All patients received 37.5 mg/day during the first week; doses after week 1 were as indicated for each body weight range.

† The dose increase was mandatory as per protocol.

- 375 patients were screened; 367 were randomized; 361 were included in the safety population; 334 were included in the intent-to-treat (ITT) population

Table 2. Demographics for Combined Studies

Characteristic	Venlafaxine ER	Placebo
Age		
Mean yrs	12.3±2.6	12.2±2.6
Range	7–17	7–17
Sex, n (%)		
Children (age ≤11 years)		
Female	27 (38)	25 (36)
Male	44 (62)	41 (62)
Adolescents (age >11 years)		
Female	46 (47)	56 (57)
Male	52 (53)	43 (43)
Ethnic origin, n (%)		
White	122 (72)	137 (83)
Nonwhite	47 (28)	28 (17)
Severity* of Illness		
Less severe	95 (57)	96 (60)
More severe	71 (43)	65 (40)

* Patients with less severe illness had baseline CGI-S scores of ≤4; patients with more severe illness had baseline CGI-S score of >4.

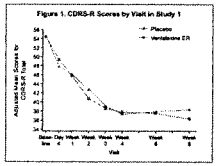
RESULTS

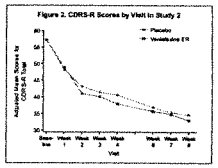
Efficacy

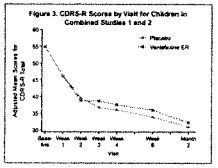
- Last-observation-carried-forward (LOCF) analysis of ITT patients indicated no significant changes between venlafaxine ER and placebo treatment groups in CDRS-R, HAM-D total, HAM-D Depressed Mood item, MADRS total, CGI-S, and Clinical Global Impression–Improvement (CGI-I) scores at week 8 in either study 1 or study 2
- There was no statistically significant difference with regard to responder rates between placebo and venlafaxine-treated patients measured by CDRS-R total, HAM-D total, MADRS, and CGI-I scores in either study 1 or study 2
- A pooled analysis, using the definition of adolescents as age 12 to 17 years (n=197), and children as age 7 to 11 years (n=137), was performed by combining the results of the 2 studies. In this analysis venlafaxine-treated children had an adjusted mean decrease of −22.7 points on the CDRS-R score versus −24.0 for the placebo group (P=0.53). Venlafaxine-treated adolescents had an adjusted mean decrease of −24.4 points on the CDRS-R score versus −19.9 for the placebo group (P=0.02)

Safety

- Serious adverse events (SAEs) occurred in 14 (8%) patients in the venlafaxine treatment group, and five (3%) patients in the placebo group. For the 14 venlafaxine-treated patients, the SAEs included: suicidal ideation (2%), suicide attempt (2%), agitation/hostility (2%), and manic reaction (1%). There were no suicides, and no deaths
- Adverse events were the primary cause of discontinuation for 18 (10%) of venlafaxine-treated patients and 5 (3%) of the placebo-treated patients. Adverse events cited as the reasons for discontinuation (venlafaxine group ≥1%) included: suicidal ideation (2%), hostility (2%), overdose (1%), and manic reaction (1%)
- The most common treatment-emergent adverse events (TEAEs) that occurred in at least 5% of venlafaxine treated patients at a rate that was at least twice the rate with placebo) were anorexia (7% in the venlafaxine group and 2% in the placebo group), and abdominal pain
- Six (3%) of venlafaxine-treated patients, and no patients in the placebo group had suicidal ideation adverse events, but all of these patients had suicidal ideation at prestudy or baseline
- Five (3%) patients in the venlafaxine treatment group, and 2 (1%) patients in the placebo group, and had hostility adverse events
- No patient had a sustained increase in supine diastolic blood pressure
- Three venlafaxine-treated patients withdrew from the studies because of vital sign or weight abnormalities
- There were no significant mean changes in PR interval, or QTc interval







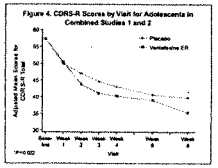


Table 3. Most Common (≥10%) TEAEs: Number (%) of Patients

Body System TEAE	Venlafaxine ER (n=182)	Placebo (n=179)
Any Adverse Event	157 (86)	143 (79)
Body as a whole		
Abdominal Pain	38 (21)	16 (10)
Accidental injury	19 (10)	12 (7)
Asthenia	10 (5)	13 (7)
Headache	63 (35)	62 (35)
Digestive system		
Nausea	30 (16)	15 (8)
Nervous system		
Dizziness	21 (12)	11 (6)
Insomnia	18 (10)	10 (6)
Respiratory system		
Pharyngitis	19 (10)	19 (11)
Rhinitis	13 (7)	18 (10)
Urogenital system		
Dysmenorrhea*	6 (10)	7 (8)

* Based on the number of females: venlafaxine ER (n=62); placebo (n=68)

CONCLUSIONS

- In study 1, children and adolescents in the venlafaxine ER group had an adjusted mean (±SE) decrease of 18.1±1.56 points on the primary efficacy variable, compared with a 18.1±1.51 point decrease for patients in the placebo group, which was not statistically significant (P=0.338)
- In study 2, children and adolescents in the venlafaxine ER group had an adjusted mean (±SE) decrease of 24.3±1.25 points on the primary efficacy variable, compared with a 22.8±1.41 point decrease for patients in the placebo group, which was not statistically significant (P=0.386)
- In the pooled analysis, children in the venlafaxine ER group had an adjusted mean (±SE) decrease of 24.0±1.47 points on the primary efficacy variable, compared with a 22.7±1.46 point decrease for patients in the placebo group, which was not statistically significant (P=0.528)
- In the pooled analysis, adolescents in the venlafaxine ER group had an adjusted mean (±SE) decrease of 24.4±1.34 points on the primary efficacy variable, compared with a 19.9±1.36 point decrease for patients in the placebo group, which was statistically significant (P=0.022)
- Venlafaxine ER may not be effective in depressed children, but may be effective in depressed adolescents
- Prescribers should be alert to signs of suicidal ideation and hostility in pediatric patients taking venlafaxine

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2. Weissman MM, Wolk S, Wickramaratne P, et al. Children with prepubertal-onset major depressive disorder and anxiety grown up. *Arch Gen Psychiatry* 1999;56:794–801.
3. Weissman MM, Wolk S, Goldstein RB, et al. Depressed adolescents grown up. *JAMA* 1999;281:1707–1713.

Long-Term Efficacy and Safety of Venlafaxine ER in Children and Adolescents With Major Depressive Disorder

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ABSTRACT

Purpose: Venlafaxine extended release (ER) is an effective treatment for adults with major depressive disorder (MDD) but no long-term data are available in pediatric patients with MDD. The purpose of this study was to review the long-term efficacy and safety data regarding venlafaxine ER in the treatment of children and adolescents with MDD.

Methods: A multicenter, open-label study enrolled 87 children and adolescents (aged 7–17 years) who received flexible doses of venlafaxine ER for up to 6 months. The primary efficacy variable was the Children's Depression Rating Scale–Revised (CDRS-R) total score; the primary endpoint was the final on-therapy evaluation.

Results: Venlafaxine-treated children and adolescents had a baseline mean CDRS-R total score of 60.1, which steadily decreased to a final on-therapy mean CDRS-R total score of 24.3 at month 6 (observed cases [OC]; 33.8 on last observation carried forward [LOCF]). The percentage of patients responding to treatment, as measured by the CDRS-R total, Hamilton Psychiatric Rating Scale for Depression (HAM-D) total, and Clinical Global Impression-Improvement (CGI-I) scores, increased over time. The most common treatment-emergent adverse events were headache (53%), nausea (25%), infection (24%), abdominal pain (22%), vomiting (21%), and pharyngitis (19%). Two venlafaxine-treated patients had hostility, and 2 patients had suicide attempts, all of which led to discontinuation from the study. There were no suicides in this study.

Conclusion: Long-term treatment with venlafaxine ER was associated with progressive improvement over time. Prescribers should be alert to signs of suicidal ideation in pediatric patients taking venlafaxine.

INTRODUCTION

In children and adolescents, MDD is a common, chronic, and recurrent condition that usually persists into adulthood. The prevalence of MDD is approximately 2% in children and 4% to 8% in adolescents.[1] These children and adolescents have a 2 to 4 times greater risk of developing MDD as adults, and 4- to 5-fold higher lifetime risk of attempted suicide.[2] Treatment options include psychotherapy and psychopharmacological interventions. After successful acute therapy, approximately 40% to 50% of depressed patients experience a relapse.[3] Venlafaxine ER, a serotonin-norepinephrine reuptake inhibitor, is an effective treatment for adults with depression or generalized anxiety disorder. However, there is a lack of data regarding the safety and efficacy of venlafaxine ER in pediatric patients with depression.

OBJECTIVES

- The primary objective of this study was to evaluate the safety and clinical acceptability of venlafaxine ER during long-term treatment in child and adolescent outpatients with major depressive disorder.
- The secondary objective was to evaluate efficacy through a 6-month treatment period.

METHODS

Design

- Multicenter, open-label study in depressed children and adolescents who were outpatients.
- Study medication was administered once daily and dosed by body weight.
- Eighty-seven (87) patients entered the on-therapy period; 65 were analyzed for safety; 65 were analyzed for efficacy; and 36 completed the 6-month, on-therapy period.
- Treatment duration consisted of a 7 ± 3-day prestudy period, up to 6 months of treatment with venlafaxine ER, followed by up to a 14-day taper period.

Inclusion Criteria

- Children and adolescents (aged 7 to 17 years) meeting the following criteria:
  - Diagnostic and Statistical Manual (DSM-IV) and Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KIDDIE-SADS-PL) criteria for MDD at prestudy visit
  - Children's Depression Rating Scale-Revised (CDRS-R) scores of ≥ 40 at prestudy and on study day 1
  - Clinical Global Impression–Severity (CGI-S) score ≥ 4 at prestudy and study day 1
  - Depressive symptoms for at least 1 month before entry into the study

Exclusion Criteria

- Patients with the following were excluded: mental disorder due to general medical condition; recent drug or alcohol dependence or abuse; history of a seizure disorder; any psychotic disorder; bipolar disorder; MDD with psychotic features; conduct disorder; anorexia or bulimia; first-degree relative with bipolar disorder; or actively suicidal.
- Patients who used the following were excluded: venlafaxine within 8 months; fluoxetine within 35 days; investigational drugs; antipsychotics or electroconvulsive therapy within 30 days; monoamine oxidase inhibitors, triptans, or herbal products within 14 days; any other antidepressants, anxiolytics, sedative-hypnotics, stimulants, other psychotropic drugs or substances or nonpsychopharmacologic drugs with psychotropic effects (except if on stable dose for >1 month) within 7 days of start of double-blind treatment.
- Psychotherapy was permitted if well established before study.

Efficacy Assessments

- Primary: CDRS-R at prestudy, baseline, and study days 7, 14, 21, 28, 42, 60, 90, 120, 150, and 180.
- Secondary:
  - HAM-D total and depressed mood item scores (21 items) at prestudy, baseline, and study days 28, 90, and 180.
  - CGI-S at prestudy, baseline, and study days 7, 14, 21, 28, 42, 60, 90, 120, 150, and 180.
  - CGI-I at study days 7, 14, 21, 28, 42, 60, 90, 120, 150, and 180.

Safety Assessments

- Adverse events
- Physical examination including vital signs, height, and weight, and laboratory examinations.
- Electrocardiograms
- Treatment-emergent adverse events were those not present during the last 7 days of full dose medication, or events that became more severe after the last 7 days of full dose medication.

Statistical Analysis

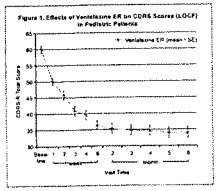
- The primary efficacy variable was the CDRS-R total score based on the LOCF principle.
- The secondary efficacy variables were HAM-D total and depressed mood item scores, and the CGI rating scores.
- Patients whose CDRS-R total scores decreased by 35% or more from baseline were considered responders.
- Patients whose HAM-D total scores decreased by 50% or more from baseline were considered responders.
- Patients who achieved a score of 1 or 2 on the CGI-I scale were considered responders.
- An alpha level of 0.05 was considered significant. The primary population was the intent-to-treat (ITT) population.

RESULTS

Table 1. Demographic Characteristics

Characteristics	Venlafaxine ER (n=65)
Age	
Mean yrs ± SD	12.3 ± 2.9
Range	7 – 17
Sex, n (%)	
Female	41 (48)
Male	44 (52)
Ethnic origin, n (%)	
White	59 (69)
Black	15 (18)
Hispanic	7 (8)
Native American	1 (1)
Asian	1 (1)
Other	2 (2)
Weight	
Mean kg ± SD	55.4 ± 20.2
Range	23.2 – 121.6
Height	
Mean cm ± SD	154.1 ± 14.5
Range	121.4 to 182.9
Duration of current episode	
Mean wks ± SD	12.3 ± 67.6
Range	4.6 – 256.4
Duration of current episode, n (%)	
5 – 12	11 (13)
13 – 24	13 (15)
25 – 48	18 (21)
49 – 96	20 (24)
>96	23 (27)

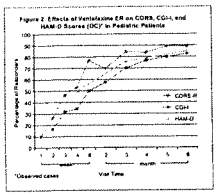
Figure 1. Effects of Venlafaxine ER on CDRS Scores (LOCF) in Pediatric Patients



Efficacy

- LOCF and OC analyses indicated progressive improvement on the CDRS-R score, as well as HAM-D total, HAM-D depressed mood item, CGI-S, and CGI-I scores.
- The baseline CDRS-R total score was 60.1, which steadily decreased to a final on-therapy mean score of 33.8 (LOCF data) and 24.3 (OC data) at month 6.
- The percentage of patients responding to venlafaxine treatment, as measured by CDRS-R total, HAM-D total, and CGI-I scores, increased over time.

Figure 2. Effects of Venlafaxine ER on CDRS, CGI-I, and HAM-D Scores (OC)* in Pediatric Patients



*Observed cases

Table 3. Baseline Scores

CDRS-R	
Mean scores ± SD	60.1 ± 10.0
Range	41 – 86
HAM-D total	
Mean scores ± SD	19.1 ± 6.0
Range	6 – 35
Depressed mood item	
Mean scores ± SD	2.8 ± 0.7
Range	1 – 4
CGI - Severity	
Mean scores ± SD	4.3 ± 0.7
CGI - Severity, n (%)	
3	1 (1)
4	48 (56)
5	27 (32)
6	9 (11)

CDRS-R = Children's Depression Rating Scale–Revised
CGI-I = Clinical Global Impressions - Improvement
CGI-S = Clinician Global Impressions - Severity of Illness
HAM-D = Hamilton Psychiatric Rating Scale for Depression

Table 2. Mean Daily Dose by Time Interval Including Days of Missed Dose

Time Interval	n	Daily Dose (mean ± SD) mg/kg
On-therapy period (excludes taper dose)		
Week 1	85	0.8 ± 0.3
Week 2	84	1.3 ± 0.5
Week 3	81	1.8 ± 0.6
Week 4	78	2.0 ± 0.6
Week 5 – 6	74	2.4 ± 0.8
Week 7 – 8	68	2.5 ± 0.8
Month 3	67	2.6 ± 0.8
Month 4	55	2.6 ± 0.8
Month 5	47	2.5 ± 0.8
Month 6	44	2.5 ± 0.8
Month > 6	22	2.5 ± 0.8
Taper	24	1.3 ± 0.4

Table 4. Most Common (≥ 10%) TEAEs Number (%) of Patients

Body System TEAE	Venlafaxine ER (n=88)
Any Adverse Event	83 (97)
Body as a whole	
Abdominal pain	19 (22)
Accidental injury	13 (15)
Asthenia	13 (15)
Headache	46 (53)
Infection	21 (24)
Pain	9 (10)
Digestive system	
Dyspepsia	10 (12)
Nausea	22 (25)
Vomiting	18 (21)
Nervous system	
Dizziness	10 (12)
Insomnia	10 (12)
Nervousness	13 (15)
Respiratory system	
Cough increased	9 (10)
Pharyngitis	16 (19)
Rhinitis	10 (12)
Upper respiratory infection	13 (15)
Unspecified system	
Dysmenorrhea*	7 (17)

*Based on the number of females, n = 41

Table 5. Number (%) of Patients Who Discontinued by Primary Reason

Primary Reason	Venlafaxine ER (n=88)
Any reason	50 (58)
Adverse event	15 (17)
Failed to return	14 (16)
Other noncompliance	8 (7)
Patient request unrelated to study	5 (6)
Unsatisfactory response-efficacy	5 (6)
Protocol violation	5 (6)

Safety

- Seven (7) patients had serious adverse events.
- Two (2) patients were hospitalized because of suicide attempts (small bottles); 1 occurred 2 days following study discontinuation, and 1 occurred while actively taking study medication; the investigators considered these not related to study medication.
- There were no patient deaths during this study.
- Two patients were hospitalized because of hostility resulting in discontinuation from the study; investigators considered one (1) to be not related and one (1) possibly related to study medication.
- Adverse events were the primary cause of discontinuation for 15 (17%) patients. The adverse event that most frequently caused discontinuation of treatment was hostility (2%).
- The most common treatment-emergent adverse events were headache (53%), nausea (26%), infection (24%), abdominal pain (22%), vomiting (21%), and pharyngitis (19%).
- Taper/probably emergent adverse events were reported by 29 (33%) of the patients treated with venlafaxine ER. Headache (12%) and dizziness (9%) were the most frequently reported events.
- At final on-therapy, supine pulse and diastolic blood pressure were 2.14 beats/min and 0.84 mm Hg higher, respectively than baseline values.
- At final on-therapy, mean body weight increased 0.04 kg. Significant mean decreases in body weight occurred at weeks 3 ($P < 0.01$) through 4 ($P < 0.001$), week 8 ($P < 0.001$), and month 2 ($P < 0.01$).
- There were no significant mean changes in PR interval, or QTc interval.

CONCLUSIONS

- Long-term treatment with venlafaxine ER was associated with progressive improvement over time based on results from both LOCF and OC analyses of the primary variable, CDRS-R total score, as well as the secondary variables, HAM-D total, HAM-D depressed mood item, CGI-S, and CGI-I scores.
- In addition a responder analyses showed that the percentage of patients responding to treatment, as measured by the efficacy variables CDRS-R total, HAM-D total, and CGI-I scores, increased over time.
- The administration of venlafaxine ER was associated with few clinically important changes in laboratory test results, vital signs and weight, or ECGs.
- Prescribers should be alert to signs of suicidal ideation and hostility in pediatric patients taking venlafaxine.

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The information contained in this poster comes in part from data not been approved by the US Food and Drug Administration.

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Venlafaxine ER in the Treatment of Children and Adolescents With Generalized Anxiety Disorder

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ABSTRACT

Objective: To determine if venlafaxine ER is an effective treatment for children and adolescents with generalized anxiety disorder (GAD).

Methods: Results were combined from two 8-week, multicenter, placebo-controlled, double-blind, flexible-dose studies in 175 children (aged 6–11 years) and 145 adolescents (aged 12–17 years) randomly assigned to receive venlafaxine ER (dosed by weight: n = 157) or placebo (n = 163). The primary efficacy variable was the Columbia- K-DIDIE Schedule for Affective Disorders and Schizophrenia (C-KIDDIE-SADS) GAD total score for 9 delineated items; the primary endpoint was the final on-therapy evaluation. Secondary efficacy variables were total scores on the C-KIDDIE-SADS GAD (also individual severity and impairment scores), Pediatric and Anxiety Rating Scale (PARS), Hamilton Anxiety Rating Scale (HAM-A), Self Report for Childhood Anxiety Related Disorders (SCARED) Parent and Child Forms, and Clinical Global Impression–Severity of Illness (CGI-S) and Cynical Global Impression–Improvement (CGI-I) scales.

Results: Venlafaxine-treated patients had an adjusted mean decrease of 17.4 points on the primary efficacy variable versus 12.7 for the placebo group ($P < 0.001$). Secondary measure results were similar. Response (CGI-I score ≤ 3) rates were 69% and 48% for the venlafaxine and placebo groups, respectively ($P = 0.004$). The most common (≥ 5% and twice that of placebo) adverse events were asthenia, anorexia, pain, and somnolence. There were no suicides in these studies.

Conclusion: Venlafaxine ER may be an effective treatment in children and adolescents with GAD. Prescribers should be alert to signs of suicidal ideation in pediatric patients taking venlafaxine.

INTRODUCTION

- Anxiety disorders are the most common psychiatric illnesses in children.[1] Although they cause substantial distress and interfere with academic as well as social functioning, anxiety disorders are often untreated. An anxiety disorder during childhood or adolescence confers a strong risk for recurrent anxiety or depressive disorders during adulthood. Generalized anxiety disorder in particular has been found to strongly predict various adult anxiety and mood disorders.[2]
- Venlafaxine extended release (ER), a serotonin-norepinephrine reuptake inhibitor, is an effective treatment for adults with depression or GAD, but few studies are available on the safety and efficacy of venlafaxine ER in pediatric patients with GAD.
- The objective of this poster is to present the combined results of 2 identical, large, and methodologically sound trials that evaluated the efficacy, safety, and tolerability of venlafaxine ER as a treatment for children and adolescents with GAD.

METHODS

Study Design

- Double-blind, placebo-controlled, parallel-group, flexible-dose studies conducted at a total of 59 sites in the United States
- After a 7-day single-blind placebo run-in period, eligible patients (n = 320) were randomly assigned to receive venlafaxine ER (n = 157) or placebo (n = 163).

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- Treatment assignment was stratified by age group: 175 children (6–11 years old) and 145 adolescents (12–17 years old) were randomly assigned to 1 of 2 treatments.
- Study medication was administered once daily and dosage was based on body weight (Table 1).
- Duration of treatment was up to 8 weeks, followed by ≤ 2-week tapered taper period.

Patients

- Outpatients aged 6 to 17 years with symptoms of anxiety for ≥ 6 months who met DSM-IV and C-KIDDIE-SADS criteria for GAD were in good health and weighed > 15 kg.
- Required scores on C-KIDDIE SADS GAD at screening and baseline (day 1):
  - Severity component (9 delineated items)
    - total score ≥ 20
    - all severity item score ≥ 4 (moderate)
  - Impairment component (4 delineated items)
    - total score ≥ 7
    - global impairment in functioning item score ≥ 4
- CGI-S score ≥ 4 at screening and baseline (day 1)
- Patients with the following were excluded: concurrent major depressive disorder (patients had to have a Children's Depression Rating Scale-Revised [CDRS-R] score ≤ 45 at screening and baseline); acutely suicidal; concurrent psychiatric disorder (except simple phobia) as confirmed by KIDDIE-SADS-PL; mental disorder due to generalized medical condition; recent drug or alcohol dependence or abuse; history of a seizure disorder; any psychotic disorder; bipolar disorder, anorexia, or bulimia; first degree relative with bipolar disorder
- Other exclusion criteria included use of venlafaxine within 6 months; use of fluoxetine within 35 days; use of investigational drugs; antipsychotic or electroconvulsive therapy within 30 days; use of MAO inhibitors, triptans, or herbal products within 14 days; use of any other antidepressants, anxiolytics, sedative hypnotics, stimulants, other psychotropic drugs or substances or nonpsychopharmacologic drugs with psychotropic effects (except if on stable dose for ≥ 1 month) within 7 days of start of double blind treatment
- Psychotherapy was permitted if well established before study.

Efficacy Assessments

- C-KIDDIE SADS GAD subsection (complete) at screening and days 1, 28, and 56
- C-KIDDIE SADS GAD (9 delineated items) only at days 7, 14, 21, 42, and 49
- PARS at days 1, 7, 14, 21, 28, 42, 49, and 56
- HAM-A at days 1, 28, and 56
- SCARED Parent and Child Forms at days 1, 28, and 56
- CGI-I at days 7, 14, 21, 28, 42, 49, and 56
- CGI-S at screening and days 1, 7, 14, 21, 28, 42, 49, and 56

Safety Assessments

- Adverse events, vital signs, and weight were recorded at each visit.
- Physical examination and laboratory determinations were made at pretrial screening and on study day 56, or at early termination.
- ECG was performed at pretrial screening and study days 1 and 56, or early termination.

Statistical Analysis

- The population analyzed consists of all randomly assigned patients who had taken ≥ 1 dose of test medication; had a baseline evaluation for the primary efficacy variable; and had ≥ 1 evaluation for the primary efficacy variable while on therapy or within 3 days of the last full dose (intent-to-treat population).
- The primary efficacy variable was the C-KIDDIE SADS GAD total score for the 9 delineated items.
- The primary efficacy time point was the week 8 last-observation carried forward evaluation.
- Response was defined as CGI-I score ≤ 3.
- C-KIDDIE SADS GAD Severity and Impairment Component scores, C-KIDDIE-SADS GAD (complete) total score, PARS total score, HAM-A total score, CGI-S score, SCARED parent and patient total scores were analyzed using an analysis of covariance with treatment and investigator as main effects, and baseline score as the covariate.
- CGI-I scores were analyzed using a 2-way analysis of variance with treatment and investigator as factors.
- Patient responder status was analyzed using the Fisher exact test.

RESULTS

Table 1. Daily Dosages of Venlafaxine (mg/day) by Patient Body Weight and Time Period

Time Period	Body Weight Range*		
	25 to 39 kg	40 to 49 kg	≥50 kg
Days 1 to 7	37.5	37.5	37.5
Days 8 to 14	37.5 or 75	75†	75†
Days 15 to 28	37.5 or 75	75 or 112.5	75 or 150
Days 29 to 56	37.5, 75, or 112.5	75, 112.5, or 150	75, 150, or 225

*All patients received 37.5 mg/day during the first week (mean after week 1 were as indicated for each body weight range.
†This dose increase was mandatory per protocol.

Table 2. Mean Demographic and Baseline Characteristics

	Placebo	Venlafaxine ER
Age ± SD (years)	11.2 ± 2.6	11.5 ± 2.3
Girls (%)	77	56
Boys (%)	82	98
Height ± SD (cm)	148.4 ± 15.1	149.8 ± 16.4
Weight ± SD (kg)	50.3 ± 19.7	50.3 ± 19.2
Duration of GAD ± SD (weeks)	164.7 ± 133.8	175.1 ± 153.6
C-KIDDIE SADS GAD (complete) ± SD	74.8 ± 5.5	74.4 ± 5.0
C-KIDDIE SADS GAD (9 delineated) ± SD	40.4 ± 4.3	39.8 ± 3.8
C-KIDDIE SADS Severity ± SD	23.6 ± 2.8	23.6 ± 2.5
C-KIDDIE SADS Impairment ± SD	16.4 ± 2.0	16.2 ± 2.3
PARS ± SD	23.4 ± 3.1	24.1 ± 3.3
CGI Severity	4.5 ± 0.6	4.4 ± 0.7

Figure 1. C-KIDDIE-SADS GAD (9 delineated items) Raw Scores by Visit for Study 1

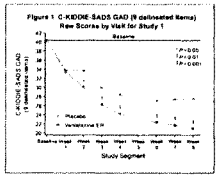


Figure 2. C-KIDDIE-SADS GAD (9 delineated items) Raw Scores by Visit for Study 2

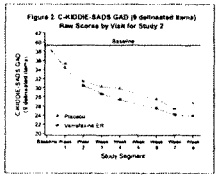


Figure 3. C-KIDDIE-SADS GAD (9 delineated items) Raw Scores by Visit for Pooled Studies

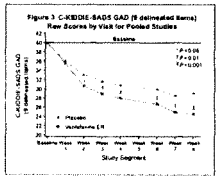


Figure 4. PARS Raw Scores by Visit for Pooled Studies

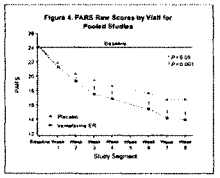


Table 3. Number (%) of Patients Who Discontinued Treatment and Primary Reason for Discontinuation

Reason	Placebo (N=163)	Venlafaxine ER (N=157)
Any reason	41 (25)	37 (24)
Adverse event	9 (6)	3 (2)
Failed to return	14 (9)	12 (8)
Other event	4 (2)	6 (4)
Patient request unrelated to study	4 (2)	4 (3)
Protocol violation	3 (2)	4 (3)
Unsatisfactory response	7 (4)	8 (5)

Figure 5. CGI-S Raw Scores by Visit for Pooled Studies

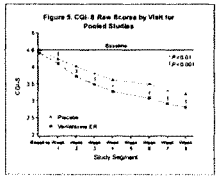
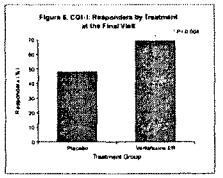


Figure 6. CGI-I: Responders by Treatment at the Final Visit



CONCLUSIONS

- In study 1, children and adolescents in the venlafaxine ER group had an adjusted mean (±SE) decrease of 18.6 ± 1.16 points on the primary efficacy variable, compared with a 12.4 ± 1.18 point decrease for patients in the placebo group, which was statistically significant ($P < 0.001$).
- In study 2, children and adolescents in the venlafaxine ER group had an adjusted mean (±SE) decrease of 15.5 ± 1.12 points on the primary efficacy variable, compared with a 13.0 ± 1.17 point decrease for patients in the placebo group, which was not statistically significant ($P = 0.06$).
- In the pooled analysis, children and adolescents in the venlafaxine ER group had an adjusted mean (±SE) decrease of 17.4 ± 0.80 points on the primary efficacy variable, compared with a 12.7 ± 0.84 point decrease for patients in the placebo group, which was statistically significant ($P < 0.001$).
- Similar results were obtained on the secondary measures, and the results in children were similar to the results in adolescents.
- Response rates were significantly higher in the venlafaxine ER group (69%) than in the placebo group (48%, $P = 0.004$).
- Three of 157 patients in the venlafaxine ER group (2%) discontinued from the study because of adverse events, compared with 3 of 163 placebo patients (6%).
- The most common treatment-related adverse events (incidence ≥ 5% and twice that of placebo) were asthenia, anorexia, pain, and somnolence. There were no significant differences between groups in the number of patients who discontinued for any reason. However, the rate of discontinuation for adverse events as a primary reason in the placebo group was 3 times that in the venlafaxine ER group.
- Venlafaxine ER may be an effective and well tolerated treatment for children and adolescents with GAD.
- Prescribers should be alert to signs of suicidal ideation and hostility in pediatric patients taking venlafaxine.

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Venlafaxine ER in Children and Adolescents With SAD

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INTRODUCTION

- Social anxiety disorder (SAD) is a prevalent, chronic, and disabling disorder characterized by an extreme fear of social or performance situations that may cause embarrassment. Exposure to such situations is almost always accompanied by an immediate anxiety response and patients generally avoid them or endure them with distress[1].
- The onset of SAD most often occurs during early to late adolescence and persists into adulthood. It is associated not only with impairments of overall functioning, but with the development of generalized anxiety disorder, depression, and personality disorders.
- Selective serotonin reuptake inhibitors, such as sertraline and paroxetine, and the serotonin-norepinephrine reuptake inhibitor venlafaxine ER, have demonstrated efficacy in the treatment of SAD in adults[2-4]; however, few if any randomized controlled studies examining the effects of treatment in children and adolescents with a specific diagnosis of SAD have been performed.
- This study was conducted to determine the anxiolytic efficacy, safety, and tolerability of venlafaxine ER in the treatment of children and adolescent outpatients with generalized SAD.

METHODS

Participants

- Outpatient children or adolescents (aged 6 through 17 years) who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for generalized social anxiety disorder as verified by completion of the Anxiety Disorders Interview Schedule (ADIS) Child and Parent versions and completion of the DSM-IV diagnostic criteria checklist for adolescent generalized social anxiety disorder without any other clinically significant Axis I or II disorders including major depressive disorder, current or within 6 months of study enrollment
- Social Anxiety Scale for Children (SASC) or Adolescents (SASA) prestudy and baseline (study day 1) scores ≥50
- Childhood Depression Rating Scale (CDRS) total score ≤40 at prestudy screen; ≤2 on item 11 (depressed feelings); ≤3 on item 13 (suicidal ideation); and ≤3 on item 15 (depressed affect)
- Clinical Global Impression- Severity of Illness (CGI-S) score ≥4 at prestudy and baseline (study day 1)
- Symptoms sufficient to require anxiolytic drug therapy
- 457 patients were screened; 293 were randomly; 285 were included in the intent-to-treat (ITT) population

Study Design

- Multicenter, randomized, placebo-controlled, double-blind, 16-week flexible-dose (dosage range determined by weight) trial of venlafaxine ER in children and adolescent outpatients (aged 7 to 17 years) who met DSM-IV criteria for generalized social anxiety disorder
- 7 ± 3-day prestudy screening period
- 16-week, randomized, double-blind, placebo-controlled period (on therapy period)
- Safety and efficacy evaluations performed on study days 7, 14, 28, 56, 84, and 112
- ± 14-day taper period

Outcome Measures

Primary

- SASC-Revised (SASC-R) for ages 8 to 11 and SASA for ages 12 to 17 combined into single outcome variable Social Anxiety Scale for Children and Adolescents (SAS CA)

Secondary

- Clinical Global Impression- Improvement (CGI-I) response (ie a rating of 1 very much improved or 2 much improved)
- Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS-CA)

Statistical Analysis

- Primary endpoint: final score on therapy
- Primary population: intent to treat, ie, all patients who had baseline primary efficacy evaluation, took at least 1 dose of double-blind study drug, and had at least 1 primary efficacy evaluation on therapy (within 3 days of last dose)
- SAS-CA total score analysis of covariance (ANCOVA) with treatment, age, and sex as main effects, and baseline score as covariate
- LSAS-CA total score: ANCOVA with treatment, age, and sex as main effects, and baseline score as covariate
- CGI-I response rate: logistic regression with treatment as a factor and baseline SAS-CA score as covariate
- Treatment-emergent adverse events (TEAEs): Fisher exact test

RESULTS

Table 1. Venlafaxine ER Doses (mg/day) by Study Day

Body Weight (kg) / Study Days	Dosage (mg/day)
25–33	
1–7	37.5
8–28	37.5 or 75
29–112	37.5 or 75 or 112.5
34–49	
1–7	37.5
8–14	75
15–21	75 or 112.5
22–112	75 or 112.5 or 150
≥50	
1–7	37.5
8–14	75
15–21	75 or 150
22–112	75 or 150 or 225

Table 2. Description of Social Anxiety Scales

Scale	Description
Social Anxiety Scale for Children–Revised	Self-assessment instrument consisting of 18 descriptive self-statements and 4 filler items with responses to each item rated using a 5-point scale from 1 (not at all) to 5 (all the time). Three factors have been identified: Fear of Negative Evaluation (FNE); Social Avoidance and Distress–New Situations (SAD-New); and General Social Avoidance and Distress (SAD-General)
Liebowitz Social Anxiety Scale	Clinician-rated assessment scale for children and adolescents, modified from the LSAS for adults. Consists of 24 items: 13 social interaction situations and 11 performance situations. Ratings of anxiety from 0 (none) to 3 (usually) and avoidance from 0 (none) to 3 (usually), are given for each item, for a total of 48 ratings

Table 3. Demographic and Baseline Characteristics ITT Population

Characteristic	Placebo (n=148)	Venlafaxine ER (n=137)
Age (years)		
Mean ± SD (range)	13.6 ± 2.63 (8-18)	13.6 ± 2.46 (8-17)
Sex, n (%)		
Female	83 (56)	78 (57)
Male	65 (44)	59 (43)
Ethnic origin		
White	110 (74)	104 (76)
Black	15 (10)	20 (15)
Hispanic	17 (11)	7 (5)
Asian	2 (1)	2 (1)
Native American	1 (<1)	1 (<1)
Other	3 (2)	3 (2)
Weight (kg)		
Mean ± SD (range)	61.9 ± 20.3 (26–128)	59.9 ± 20.9 (26–130)
Duration of current episode, months	39 ± 39 †	57 ± 36
Duration of current episode (months), n (%)		
0 to <12	12 (8)	7 (5)
12 to 24	16 (11)	15 (11)
24 to 36	21 (14)	26 (19)
36 to <48	18 (12)	17 (12)
48 to <60	20 (14)	15 (11)
≥60	61 (41)	57 (42)
Baseline scores		
SAS-CA (range)	66.2 ± 10.5 (31–88)	64.8 ± 10.1 (48–85)
LSAS Total	91.1 ± 22.4	88.4 ± 24.2
CGI-S, n (%)		
4	49 (33)	52 (38)
5	70 (47)	63 (46)
6	29 (19)	22 (16)
7	1 (1)	0 (0)

Table 4. Selected Final On-Therapy Assessments

	Placebo N=148	Venlafaxine ER N=137
SAS-CA* (last-observation) mean	50.6 (30.6)	42.4* (43.0)
LSAS-CA* (last-observation) mean	65.9 (97.8)	47.9* (52.8)
CGI-I†, n (%)	54.0 (37.9)	76.0* (56.0)

*ANCOVA with treatment, age, and sex as main effects, and baseline score as covariate. †ANCOVA with treatment, age, and sex as main effects, and baseline score as covariate. ‡Logistic regression with treatment as factor and baseline SAS-CA score as covariate
*P < 0.001. †P < 0.001

Table 5. Treatment-Emergent Adverse Events*

	Placebo (n=150) n (%)	Venlafaxine ER (n=140) n (%)	P-value†
Asthenia	14 (9)	28 (20)	0.012
Anorexia	5 (3)	31 (22)	<0.001
Nausea	17 (11)	32 (23)	0.012
Weight loss	4 (3)	15 (11)	0.008
Abnormal/ Changed behavior	0	6 (4)	0.012
Pharyngitis	13 (9)	26 (19)	0.016
Mydriasis	0	6 (4)	0.012

*Safety population, includes TEAEs that occurred during the double-blind period at an incidence ≥ 2% and at least twice the placebo rate, and for which the difference between placebo and venlafaxine ER groups was statistically significant. †Fisher exact test

Table 6. Selected Final On-Therapy Safety Assessments*

	Placebo (N=109)	Venlafaxine ER (N=109)	P-value†
ECG Findings			
ECG Heart Rate (bpm)	71	77	<0.001
PR interval (msec)	142	138	<0.001
QT interval (msec)	383	372	<0.001
QTc interval (msec)	415	417	0.623
Vital Signs			
Heart Rate (pulse)	74	78	0.003
Systolic Blood Pressure (mm Hg)	110	111	0.403‡
Diastolic Blood Pressure (mm Hg)	63	69	<0.001
Weight (kilograms)	63	59	<0.001
Laboratory Tests			
ALT/SGPT (mU/mL)	18.4	19.7	0.039
Urine protein (positive result), n (%)	19 (17)	30 (28)	0.0498‡

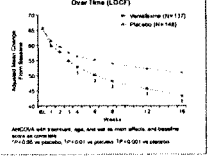
*Mean values, except as noted. †ANOVA, except as noted. Tolls baseline. ‡P < 0.05, at weeks 1, 2, 4, and 8

Table 7. Suicidality and Behavior Change

	Placebo N=150	Venlafaxine ER N=140
Suicidal ideation	0	3*
Intentional injury	1	1
Hypomania	0	1
Hyperkinesia	6	4
Agitation	3†	1
Hostility	0	0
Suicide attempt or intentional overdose	0	0
Accidental overdose	1	0
Suicide	0	0

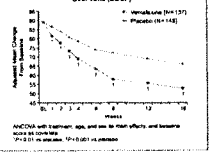
†1 during double-blind period, 1 during taper period
‡1 during pre-randomization period

Figure 1. Adjusted Mean SAS-CA Scores Over Time (LOCF)



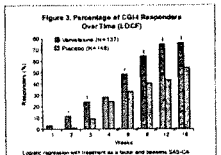
ANCOVA with treatment, age, and sex as main effects, and baseline score as covariate
*P < 0.05 vs placebo, †P < 0.01 vs placebo, ‡P < 0.001 vs placebo

Figure 2. Adjusted Mean LSAS-CA Scores Over Time (LOCF)



ANCOVA with treatment, age, and sex as main effects, and baseline score as covariate
*P < 0.01 vs placebo, †P < 0.001 vs placebo

Figure 3. Percentage of CGI-I Responders Over Time (LOCF)



Logistic regression with treatment as a factor and baseline SAS-CA score as covariate
*P < 0.05 vs placebo, †P < 0.01 vs placebo, ‡P < 0.001 vs placebo

CONCLUSIONS

- The mean daily dose ± SD (including days of missed doses) of venlafaxine ER in patients given active treatment (safety population) was 141.5 ± 47.5 mg for > 0 days of exposure (n=140) and 155 ± 39.0 mg for > 112 days of exposure (n=54).
- Venlafaxine-treated patients showed significantly greater improvement than placebo-treated patients at the final on-therapy evaluation (week 16) on the SAS-CA, the primary outcome measure.
- Baseline-to-endpoint change/variation in total SAS-CA scores was 22.5 points for the venlafaxine ER group vs 14.9 for the placebo group (adjusted change, P < 0.001).
- Treatment with venlafaxine ER was also associated with significantly greater improvement than placebo on secondary outcome measures, the LSAS-Child/Adolescent and CGI improvement.
- The administration of venlafaxine ER to children and adolescents was associated with few clinically important changes in laboratory test results, vital signs, body weight, or ECG findings. The adverse events were comparable to those reported in previous venlafaxine ER pediatric studies. There were no suicides or suicide attempts. Adverse events leading to discontinuation followed no pattern in either treatment group.
- Venlafaxine ER may be an effective treatment for children and adolescents with SAD who do not have major depressive disorder.
- Physicians should be alert to signs of suicidal ideation in children and adolescents taking venlafaxine ER.

Although not evident in this study, physicians should also be alert to signs of hostility in children and adolescents taking venlafaxine ER.

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The abbreviated summary of what scientific content is and that has not been approved by the US Food and Drug Administration.

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WYETH RESEARCH
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CSR-44693
Version No. 1.0
Project No.: 0600B1
Compound No.: WY-045,030
Wyeth Research Drug Name: Venlafaxine ER

Title: DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VENLAFAXINE ER IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER: FINAL REPORT

Protocol No.: 0600B1-394-US

Trial Phase (Check box): 1 ☐ 2 ☐ 3 ☒ 4 ☐ Other ☐

Study Dates: August 2000 to August 2001

Name and Affiliation of Principal Investigators: This was a multicenter study; the list of investigators follows the synopsis.

This study was designed and performed according to the guidelines for Good Clinical Practice.

Internal Reports Referenced: None

Related Reports: None

Number of Pages (Excluding supplemental volumes): 4375

Date of Report: 01 Jul 2002

Date of Current Version: 01 Jul 2002

Document Identification: draft: CLINICAL R&D/DRAFT CLINICAL STUDY REPORTS/DRAFT 0600B1 VENLAFAXINE/DRAFT 394

WYETH RESEARCH
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CSR-44693
Project No.: 0600B1
Compound No.: WY-045,030
Wyeth Research Drug Name: Venlafaxine ER

TITLE: DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VENLAFAXINE ER IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER: FINAL REPORT

PROTOCOL NO.: 0600B1-394-US

PREPARED BY:

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Times are by 24-hour clock. Zones: ET (US. Eastern Time), GT (Slough, Greenwich Time), or CET (Paris, Central European Time); for other zones consult Document Standards.

SYNOPSIS

COMPANY NAME: Wyeth	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	*(For National Authority Use Only)*
NAME OF FINISHED PRODUCT: Venlafaxine ER	VOLUME:	
NAME OF ACTIVE INGREDIENT: Venlafaxine HCl	PAGE:	

Title of the study: DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VENLAFAXINE ER IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER: FINAL REPORT (Protocol 0600B1-394-US, CSR-44693)

Investigators: The list of investigators and study centers follows the synopsis.

Study centers: The sites are listed on the list of investigators.

Publication (reference): None

Study period: August 2000 to August 2001 **Clinical phase:** 3

Objective: The objective of this study was to compare the antidepressant efficacy and safety of venlafaxine extended release (ER) with placebo in children and adolescents with major depressive disorder.

Methodology: Following a 7 ± 3-day single-blind placebo lead-in period, eligible patients were randomly assigned to receive double-blind, flexible-doses of venlafaxine ER or placebo for up to 8 weeks, followed by an optional taper period of 14 days or more. The prestudy period could be extended by 4 ± 3 days for some patients.

Number of patients: 201 entered the double-blind period; 196 analyzed for safety; 193 analyzed for efficacy (intent-to-treat, ITT); and 148 completed the on-therapy period.

Diagnosis and main criteria for inclusion: Outpatient children (7 through 12 years of age) or adolescents (13 through 17 years of age) who met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version (KIDDIE-SADS-PL) criteria for major depressive disorder; had prestudy and baseline scores of > 40 on the Childhood Depression Rating Scale, Revised (CDRS-R); had no greater than a 30% decrease in CDRS-R score between the prestudy and baseline evaluations; had Clinical Global Impressions (CGI) Severity score ≥ 4 at prestudy and baseline evaluations; and had depressive symptoms for at least 1 month before entry into the study.

Test product, dose and mode of administration, batch number: Venlafaxine ER capsules 37.5 mg, oral, X27931A and X10603B; and venlafaxine ER capsules 75 mg, oral, X28195A and X10603A.

Duration of treatment: 7 ± 3-day single-blind placebo lead-in period,; 8-week randomized, double-blind, placebo-controlled period (on-therapy period); and up to 2-week dose taper period.

Reference therapy, dose and mode of administration, batch number: Placebo to match 37.5-mg capsule, oral, X10603C and X27930A; placebo to match 75-mg capsule, oral, X27929A and X10603D.

Criteria for evaluation:

Efficacy assessment methods: The primary efficacy variable was the CDRS-R total score. The secondary efficacy variables were the Hamilton Psychiatric Rating Scale for Depression (HAM-D) total and Depressed Mood item scores, Montgomery-Asberg Depression Rating Scale (MADRS) total score, and the CGI Severity of Illness (CGI-S) and Global Improvement (CGI-I) scores. The primary time point was the week 8 on-therapy, last-observation-carried-forward (LOCF) on-therapy evaluation.

Safety assessment methods: Safety assessments were based on reports of adverse events and results of routine physical examinations; vital signs, height, and weight recordings; laboratory evaluations; and

SYNOPSIS

COMPANY NAME: Wyeth	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	*(For National Authority Use Only)*
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electrocardiograms (ECGs).

Statistical methods:
Statistical analyses were performed by the Clinical Biostatistics department of Wyeth Research. The alpha level for all statistical tests was set at 0.05, and all tests were 2-sided, unless otherwise indicated.

The primary efficacy time point was the week 8 LOCF on-therapy evaluation. An observation was considered on-therapy if it occurred within 3 days of the last full dose. The primary analysis used the LOCF method. To implement the LOCF method, a dataset of the observed scores at each time point was created; if the score for a given time point was missing, the last available score from an earlier time point was used.

The primary efficacy analysis population was the intent-to-treat population, which included all patients who had entered double-blind therapy, had taken at least 1 dose of their assigned medication, had at least 1 baseline evaluation for the primary efficacy variable, and had at least 1 evaluation for the primary efficacy variable either during therapy or within 3 days of the last day of treatment.

Changes from baseline for the primary and secondary efficacy variables (ie, CDRS-R total, HAM-D total and Depressed Mood item, MADRS total, and CGI-S scores) were analyzed at each time point using a parametric 2-way analysis of covariance (ANCOVA) with treatment and investigator as main effects and the baseline score as the covariate. The CGI-I scores were analyzed using a parametric 2-way analysis of variance (ANOVA) with treatment and investigator as factors.

Treatment response was assessed for 4 of the scales. Patients whose total score for the CDRS-R decreased by 35% or more from baseline were considered CDRS-R responders. Patients whose total scores for the HAM-D or MADRS scales decreased by 50% or more from baseline were considered responders for these scales. On the CGI-I scale, patients with a score of 1 (very much improved) or 2 (much improved) were considered responders. Methods based on categorical data analysis were applied to the response data.

In addition to analyses of the LOCF data, observed cases analyses were employed that used only the data available for a particular time point.

SUMMARY – CONCLUSIONS:
Efficacy results: The results of the LOCF analysis showed no significant differences between treatment groups for CDRS-R scores, the primary variable, in all ages or in separate analyses in children or adolescents. However, the improvement in efficacy scores tended to be greater with venlafaxine ER than with placebo in all ages, and the treatment group difference was greatest in the results for adolescents. There were significant differences between treatment groups in favor of venlafaxine ER at occasional time points for some of the secondary efficacy variables in the LOCF analysis for all ages and adolescents.

The observed-cases analysis showed significant treatment group differences in favor of venlafaxine ER in the

SYNOPSIS

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CDRS-R and some secondary efficacy variables for all ages and adolescents.

Safety results: No patients died during this study. Four (4) patients had serious adverse events: all were venlafaxine ER-treated patients. Eighteen (18) patients were considered to have had adverse events of clinical interest that were not serious adverse events and did not lead to discontinuation. Fourteen (14) of these were venlafaxine ER-treated patients and 4 were placebo-treated patients.

Adverse events were the primary cause of discontinuation during the on-therapy period for 8 (8%) of the venlafaxine ER-treated patients and 1 (1%) of the placebo-treated patients. The adverse events that most frequently (≥ 2%) caused discontinuation of treatment in the venlafaxine group were hostility (2%) and suicidal ideation (2%).

The most common treatment-emergent adverse events (TEAEs) reported during the on-therapy period by at least 5% of patients in the venlafaxine ER group and at twice the rate for placebo-treated patients were nausea (18%), dizziness (16%), anorexia (9%), dyspepsia (8%), somnolence (7%), and hostility (6%). The most common TEAE in the placebo group, ie, reported by at least 5% of the placebo-treated patients and at twice the rate for venlafaxine ER-treated patients, was sweating (5%).

Taper/poststudy-emergent adverse events were those not present during the last 7 days of full-dose medication, or events that became more severe after the last 7 days of full-dose medication. Taper/poststudy-emergent adverse events were reported by 34 patients (33%) in the venlafaxine ER group and 20 patients (21%) in the placebo group. Headache was the most common taper/poststudy-emergent adverse event (reported by at least 5% of the venlafaxine ER group patients and at twice the rate for placebo group patients) for venlafaxine ER-treated patients (11%). Headache also was the most frequent taper/poststudy-emergent adverse event for placebo-treated patients (5%).

Laboratory results: The analysis of mean changes from baseline showed only minor changes. There were small but statistically significant mean increases from baseline in AST (approximately 2 mU/mL) and mean decreases from baseline in alkaline phosphatase (approximately 11 to 12 mU/mL) and total protein (1.5 g/L) at the week 8 and final on-therapy evaluations in the venlafaxine ER-treated patients, but similar changes from baseline were observed in the placebo-treated patients, and there were no statistically significant differences between treatment groups for any of these laboratory parameters. Two (2) venlafaxine-treated patients and 2 placebo-treated patients had clinically important laboratory results.

Vitals signs results: Mean increases from baseline in supine pulse rate (approximately 3 to 5 beats/min) with venlafaxine ER were statistically significant at weeks 4 ($p < 0.05$) through 8 ($p < 0.001$), final on-therapy ($p < 0.05$), and poststudy ($p < 0.001$). The changes from baseline were significantly different from those in the placebo group at weeks 2 and 6 ($p < 0.05$). Mean decreases from baseline in supine diastolic blood pressure with placebo (1.6 to 3.5 mm Hg) were significant at weeks 1, 4, 6, and 7, and the mean increase from baseline in supine diastolic blood pressure with venlafaxine ER (2 mm Hg) was significant at week 7.

SYNOPSIS

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The mean increase with venlafaxine ER and mean decrease with placebo were significantly different at weeks 4 ($p = 0.027$) and 7 ($p = 0.002$). Mean decreases from baseline in supine systolic blood pressure with placebo (3.1 to 3.6 mm Hg) were significant at weeks 3, 4, and 7, and the mean increases from baseline in supine systolic blood pressure with venlafaxine ER (2.5 to 3.8 mm Hg) were significant at weeks 2, 6, and 7. These changes from baseline for the 2 treatment groups were significantly different for weeks 2 ($p < 0.05$) through 7 ($p < 0.001$).

Weight results: Small but significant mean increases from baseline in weight with placebo (0.3 to 1.1 kg) at all time points and significant decreases from baseline with venlafaxine ER (0.3 to 0.7 kg) at all evaluations except week 7 and poststudy resulted in significant treatment differences for all on-therapy evaluations ($p < 0.001$) and poststudy ($p = 0.02$). Two (2) venlafaxine ER-treated patients and no placebo-treated patients had clinically important changes in weight.

ECG results: Significant mean increases from baseline in heart rate at week 8 and final on-therapy evaluations with venlafaxine ER (5 and 3 beats/min, respectively) were significantly different from the 1 beat/min decreases with placebo ($p = 0.006$ and <0.001, respectively). QT interval values at week 8 and final on-therapy evaluations with venlafaxine ER were significantly decreased from baseline (11 and 8 msec, respectively) and significantly different from the values with placebo at those time points ($p = 0.008$ and 0.004, respectively). There were no significant mean changes in QTc values. Two (2) venlafaxine ER-treated patients and 2 placebo-treated patients had clinically important ECG results.

Conclusion: Venlafaxine ER was found to be safe and well tolerated in pediatric patients with major depressive disorder. The safety profile of venlafaxine ER in children and adolescents was generally similar to that in the adults with major depression.

There were no significant differences between treatment groups in the LOCF results for the primary efficacy variable, CDRS-R total score, in all ages or in separate analyses in children or adolescents. However, the improvement in efficacy scores tended to be greater with venlafaxine ER than with placebo in all ages, and the treatment group difference was greatest in the results for adolescents. There were significant differences between treatment groups at occasional time points for some of the secondary efficacy variables.

Date of the report: 01 Jul 2002

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CSR-43456
Version No. 1.0
Project No.: 0600B1
Compound No.: WY-045,030
WR Drug Name: Venlafaxine ER

Title: DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VENLAFAXINE ER IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSION: FINAL REPORT

Protocol No.: 0600B1-382-US

Trial Phase (Check box): 1 ☐ 2 ☐ 3 ☒ 4 ☐ Other ☐

Study Dates: October 1997 to September 2000

Name and Affiliation of Principal Investigator(s): This was a multicenter study; the list of investigators follows the synopsis.

This study was designed and performed according to the guidelines for Good Clinical Practice.

Internal Reports Referenced: None

Related Reports: None

Number of Pages (Excluding supplemental volumes): 2867

Date of Report: 23 Jul 2002

Date of Current Version: 23 Jul 2002

Document Identification: EDMS/draftCR&D/draft clinical study reports

WYETH RESEARCH
P.O. BOX 42528
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CSR-43456
Project No.: 0600B1
Compound No.: WY-045,030
WR Drug Name: Venlafaxine ER

TITLE: DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VENLAFAXINE ER IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSION: FINAL REPORT

PROTOCOL NO.: 0600B1-382-US

PREPARED BY:

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Times are by 24-hour clock. Zones: ET (US, Eastern Time), GT (Slough, Greenwich Time), or CET (Paris, Central European Time); for other zones consult Document Standards.

SYNOPSIS

COMPANY NAME: Wyeth	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	*(For National Authority Use Only)*
NAME OF FINISHED PRODUCT: Venlafaxine ER	VOLUME:	
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Title of the study: DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF VENLAFAXINE ER IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSION: FINAL REPORT (Protocol 0600B1-382-US, CSR-43456)

Investigators: The list of investigators and study centers follows the synopsis.

Study centers: The sites are listed on the investigators list.

Publication (reference): None

Study period (years): October 1997 to September 2000 **Clinical phase:** 3

Objective: The objective of this study was to compare the antidepressant efficacy and safety of venlafaxine extended release (ER) with placebo in children and adolescents with major depression.

Methodology: Following a 14 ± 3 day single-blind placebo lead-in period, eligible patients were randomly assigned to receive venlafaxine ER or placebo for up to 8 weeks, followed by a taper period of up to 14 days. The prestudy period could be extended by 4 ± 3 days for some patients.

Number of patients: 166 entered the double-blind period, 165 analyzed for safety, 161 analyzed for efficacy (intent-to-treat [ITT]), and 103 completed the on-therapy period.

Diagnosis and main criteria for inclusion: Outpatient children (7-12 years of age) or adolescents (13-17 years of age), who met Diagnostic and Statistical Manual, Fourth Edition (DSM- IV), and Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KIDDIE-SADS-PL) criteria for major depressive disorder, had minimum prestudy and study day -1 scores of >40 on the Childhood Depression Rating Scale, Revised (CDRS-R) and no greater than a 30% decrease in CDRS-R score between the prestudy and study day -1 evaluations, a Clinical Global Impressions Severity of Illness (CGI-S) score ≥ 4 at day -1; and depressive symptoms for at least 1 month prior to entry into the study.

Test product, dose and mode of administration, batch number: Venlafaxine ER capsules 37.5 mg, oral, W22350A/9510308 and 75 mg, oral, W22696A/9610300.

Duration of treatment: 14 ± 3 day single-blind placebo lead-in period, 8-week, randomized, double-blind, placebo-controlled period (on-therapy period); and up to 2 weeks for taper-dose period.

Reference therapy, dose and mode of administration, batch number: Placebo to match 37.5-mg capsule, oral, W22351A/9510311; and placebo to match for 75-mg capsule, oral, 9720041.

Criteria for evaluation:

Efficacy assessment methods: The primary efficacy variable was the CDRS-R total score. The secondary efficacy variables were the Hamilton Psychiatric Rating Scale for Depression (HAM-D) total and depressed mood item scores, the Montgomery-Asberg Depression Rating Scale (MADRS) total score, and the CGI-S and the CGI Global Improvement (CGI-I) scores. The primary time point was the last observation carried forward (LOCF) on-therapy week 8 evaluation. Other time points included baseline and on-study days 4, 7, 14, 21, 28, and 42.

Safety assessment methods: Safety assessments were based on reports of adverse events and results of routine physical examinations including vital signs, height and weight, laboratory determinations, and electrocardiograms (ECGs).

SYNOPSIS

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Statistical methods:

Statistical analyses were done by the Clinical Biostatistics department of Wyeth Research. The alpha level for all statistical tests was set at 0.05, two-sided, unless otherwise indicated. The primary efficacy time point was the LOCF week 8 on-therapy evaluation. An observation was considered on-therapy if it occurred within 3 days of the last full dose. Doses taken during the taper period were not considered in determining whether an observation was on therapy. Secondary LOCF analyses were performed at all other time points at which efficacy data were collected.

The primary analysis used the LOCF method. To implement this analysis, a dataset was constructed that used the observed score at each time point. If the score for a given time point was missing, the last available score from an earlier time point was used.

The CDRS-R, HAM-D total and depressed mood item, MADRS total, and CGI-S item scores were analyzed using an analysis of covariance with treatment and investigator as main effects and baseline score as the covariate. The CGI-I item score was analyzed using an analysis of variance (ANOVA) with treatment and investigator as factors.

Treatment response was assessed for 4 of the scales. On the CDRS-R scale, patients whose total scores decreased by 35% or more from baseline were considered responders. On the HAM-D and MADRS scales, patients whose total scores decreased by 50% or more from baseline were considered responders. On the CGI-I scale, patients who achieved a score of 1 (very much improved) or 2 (much improved) were considered responders. Methods based on categorical data analysis were applied to the responder data.

The primary comparison was between the venlafaxine ER group and the placebo group. The study population was the "intent-to-treat" population. This population included all patients randomly assigned to double-blind therapy who had taken at least 1 dose of the study medication and had a baseline evaluation and at least 1 evaluation for the primary efficacy parameter, either during therapy or within 3 days of the last day of treatment. In addition to analyses of the LOCF data, observed-case analyses were employed, in which only the data that were available at the time point were used.

SUMMARY - CONCLUSIONS:

Efficacy results: Improvement in efficacy scores was of similar magnitude for both the venlafaxine ER group and the placebo group. After 8 weeks of treatment, improvement was slightly better in the venlafaxine ER group than in the placebo group. The greatest improvement was seen in the adolescent subpopulation treated with venlafaxine ER. Although a consistent advantage over placebo was seen for adolescents, the differences between venlafaxine ER and placebo did not reach statistical significance. In the subpopulation of children, there was no advantage for venlafaxine ER over placebo. Few statistically significant differences between treatment groups on the CDRS-R or on the secondary efficacy parameters were observed.

SYNOPSIS

COMPANY NAME: Wyeth	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	*(For National Authority Use Only)*
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Safety results: No patients died during this study. Fifteen (15) patients had serious adverse events after randomization: 10 venlafaxine ER-treated patients and 5 placebo-treated patients. Five (5) patients were considered to have had other adverse events of clinical interest after randomization that were not a cause of discontinuation: 3 venlafaxine ER-treated patients and 2 placebo-treated patients. In addition, 5 patients had serious adverse events during the prestudy placebo lead-in period.

Adverse events were the primary or secondary cause of discontinuation during the on-therapy period for 10 (13%) of the venlafaxine ER-treated patients and 4 (5%) of the placebo-treated patients. The adverse events that most frequently (≥ 2%) caused discontinuation of treatment in the venlafaxine ER group were manic reaction (3%) and suicidal ideation (3%). None of the adverse events leading to discontinuation for the placebo group had an incidence ≥ 2%.

The most common treatment-emergent adverse events (TEAEs) during the on-therapy period reported by at least 5% of the venlafaxine ER-treated patients and at twice the rate for placebo-treated patients were abdominal pain (28%), anorexia (5%), dry mouth (6%), dysmenorrhea (6%), epistaxis (5%), flu syndrome (8%), insomnia (9%), mydriasis (10%), pain (8%), and vomiting (5%).

The most common TEAEs during the on-therapy period reported by at least 5% of the placebo-treated patients and at twice the rate for venlafaxine ER-treated patients were asthenia (7%), diarrhea (11%), infection (8%), rhinitis (12%), and somnolence (7%).

Taper/poststudy-emergent adverse events were those adverse events not present during the last 7 days of full dose medication, or events that became more severe after the last 7 days of full dose medication. Taper/poststudy emergent adverse events were reported by 17 (21%) venlafaxine ER-treated patients and 19 (22%) of placebo-treated patients. Abdominal pain was reported as a taper/poststudy-emergent adverse event by 5% of venlafaxine ER-treated patients compared with 0% of placebo-treated patients.

The administration of venlafaxine ER was associated with few clinically important changes in laboratory test results, vital signs and weight, or ECGs.

Laboratory test results: At the month 2 and the final on-therapy evaluation, the venlafaxine ER group had small but not statistically significant increases from baseline in mean total cholesterol (0.075 and 0.085 mmol/L, respectively) values; the increase at the final on-therapy evaluation was significantly different from the decrease in the placebo group at this time point.

Vitals signs results: In the venlafaxine ER group, changes in mean supine pulse rate ranged from -1.53 to 4.43 beats/min during the study and mean supine pulse rate had increased by 3.54 and 4.04 beats/min for final on-therapy and poststudy, respectively. The increases at week 6 (4.43 beats/min) and poststudy (4.04 beats/min) were significantly different from the mean changes in the placebo group. In the venlafaxine ER group, increases in mean supine diastolic blood pressure (SDBP) ranged from 0.82 to 3.13 mm Hg during

SYNOPSIS

COMPANY NAME: Wyeth	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	*(For National Authority Use Only)*
NAME OF FINISHED PRODUCT: Venlafaxine ER	VOLUME:	
NAME OF ACTIVE INGREDIENT: Venlafaxine HCl	PAGE:	

the study and were 2.65 and 3.28 mm Hg for final on-therapy and poststudy, respectively. The increases at weeks 3 through 6, final on-therapy, and poststudy were significantly different from the mean changes in SDBP for the placebo group. In the venlafaxine ER group, changes in mean supine systolic blood pressure (SSBP) ranged from 0.10 to 2.77 mm Hg during the study and were 0.48 and 2.40 mm Hg for final on-therapy and poststudy, respectively. The increases at weeks 2 and 3 were significantly different from the mean changes in SSBP for the placebo group.

Weight results: Mean weight for the venlafaxine ER group showed significant decreases from baseline at week 1 through week 6 and at the final on-therapy evaluation (decrease of 0.47 kg). Mean weight for the placebo group showed significant increases from baseline at week 1 through month 2 and at the final on-therapy (increase of 0.72 kg) and poststudy (increase of 0.85 kg) evaluations. The decreases for the venlafaxine ER group were significantly different from the significant increases for the placebo group at all evaluations.

ECG results: Mean heart rate at week 6 and at the final on-therapy evaluation for the venlafaxine ER group showed significant increases (5.14 and 4.24 beats/min, respectively) from baseline; these changes were significantly different from the changes (-1.35 and -2.09 beats/min, respectively) for the placebo group at those time points. There were no significant changes in mean QTc interval for either treatment group.

Conclusion: Improvement in efficacy scores was of similar magnitude for both the venlafaxine ER group and the placebo group. The safety profile for pediatric patients was generally similar to that for adults.

Date of the report: 23 Jul 2002

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-151/S-028/S-030/S-032
NDA 20-699/S-041/S-048/S-052

40

Wyeth Pharmaceuticals, Inc.
Attention: Kenneth R. Bonk
Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Mr. Bonk:

We acknowledge receipt of your supplemental new drug applications dated April 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effexor (venlafaxine hydrochloride) Immediate Release Tablets (NDA 20-151/S-032) and Effexor XR (venlafaxine hydrochloride) Extended Release Capsules (NDA 20-699/S-052).

Your April 30, 2004, submission also constituted a complete response to our action letter dated March 19, 2004 for supplemental applications 20-151/S-028/S-030 and 20-699/S-041/S-048.

Reference is also made to a conference call dated April 28, 2004 between representatives of the Agency and yourself to discuss the Agency's class labeling initiatives.

The above supplemental applications provide for the following changes to product labeling:

NDAs 20-151/S-028 & 20-699/S-041

1. Revisions to the **PRECAUTIONS-Usage in Children** section to denote hostility and suicide related adverse events in pediatric clinical trials.
2. The addition of the term "tinnitus" to the **DOSAGE AND ADMINISTRATION-Discontinuing Effexor** or **Effexor XR** sections.
3. Revisions to the Patient Brief Summary.

We note your agreement to our request to remove your proposed addition of hostility and suicide related adverse events from the **PRECAUTIONS-Usage in Children** section. As discussed during that April 28, 2004 meeting, we continue to feel that it would not be helpful to include the language regarding reports of hostility and suicidality that you have proposed for the **Pediatric Use** section. As currently written, the language is uninterpretable, since it notes that there were increased reports, but without noting with reference to what data. If a reference to placebo data were added, this would suggest a causal association, however, this suggestion would be contradicted by the new language that follows. The difficulty, of course, is that it remains unclear at this point exactly what has been captured under the crude terms used to capture events. The currently proposed language for **WARNINGS** is intended to comprehensively address this complex issue and our current understanding of the available data, and we feel it would be confusing and potentially misleading to maintain your proposed language for the **Pediatric Use** section.

NDAs 20-151/S-030 & 20-699/S-048

These applications provide for revisions to the **DOSAGE and ADMINISTRATION/Discontinuing Effexor** or **Effexor XR** sections of product labeling.

Again, we note your agreement to revise product labeling to incorporate the class labeling initiative for all of the selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), to change labeling in regards to discontinuation symptoms and to adverse events occurring in neonates exposed to any of the SSRIs or SNRIs late in the third trimester.

NDAs 20-151/S-032 & 20-699/S-052
These applications provide for antidepressant class labeling revisions to incorporate the following changes to product labeling:

1. The addition of a new subsection under **WARNINGS** entitled **Clinical Worsening and Suicide Risk**.
2. Revisions to the **PRECAUTIONS-Information for Patients** section.
3. Delete the section in **PRECAUTIONS-General** entitled "Suicide".
4. Add a reference to the **WARNINGS** section at the end of the **PRECAUTIONS- Pediatric Use** section, i.e., (see **WARNINGS-Clinical Worsening and Suicide Risk**).

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your labeling submitted on April 30, 2004 and as attached to this letter. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

Wyeth®

41 August 22, 2003

Dear Health Care Professional,

Wyeth wishes to inform you about an update to the prescribing information for Effexor® (venlafaxine HCl) Tablets and Effexor® XR (venlafaxine HCl) Extended-Release Capsules to reflect important safety information on the use of venlafaxine in children and adolescents. In clinical studies in pediatric patients (ages 6 to 17), efficacy was not established for major depressive disorder (MDD) or generalized anxiety disorder (GAD), and there were increased reports among those patients on Effexor XR, vs. placebo, of hostility and suicide-related adverse events, such as suicidal ideation and self-harm. Effexor and Effexor XR have not been and are not now recommended for use in pediatric patients. We have updated the prescribing information for Effexor and Effexor XR with the following information shown here in italics:

PRECAUTIONS

Usage in Children/ Pediatric Use

Safety and effectiveness in pediatric patients (individuals below 18 years of age) have not been established.

In pediatric clinical trials, there were increased reports of hostility and, especially in Major Depressive Disorder, suicide-related adverse events such as suicidal ideation and self-harm.

The most common adverse events leading to discontinuation in at least 1% of children and adolescents treated with Effexor XR, and at a rate twice that of placebo, were as follows (percentages listed for Effexor XR and placebo, respectively): MDD studies, hostility (2%, <1%) and suicidal ideation (2%, 0%); GAD studies, abnormal/changed behavior (1%, 0%). In these clinical trials there were no suicides.

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor. Effexor XR Extended-Release Capsules are indicated in adults for the treatment of MDD, GAD, and social anxiety disorder (SAD). Effexor Tablets are indicated in adults for the treatment of MDD.

In light of this important information, you should be alert to signs of suicidal ideation in children and adolescent patients prescribed Effexor or Effexor XR. You may need to reassess the benefit-risk balance when treating individual patients with Effexor or Effexor XR. If a decision is made to discontinue a patient from Effexor or Effexor XR, treatment should not be discontinued abruptly, due to

risk of discontinuation symptoms. A gradual reduction in dose under medical supervision is recommended. Please see the prescribing information for additional information with regard to discontinuation.

Wyeth is committed to global surveillance of all its products and to providing you with current product information, and therefore is sending you this letter. Should you have any questions, or wish to report any adverse event associated with Effexor or Effexor XR, please call Wyeth at 1-800-934-5556. In addition, you can send adverse event information directly to Wyeth Global Safety Surveillance and Epidemiology (GSSE) by fax to 610-989-5544 or by mail to GSSE, 500 Arcola Road, Collegeville, PA 19426.

Adverse event information may also be reported to the FDA's MedWatch Reporting System by phone (1-800-FDA-1088), fax (1-800-FDA-0178), via the MedWatch Web site at www.fda.gov/medwatch, or by mail (using postage paid form) to MedWatch, HF-2, 5600 Fisher's Lane, Rockville, MD 20852-9787.

Enclosed is a copy of the revised labeling for Effexor and Effexor XR.

Sincerely,

Victoria Kusiak

Victoria Kusiak, M.D.
Vice President, Global Medical Affairs and
North American Medical Director for Wyeth Pharmaceuticals

Enclosures

ATTACHMENT D
August 2003 Response Letter 42

Use of Venlafaxine in Children or Adolescents

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor (SNRI).[1,2] Its active metabolite, O-desmethylvenlafaxine (ODV), also inhibits serotonin and norepinephrine reuptake, with similar potency to venlafaxine. Venlafaxine and ODV are weak inhibitors of dopamine reuptake and have no significant affinity for muscarinic cholinergic, H1-histaminergic, or a1- adrenergic receptors in vitro. Effexor XR Capsules are indicated for the treatment of major depressive disorder (MDD), generalized anxiety disorder (GAD) and social anxiety disorder (SAD). Effexor Tablets are indicated for the treatment of MDD. Please see the prescribing information for recommended dosage and administration.

Summary Points

- The safety and effectiveness of venlafaxine in children and adolescents less than 18 years of age have not been established; therefore, venlafaxine is not recommended in this patient population.[3,4]
- In pediatric clinical trials, there were increased reports of hostility and, especially in MDD, suicide-related adverse events such as suicidal ideation and self-harm.[3,4]
- The safety and efficacy of venlafaxine XR for the treatment of MDD in children and adolescents was assessed in 2 randomized, placebo-controlled trials.[5,6] Venlafaxine XR did not separate from placebo on the primary efficacy variable in either study.
- The safety and efficacy of venlafaxine extended-release (XR) for the treatment of GAD in children and adolescents was assessed in 2 randomized, placebo-controlled trials.[7,8,9] Venlafaxine XR was significantly ($P < .001$) better than placebo on the primary efficacy variable in only 1 of these studies.
- The most common adverse events leading to discontinuation in at least 1% of venlafaxine XR-treated pediatric patients and at a rate twice that of placebo were as follows (percentages listed for venlafaxine XR and placebo, respectively): GAD studies: abnormal/changed behavior (1%, 0%); MDD studies: hostility (2%, <1%) and suicidal ideation (2%, 0%).[10] In addition, the following adverse events were observed at higher incidences than in adult patients: abdominal pain, agitation, dyspepsia, ecchymosis, epistaxis, and myalgia.
- The long-term safety of venlafaxine XR in pediatrics with MDD was evaluated in a 6-month open-label study.[11] Adverse events were the primary cause of discontinuation for 17% of patients, with hostility (3%) being most common.
- In a 5-week, open trial of 16 patients (ages 8-16) with attention deficit hyperactivity disorder (ADHD), 44% of the patients responded to venlafaxine therapy based on the Conners Parent Rating Scale (CPRS), while no significant effects were found on the Continuous Performance Test (CPT).[12]
- In an open-label, retrospective evaluation of 10 patients (ages 3-21) with autism, 60% of the patients were rated as sustained responders with a Clinical Global Impression

(CGI) improvement score of 1 or 2 and showed improvement of symptoms in autism.[13]

- Pharmacokinetic studies demonstrated that the mean clearance (normalized-body weight) of venlafaxine and ODV was 2.5-fold to 3.0-fold higher, and plasma concentrations lower, in children and adolescents compared to adults who received the same mg/kg dose.[14,15]
- The safety concerns and adverse event profile for venlafaxine in pediatric patients are generally similar to those described for adult patients.[10] As with adults, decreased appetite and weight loss, increased blood pressure, and increased cholesterol have been observed. Consequently, the warnings and precautions as described in the prescribing information for adults apply to pediatric patients, including the recommendation for regular monitoring of blood pressure.
- The risks that may be associated with long-term use of venlafaxine in children and adolescents have not been systematically evaluated. In particular, there are no studies that directly evaluate the effects of long-term venlafaxine use on growth, development, and maturation.

Depression

The safety and efficacy of venlafaxine XR for the treatment of depression in pediatric patients ages 6-17 years was assessed in 2 double-blind, 8-week, placebo-controlled trials,[5,6] and one open-label 6-month trial.[11] The double-blind trials included 166 and 201 patients, respectively,;[5,6] the open-label trial included 87 patients.[11] For all 3 trials, patients met DSM-IV and Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (KIDDIE-SADS-PL) criteria for major depressive disorder. Patients also had a Childhood Depression Rating Scale, Revised (CDRS-R) score > 40 at baseline, with no greater than a 30% decrease during screening; a Clinical Impressions Severity of Illness (CGI-S) score ≥ 4; and depressive symptoms for at least 1 month prior to entry into the study. All patients in the active-treatment groups started venlafaxine at 37.5 mg/day for the first week. The doses were then titrated according to weight and response, as per the same dosing protocol as the GAD studies described above. The primary efficacy variable was the CDRS-R total score.

There was no significant difference between venlafaxine XR- and placebo-treated patients in CDRS-R scores in either of the placebo-controlled trials. Venlafaxine XR was found to be well tolerated in all 3 trials, with a safety profile that was generally similar to that seen in adults with major depression. No patients died in any of the studies. In one placebo-controlled trial,[5] adverse events were the primary or secondary cause for discontinuation of study drug in 13% of venlafaxine XR-treated patients compared with 5% of placebo-treated patients. The adverse events that most frequently caused discontinuation of treatment in the venlafaxine XR group were manic reaction (3%) and suicidal ideation (3%). In the other placebo-controlled trial,[5] adverse events were the primary cause for discontinuation of study drug in 8% of venlafaxine XR-treated patients compared with 1% of placebo-treated patients. The adverse events that most frequently caused discontinuation of treatment in the venlafaxine XR group were hostility (2%) and suicidal ideation (2%). In the open-label 6-month trial, adverse events were the primary

reason for discontinuation for 17% of patients, with hostility (3%) being the most commonly cited event.[11]

In a pooled analysis of the 2 randomized controlled trials in MDD, the most common adverse events leading to discontinuation in at least 1% of venlafaxine XR-treated patients and at a rate twice that of placebo were (percentages listed for venlafaxine XR and placebo, respectively): hostility (2%, <1%) and suicidal ideation (2%, 0%).[10] The most common treatment-emergent adverse events with venlafaxine XR (incidence ≥ 5% and at least twice that of placebo were abdominal pain (21%) and anorexia (7%).

In another double blind, placebo-controlled, study (N = 40), Mandoki et al[16] found no efficacy difference between venlafaxine immediate-release (IR) and placebo in the treatment of depression in pediatric patients (ages 8-17 years). A higher percentage of venlafaxine-treated patients reported adverse events than the placebo group at almost every weekly assessment.[16] However, only the incidence of nausea at week 2 (all ages compared) and increased appetite (only adolescents compared) were significantly different from placebo.

GAD

The safety and efficacy of venlafaxine XR for the treatment of GAD in pediatric patients ages 6-17 years was assessed in 2 double-blind, 8-week, placebo-controlled trials that evaluated 158 and 164 patients, respectively.[7,8,9] For both trials, patients had symptoms of anxiety for ≥ 6 months and met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia (C-KIDDIE-SADS) criteria for GAD. Primary efficacy assessments were obtained on days 7, 14, 21, 42 and 49, and safety assessments were obtained at each visit. The primary efficacy variable was the C-KIDDIE-SADS GAD (9 delineated items).

All patients in the active-treatment groups started venlafaxine XR at 37.5 mg/day for the first week. The doses were then titrated according to weight and response using a flexible-dosing regimen. On study day 8, the doses were increased to 75 mg/day for all patients weighing ≥ 40 kg; the dose increase was optional for patients in the 25-39 kg group. On study day 15, the doses were titrated to a maximum of 75 mg, 112.5 mg, or 150 mg daily for the 25-39 kg group, 40-49 kg group, and ≥ 50 kg group, respectively. On day 29, the doses were further titrated to a maximum of 112.5 mg, 150 mg, and 225 mg, respectively, for the 25-39 kg, 40-49 kg, and ≥ 50 kg patient weight groups.

In the first randomized controlled trial, patients in the venlafaxine XR group had a significant mean decrease at week 8 of 18.6 points on the primary efficacy variable compared to the 12.4 point decrease in the placebo group ($P < .001$).[7,8] Adverse events were cited as a cause of discontinuation in 3% and 9% of venlafaxine XR- and placebo-treated patients, respectively. The most common treatment-emergent adverse events for venlafaxine XR (incidence ≥ 5% and at least twice the placebo rate) were: asthenia

(10%), anorexia (10%), hyperkinesia (6%), epistaxis (6%), thinking abnormal (5%), and weight loss (5%).

In the second trial, the decrease from baseline in the C-KIDDIE-SADS GAD was greater in venlafaxine XR- compared with placebo-treated patients (15.8 versus 13); however, this difference did not reach statistical significance ($P = .060$).[9] The adverse events observed in venlafaxine XR-treated patients were similar to that observed in adult patients with GAD. Adverse events were the primary or secondary cause of discontinuation in 4% of venlafaxine-treated patients and 2% of placebo-treated patients. The most common treatment-emergent adverse events for venlafaxine XR (incidence ≥ 5% and at least twice the placebo rate) were: anorexia (15%), nausea (13%), pain (9%), somnolence (8%), nervousness (8%), dizziness (6%), and dry mouth (5%).

In a pooled analysis of the 2 GAD studies, the most common adverse event leading to discontinuation in at least 1% of venlafaxine XR-treated patients and at a rate twice that of placebo was (percentages listed for venlafaxine XR and placebo, respectively): abnormal/changed behavior (1%, 0%).[10]

Anorexia/Weight Loss in MDD and GAD Trials

In a pooled analysis of the 4 randomized controlled trials of venlafaxine XR in pediatric patients (2 in MDD and 2 in GAD), treatment-emergent anorexia was reported in 10% and 3% of patients (ages 6-17) receiving venlafaxine XR and placebo for up to 8 weeks, respectively.[10] A loss of 5% or more of body weight occurred in 14% of the venlafaxine XR-treated and 1% of the placebo-treated patients in these trials.

ADHD

Olvera et al[12] conducted a 5-week, open trial of venlafaxine in the treatment of ADHD. Sixteen children and adolescents (ages 8-16 years; mean 11.6 years) meeting DSM-III-R criteria for ADHD (based on the Diagnostic Interview Schedule for Children) participated in the study. The patient was also required to have a score of at least 1.5 standard deviations above the mean for the patient's age and sex on the Inattention or Impulsivity/Hyperactivity factor of the CPRS. Venlafaxine was initiated at a dose of 12.5 mg/day for the first week. Based on the patient's tolerability, the daily dose was increased by 25 mg each week until a target dose of 75 mg/day was achieved. For children weighing less than 40 kg, daily venlafaxine doses were increased by 12.5 mg weekly up to a maximum of 50 mg. If a patient experienced side effects, the dosage was reduced to the previous level. The child's parent completed the CPRS, and the child performed the CPT at baseline and at the end of the 5-week trial. In addition, telephone interviews of the child and parent were conducted weekly to assess the effects of venlafaxine treatment on ADHD symptoms.

Of the 16 enrolled patients, 10 patients completed the study (mean venlafaxine dose, 60 mg/day).[12] Two patients were lost to follow-up, 3 discontinued therapy due to an increase in hyperactivity, and 1 discontinued due to nausea. Of the evaluable patients,

treatment with venlafaxine resulted in significant improvement ($P < .01$) in the Impulsivity/Hyperactivity Factor and Hyperactivity Index of the CPRS. However, there were no significant changes in the Conduct Index Factor, nor were there any significant effects of venlafaxine therapy on the CPT. Overall, 44% (7/16) subjects responded favorably to venlafaxine therapy based upon the CPRS.

The most common adverse experiences were drowsiness, nausea, irritability, and worsening of hyperactivity.[12] Other reported adverse events included insomnia, dizziness, decreased appetite, dry mouth, anxiety, and headache. No appreciable effects on blood pressure or heart rate were noted.

Autism

Hollander et al[13] conducted an open, retrospective evaluation of the treatment responses to venlafaxine in children, adolescents or young adults with autistic spectrum disorders. Ten patients between the ages of 3 and 21 (mean 10.5 ± 5.5) years old who met the DSM-IV criteria for pervasive developmental disorders, including autism and Asperger's Syndrome, were evaluated. Five patients had comorbid disorders including ADHD, body dysmorphic disorder, separation anxiety, obsessive-compulsive disorder, and Tourette's syndrome. Patients were treated with an initial dose of venlafaxine 12.5 mg/day. The venlafaxine dose was gradually increased based on clinical response and adverse events. Efficacy was assessed using the CGI improvement scale. Responders were defined as those patients who obtained a score of 1 (very much improved) or 2 (much improved).

Six of the 10 patients were rated as sustained responders with a CGI improvement score of 1 or 2.[13] The mean endpoint venlafaxine dose in these patients (25±14 mg/day) did not differ from that of the nonresponders. The mean duration of treatment was 4.8±2.5 months. Venlafaxine treatment was noted to improve symptoms in all 3 core dimensions of autism (social deficits, language and communication impairment, restricted interests and repetitive behaviors). Improvements were also noted in eye contact, socialization, complexity of play, contextual language use, and abnormal vocalizations. According to the investigators, 5 of the 6 responders also showed signs of improvement in features of ADHD including inattention, lack of focus, impulsivity, and hyperactivity.

Adverse events included polyuria, nausea, inattention and behavioral activation.[13] According to the authors, the behavioral activation symptoms were transient or disappeared with dose reduction in 3 patients, but resulted in withdrawal from the study for 2 patients because of persistent symptoms.

While the results of this retrospective evaluation were generally positive, randomized controlled studies are necessary to adequately evaluate the safety and efficacy of venlafaxine for autism spectrum disorders.

Pharmacokinetics

Venlafaxine IR

The oral-clearance values (normalized for body weight) for venlafaxine IR were approximately 2.5-fold higher in children and adolescents with conduct disorder than in a historical control of healthy adult subjects who received similar mg/kg doses.[14] It was calculated that children who received 3.3 mg/kg/day and adolescents who receive 2.8 mg/kg/day had plasma concentrations of venlafaxine and ODV similar to typical adult populations that received 150 mg (approximately 2.0 mg/kg/day).

Venlafaxine XR

In an open-label, single-dose study, 18 subjects were enrolled to evaluate the pharmacokinetic profile of a single dose of venlafaxine XR in pediatric patients.[15] There were 6 subjects each in 3 age groups (6-7 years, 8-11 years, and 12-17 years). The results of this study are similar to those reported above for venlafaxine IR. The single-dose clearance (normalized-body weight) of venlafaxine and ODV was 2.5-fold to 3.0-fold higher, and plasma concentrations lower, in children and adolescents compared to a historical control of adults who received the same mg/kg dose. It was calculated that children who receive 3.1 mg/kg and adolescents who receive 2.0 mg/kg would have plasma concentrations of venlafaxine and ODV similar to typical adult populations that received 150 mg.

Summary/Conclusion

The efficacy of venlafaxine in children or adolescents less than 18 years of age has not been established for any indication; therefore, we cannot recommend the use of venlafaxine in this patient population.[3,4]

In depression studies, suicidal ideation and hostility were the most common reasons for discontinuation that occurred at a rate ≥1% and at least 2 times that for placebo.[5,6]

Based on studies in MDD and GAD, the safety profile for venlafaxine in pediatric patients is generally similar to those described for adult patients; consequently, the contraindications, warnings and precautions for adults apply to pediatric patients (consult prescribing information).

Preliminary investigations into the safety and/or efficacy of venlafaxine for various other disorders in children and adolescents have been reported.[12,13,15] Larger randomized controlled trials are necessary to establish the safety and efficacy of venlafaxine in these populations.

BKS/EFF022/rr 7-9-2003

References:

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3. Effexor® - current US prescribing information, Wyeth Pharmaceuticals.

4. Effexor® XR - current US prescribing information, Wyeth Pharmaceuticals.

5. Data on file (Protocol 0600B1-382-US, CSR-43456, 2002), Wyeth Pharmaceuticals.

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7. Khan A, Kunz NR, Nicolacopoulos E, Jenkins L, Yeung PP. Venlafaxine extended release for the treatment of children and adolescents with generalized anxiety disorder [poster]. American Psychiatric Association 2002 Annual Meeting, Philadelphia, Pennsylvania, May 2002.

8. Data on file (Protocol 0600B2-397-US, CSR-44734, 2002), Wyeth Pharmaceuticals.

9. Data on file (Protocol 0600B2-396-US, CSR-44723, 2002), Wyeth Pharmaceuticals.

10. Data on file (Pediatric Integrated Summary of Safety), Wyeth Pharmaceuticals.

11. Data on file (Protocol 0600B1-395-US, CSR-44610, 2002), Wyeth Pharmaceuticals.

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14. Data on file (Protocol 0600A-126-US, CSR-26710, 2002), Wyeth Pharmaceuticals.

15. Data on file (Protocol 0600B1-169-US, CSR-44894, 2002), Wyeth Pharmaceuticals.

16. Mandoki MW, Tapia MR, Tapia MA, Sumner GS, Parker JL. Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacol Bull.* 1997;33:149-154.

PROPRIETARY INFORMATION

43

Project Name:	A Multi-center, Randomized, Double-blind, Placebo-controlled Efficacy and Safety Study of Remeron in Outpatient Children and Adolescents with Major Depressive Disorder
Type of Study:	Organon-sponsored study (003-045) via Clinical Development Department
Principle Investigator:	Dr. Graham Emslie; Department of Psychiatry, University of Texas, Southwestern Medical Center, Dallas, Texas
Type of Presentation:	Oral (with accompanying slides) as part of a symposium on major depressive disorder. The symposium was not supported by grants from Organon.
Presented at:	The American Academy of Child and Adolescent Psychiatry (AACAP) Conference; Honolulu, Hawaii; October 25, 2001

AN 00249

CONFIDENTIAL

PROPRIETARY INFORMATION

AN 00250

MIRTAZAPINE

CONFIDENTIAL

2 IDENTICAL STUDIES

- Multicenter, double-blind, placebo-controlled study of mirtazapine
- Outpatients, ages 7-17, with MDD
- 8-week trial
- Total Intent-to-Treat: 250
  - Mirtazapine (n=165)
  - Placebo (n=85)
- Dose: 15-45mg/day

STUDY 1

Demographic Characteristics (*AST)

	Mirtazapine (n=82)	*Placebo (n=44)*
Age	12.3 ±2.5	12.4 ±2.6
Age Group		
7-11 years	36.6% (30)	43.2% (19)
12-17 years	63.4% (52)	56.8% (25)
Gender		
% Female	47.6% (39)	56.8% (25)
Race		
% Caucasian	81.7% (67)	86.4% (38)

***All Subjects Treated**

STUDY 2

Demographic Characteristics (*AST)

	Mirtazapine (n=88)	*Placebo (n=44)*
Age	11.9 ±2.9	12.3 ±3.0
Age Group		
7-11 years	46.6% (41)	40.9% (18)
12-17 years	53.4% (47)	59.1% (26)
Gender		
% Female	52.3% (46)	54.5% (24)
Race		
% Caucasian	79.5% (70)	75.0% (33)

***All Subjects Treated**

BOTH STUDIES

Demographic Characteristics (*AST)

	Mirtazapine (n=170)	*Placebo (n=88)*
Age	12.1 ±2.7	12.3 ±2.8
Age Group		
7-11 years	41.8% (71)	42.0% (37)
12-17 years	58.2% (99)	58.0% (51)
Gender		
% Female	50.0% (85)	55.7% (49)
Race		
% Caucasian	80.6% (137)	80.7% (71)

*All Subjects Treated

DOSING

- Dosing occurred in evenings
- 15mg/day for 1 week
- Titration schedule
  - Physician decision
  - Increase by 15mg/day per week
  - Up to 45 mg/day
  - No further increase after Day 28
- No less than 15mg/day

RESULTS
(Study 1)

	MIRTAZAPINE (N=82)	PLACEBO (N=44)
BASELINE	57.8 ±9.9	59.4 ±9.
WEEK 8	35.1 ±1.6	37.2 ±2.

***ITT, LOCF**

RESULTS
(Study 2)

	MIRTAZAPINE (N=83)	PLACEBO (N=41)
BASELINE	58.3 $\pm$10.1	57.6 $\pm$9.0
WEEK 8	35.4 $\pm$1.5	38.8 $\pm$2.1

*ITT, LOCF

CGI IMPROVEMENT
(1 or 2)

	MIRTAZAPINE	PLACEBO
STUDY 1	59.8%	56.8%
STUDY 2	53.7%	41.5%

AN 00258

*ITT, LOCF

DISCONTINUATIONS (*AST)

- Adverse events
  - Mirtazapine: 9 (5.3%)
  - Placebo: 3 (3.4%)
- Lack of efficacy
  - Mirtazapine: 8 (4.7%)
  - Placebo: 6 (6.8%)
- Other
  - Mirtazapine: 15 (8.8%)
  - Placebo: 8 (9.1%)

***All Subjects Treated**

CONCLUSIONS

- First large, placebo controlled study in children & adolescents with mirtazapine
- Well tolerated
  - Few drop-outs with mirtazapine (5.3% discontinued due to AEs)
- High placebo response rate

PROPRIETARY INFORMATION

Organon

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CLINICAL TRIAL REPORT

CONFIDENTIAL

Research & Development
Dept. of Clinical Trial Operations
Organon West Orange

R&D Release Report
No.: US0001102
Core Report
Appendices A to I

Authors: K. Boyle
M. Annett
H. J. Kleijn
R. Weinfeld

Name of Investigational Product:
Remeron®

Sponsor signatory: J. Panagides

Date: April, 2001

A multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of Remeron® in outpatient children and adolescents with major depressive disorder.
Clinical Trial Report on Protocol 003045

IND Number: 20-522
NDA Number: 20,415

Critical objective: Depression

Clinical Trial Start: February, 1999
Clinical Trial Completion: November, 2000

AN 00013

Report/Publication (Ref)

US0001102/None

Studied Period (Years)

Start Date: February, 1999

End Date: November, 2000

Clinical Phase

Phase IIIa

Objectives

The objective of this study was to compare the efficacy (separately for Study 1 and Study 2) and safety of Remeron® to placebo in the treatment of outpatient children and adolescents with major depression (per Amendment 1, dated September 14, 1999).

Methodology

This was a multicenter, double-blind, placebo-controlled, flexible/fixed dose study in outpatient children and adolescents with Major Depressive Disorder. This study was conducted at 34 study centers. All subjects were to begin with a screen visit approximately 14 days (Day -14) prior to Baseline. This was to be followed by a second screen visit seven days later (Day -7) for completion of the screening checklist. After completion of the second screen week and after meeting the baseline checklist criteria, each subject was to be randomized to an active or placebo treatment group. The active treatment group was to receive a starting dose of 15 mg of Remeron® to be taken each evening, with the option to increase the dose to 30-45 mg in 15 mg increments during subsequent weeks of treatment (up to Study Day 28). On and after Day 28, there were to be no further dose adjustments for the remaining 4 weeks of the study. Subjects randomized to the placebo group were to receive placebo each evening.

Number of Subjects (total and for each treatment)

Study subjects were assigned to "Study 1" or "Study 2".
Study 1 enrolled a total of 126 subjects across 17 study sites.
Study 2 enrolled a total of 133 subjects across 17 study sites.

	Study 1	Study 2	Total # Subjects
Remeron® subjects	82	88	170
Placebo subjects	44	45	89

Diagnosis and Criteria for Inclusion
To be considered for inclusion in the study, subjects were to meet the following inclusion criteria:
They were to provide written informed consent (parents/guardian and subject) after the scope and nature of the study had been explained to them, but before beginning any study-related activities, including screening evaluations. A parent/guardian had to sign the consent form (subject was to provide assent); the subjects were to be at least 7 and less than 18 years of age (at the time of enrollment {Baseline}); they were to be able to understand English and to have the ability to respond to questions and follow instructions as presented by the investigator and parent/guardian; they could be either male or female; females had to be non-pregnant and, if females were fertile and sexually active, they were to be using a method of birth control that was acceptable to the investigator; subjects were to be judged as reliable. He/she was to agree to keep appointments and cooperate during all evaluations.

Psychiatric status:
- At the initial screening interview, subjects were to be diagnosed according to DSM-IV criteria, with a primary diagnosis of major depressive disorder (non-psychotic, chronic or recurrent) on the Kiddie-SADS P-L.
- At the Baseline (Day 0) interview, subjects were to have a score of ≥ 15 on the first 17 items of the HAM-D 21;
- At the Baseline (Day 0) interview, subjects were to have a score of less than 70 on the Children's Global Assessment Scale (C-GAS).
- At the Baseline (Day 0) interview, subjects were to have a raw score of 40 or greater on the Children's Depression Rating Scale–Revised (CDRS-R).

Psychiatric Treatment:
- Subjects were not to have received MAO Inhibitors, Investigational Compounds, or Psychotropic Drugs, within 14 Days, 30 Days, and 7 Days before Baseline, respectively.
- Subjects could not begin receiving formal psychotherapy during the study period. Subjects who had an inadequate response to psychotherapy during the past six (6) months (i.e., they still met all criteria for major depressive disorder at the Screening and Baseline Visits), were eligible for enrollment. Supportive care was to be allowed. Supportive care was defined as follows:
  - Explanation of the subjects' understanding of the illness;
  - Discussion of improvement or lack of improvement,
  - Discussion of reaction to pharmacological treatment, and
  - Other interventions included in an acceptable level of care for subjects beginning a new therapeutic regimen;
- Subjects were to never have taken Remeron® and were not to have participated in any previous Remeron® (Org 3770) clinical trial.

Exclusion Criteria
Potential participants were to be excluded from further consideration if:

Medical History:
- They had any untreated or uncompensated clinically significant renal, endocrine, hepatic, respiratory, cardiovascular, hematologic, immunologic, cerebrovascular disease, or malignancy;
- They had a history of seizures (other than childhood febrile seizures) or were taking anticonvulsants to prevent seizures;
- At the two (2) screening interviews or at Baseline (Day 0), they had any clinically significant abnormal laboratory, vital sign, or physical examination findings which, in the opinion of the investigator, would have precluded study participation. Any important changes during the 14-day screen period were to be discussed with the Medical Monitor prior to randomization;
- They had SGOT or SGPT values on screening labs which were equal to or more than 1.25 times the upper limit of normal;

Psychotropic Drug Use:
- They required concomitant treatment with psychotropic drugs (including melatonin);
- At the second screening interview, they had a confirmed positive result on the alcohol/drug screen test for alcohol, or any psychotropic drug (prescribed or OTC, legal or illegal).

Psychiatric History:
- They had a history of drug and/or alcohol abuse (according to DSM-IV criteria: 305.00) within the 90 days before the first screen visit;
- They had a Bipolar disorder (Bipolar I or II); or they had a parent(s) with Bipolar I disorder;
- They had a concurrent psychiatric diagnosis of anorexia or bulimia with vomiting, or had ever been diagnosed with an eating disorder; or they had a concurrent psychiatric diagnosis of obsessive compulsive disorder or schizophrenia;
- They had made a serious suicide attempt during the current major depressive episode, or had ever made a suicide attempt which resulted in hospitalization;

- They had cognitive deficiencies which could have impaired their ability to complete required assessments during study participation;
- They had failed more than two adequate trials of antidepressants. An adequate trial was defined as treatment within the dose range specified in the Package Insert for the specified antidepressant for at least 4 weeks. In the event that SSRI treatment was stopped due to intolerance, the subject had to have been taking the SSRI for at least four days and less than four weeks before discontinuation.

Test Product, Dose and Mode of Administration, Batch No.
Treatment groups: Remeron® (mirtazapine): 15-45 mg qhs, Batch numbers: PD0628, PD0629, PD0630.

Duration of Treatment

Screen period: (Days -14 and -7)		14 days, +/- 3 days, during which time subjects were to receive two screening interviews
Active treatment:	total:	56 days, +/- 3 days to allow for scheduling difficulties
Follow-up:		30 days after final dose of study drug

Reference Therapy, Dose and Mode of Administration, Batch No.
placebo qhs, Batch numbers: PD0631, PD0632, PD0633.

Criteria for Evaluation
Diagnostic tool:
Kiddie Schedule for Affective Disorders & Schizophrenia (Kiddie-SADS) P-L (present and lifetime)
Efficacy:

The following scales were to be used to determine efficacy:

- Children's Depression Rating Scale—Revised (CDRS-R) [primary outcome measure, per Amendment 1, dated September 14, 1999]
- Children's Global Assessment Scale (CGAS)
- Hamilton Scale for Depression, 21 items (HAM-D 21)
- Clinical Global Impressions Scale (CGI)
- Self-Report for Childhood Anxiety Related Disorder (SCARED) [subject self-rating scale]
- Conners' Global Index – Parent and Teacher Versions

Rater training on the use of the Kiddie-SADS and efficacy measures occurred at the Investigator's Meeting; inter-rater reliability testing was to be assessed periodically during the study.
Safety:

Safety evaluations were to include the following:

- Adverse Events. Treatment-emergent adverse events (AEs) were to be recorded immediately after the first dose on Day 0 through the subject's final day of active treatment. Post-treatment adverse events occurring during the first month following the treatment period were to be recorded. Pre-Treatment Signs and Symptoms were to be recorded at each screening visit, through the baseline day.
- Vital Signs. Blood pressure, heart rate and body weight were to be recorded at every subject visit, beginning with the first screening interview. Height was to be recorded at Screen Visit 1 and at Endpoint (Day 56 or the subject's final day of treatment – End-of-Trial Physical Exam).
- Physical Examinations. Complete physical examinations were to be performed at the first screening interview (Pre-Treatment Physical Exam) and Endpoint.
- ECG. An ECG (12-lead at rest) was to be performed at the second screening interview (to serve as baseline measurement), and on Study Day 56 (or the subject's final day of treatment).
- Laboratory evaluations, including hematology, blood chemistry, and urine analysis, were to be completed at the second screening visit (to be considered baseline values), and on Days 28 and 56 (or the subject's final day of treatment).
- A urine alcohol/drug test was to be done at the second screening interview. Investigators, at their discretion, could perform additional tests during the trial, on a prn basis.
- Pregnancy testing (urine) was to be performed on all females of child-bearing potential at the second screen visit; investigators could perform additional tests at their discretion during the trial, on a prn basis.

Approximately 1 month after treatment was completed, a follow-up interview was to be done to evaluate any after effects of drug treatment.

Pharmacokinetics:
Plasma samples, for the purpose of measuring mirtazapine, (Org 3770) concentrations, were to be collected on Study Days 28 and 56 (or the subject's final day of treatment). Org 3770 concentrations were to be compared with historical data on file from adult males and the influence of demographic variables age, weight and gender were to be explored.

Statistical Methods

Sample Size:
The sample size for each study was based on the following considerations. The primary efficacy variable used for the power calculation was to be the total CDRS-R raw score. Based on Emslie's (1997) study of fluoxetine and placebo in children and adolescents, the estimated common variance of the total CDRS-R raw score at endpoint (Week 8, using LOCF approach) is 254.02. Because no efficacy data for Remeron® were available in this subject population, a study of another antidepressant was considered. Based on a two-sample t-test at the α=0.05 significance level, there is at least 80% power to detect a treatment difference of 8.7 on the total CDRS-R raw score when the total sample size is 123, using a 2:1 ratio in treatment group allocation (Remeron® to placebo).

Efficacy:
The primary efficacy parameter for the study was to be the total CDRS-R (Children Depression Rating Scale-Revised) raw score. A statistical comparison of the mean total CDRS-R raw score between Remeron® and Placebo group was to be performed at all time points, including endpoint, using analysis of covariance (ANCOVA) with the baseline total CDRS-R raw score as covariate and with treatment and center as factors.
Analyses of the total CDRS-R raw score was to be also performed for each subset of subjects belonging to the following age categories: 1) ≤ 11 years, and 2) ≥ 12 years.
Secondary efficacy parameters were to include the proportion of subjects with a Clinical Global Impression (CGI) scale improvement rating of 1 or 2 ("very much" or "much" improved), the three components of CGI (Severity of Illness, Global Improvement, and Quality of Life), HAM-D 21, and the CGAS (Children's Global Assessment Scale).

Safety:
The number and percentage of subjects with 1) at least one AE, 2) with AEs causing early termination, 3) with AEs of known severe intensity, 4) with SAEs, 5) with drug-related AEs, and 6) who died during the study were to be presented by treatment group for each WHO system-organ class and preferred term.
The number and percentage of subjects with one or more clinically significant laboratory values were to be tabulated by laboratory parameter and treatment group at baseline and post-baseline.
The number and percentage of subjects with clinically significant physical examination findings were to be provided by treatment group and physical examination area (e.g., head and neck, etc.) for screen and for endpoint (the post-baseline assessment).
At all visits, including both screening visits, blood pressure, heart rate, and body weight were to be measured and recorded. For each parameter, the number (percentage) of subjects having one or more clinically significant vital sign values were to be presented by treatment group.

Pharmacokinetics:
Analysis of covariance on residuals (dose-normalized study data compared to average dose-normalized adult Org 3770 profile) was to be performed to study effects of covariates age, body weight and gender.

SUMMARY

Primary Efficacy Parameter
The primary efficacy parameter for the study was the total CDRS-R (Children Depression Rating Scale-Revised) raw score.

The results of the analyses of the Children's Depression Rating Scale-Revised (CDRS-R) total raw scores at Week 8/Endpoint in Study 1 for the Remeron®-treated group, mean total raw scores 34.63±2.48(SE) for the 7-11 year old age group and 35.4±2.09(SE) for the 12-17 year old age group. In the placebo-treated group, the mean total raw scores at Week 8/Endpoint were 36.01±3.13(SE) for the 7-11 year old age group and 38.06±3.01(SE) in the 12-17 year old age group. The results of the analyses of all subjects in the Remeron®-treated group were 35.08±1.58(SE) mean total raw scores at Week 8/Endpoint versus 37.24±2.16(SE) in the placebo-treated group. Although a trend of reduction of CDRS-R mean total raw scores was observed from Week 1 to Week 8/Endpoint in both age groups in the Remeron®-treated group, there were fluctuations observed at Week 5 and Week 7 in the 7-11 year age group. A similar trend and fluctuations were observed in the placebo-treated group. No statistically significant difference was observed by comparison of mean total raw CDRS-R scores between treatment groups at any time point. The results of the analyses of the total CDRS-R mean total raw scores at Week 8/Endpoint in Study 2 were mean total raw scores at Week

8/Endpoint in the Remeron®-treated group were 32.64±2.31(SE) for the 7-11 year old age group and 37.44±1.83(SE) for the 12-17 year old age group. In the placebo-treated group, the mean total raw scores at Week 8/Endpoint were 35.95±3.31(SE) for the 7-11 year old age group and 41.38±2.57(SE) in the 12-17 year old age group. The results of the analyses of all subjects in the Remeron®-treated group at Week 8/Endpoint were 35.39±3.31(SE) versus 38.78±2.09(SE) in the placebo-treated group. A trend of reduction of scores from Week 1 to Week 8/Endpoint, in both age groups, was observed in both the Remeron®-treated and placebo-treated groups. No statistically significant difference was observed by comparison of mean total raw CDRS-R scores by week between treatment groups.

Secondary efficacy parameters included the proportion of subjects with a Clinical Global Impression (CGI) scale improvement rating of 1 or 2 ("very much" or "much" improved), the three components of CGI (Severity of Illness, Global Improvement, and Quality of Life), HAM-D 21, the CGAS (Children's Global Assessment Scale), the Self Report for Childhood Anxiety Related Disorder (SCARED) and the Connors' Global Index Scale (teacher and parent versions).

Results for the Clinical Global Impressions (CGI) global improvement responders "much improved " or "very much improved" for Study 1 were that the percentage of subjects who were responders with "much improved" or "very much improved" scores in both treatment groups was comparable at Week 8/Endpoint. In the Remeron®-treated group, at Week 8, 59.76% of subjects were responders with "much improved" or "very much improved" scores from baseline. In the placebo-treated group, 56.82% of subjects were responders. A trend toward and increasing percentage of subjects reporting "much improved" or "very much improved" was observed across visits in both the Remeron®-treated and placebo-treated groups; however, there was no statistically significant difference observed at any time point by comparison of the number of CGI-global improvement responders between treatment groups. In Study 2 the CGI global improvement responders results in the Remeron®-treated group, at Week 8/Endpoint, were that 53.66% of subjects were responders with "much improved" or "very much improved" scores from baseline. In the placebo-treated group, 41.46% of subjects were responders. There was no statistically significant difference observed between the Remeron®-treated and placebo-treated groups at any time points.

The results of the CGI – severity of illness – mean change from baseline for Study 1 was that although the change from baseline in the Remeron®-treatment group was numerically greater than placebo at all weeks measured except at Weeks 1 and 2, the difference between the treatment groups was not statistically significant at any time point. At Week 8/Endpoint, the Remeron®-treated group showed a mean change from baseline of 1.71±0.14(SE), and 1.48±0.19(SE) in the placebo-treated group. In Study 2 for the results of the CGI-severity of illness, at Week 8/Endpoint, the Remeron®-treated group showed a mean change from baseline of 1.51±0.14(SE) and 1.15±0.19(SE) in the placebo-treated group. However, at earlier weeks, the numeric difference between the treatment groups was not as large, and in several cases the placebo-treated group showed a greater mean change from baseline than the Remeron®-treated group. Overall, there was no statistically significant difference observed between treatment groups at any time point.

CGI-global improvement-mean scores by week and treatment group for Study 1 showed that although slightly greater improvement was seen at almost all weeks in Study 1, at Week 8/Endpoint, the mean scores were comparable in both treatment groups: 2.29±0.13(SE) in the Remeron®-treated group and 2.34±0.18(SE) in the placebo-treated group. No statistically significant difference was found between groups at any point. In Study 2, results for CGI-global improvement scores, a similar trend towards improvement was observed from Week 1 to Week 8/Endpoint with slight loss of improvement in the placebo-treated group at Week 7. At Week 8/Endpoint the mean scores were: 2.52±0.13(SE) in the Remeron®-treated group and 2.78±0.19(SE) in the placebo-treated group. No statistically significant difference was found between treatment groups at any time point.

Results of the CGI-quality of life-mean score by week and treatment group for Study 1 showed that although the Remeron®-treated group consistently showed greater improvement in mean scores at every week (with the exception of Week 7 fluctuation) the mean scores at Week 8/Endpoint were comparable in both treatment groups: 2.35±0.13(SE) in the Remeron-treated group and 2.41±0.17(SE) in the placebo-treated group. In Study 2, the same trend of reduction of mean scores was observed, and at Week 8/Endpoint the mean scores were: 2.76±0.14(SE) in the Remeron-treated group and 3.07±0.19(SE) in the placebo-treated group. There was no statistically significant difference found between treatment groups at any time point.

The results of the HAM-D 21 change from baseline were that at Week 8/Endpoint in the Remeron®-treated group, the mean change from baseline was 12.22±0.84(SE), compared to 11.07±1.15(SE) at Week 8Endpoint in the placebo-treated group. There was no statistically significant difference observed between treatment groups at any time point.

In Study 2, the results of the HAM-D 21 at Week 8/Endpoint, in the Remeron®-treated group, were that the mean change from baseline was 11.82±0.73(SE), compared to 9.76±1.06(SE) in the placebo-treated group. Overall, in Study 2, there was no statistically significant difference observed between treatment groups at any time point.

The results for the CGAS general level of functioning in Study 1 were that at Week 8/Endpoint, the percentage of subjects at the level of functioning in the Remeron®-treated group for the categories 41-50 (moderate degree of interference), 22.5%, 51-60 (sporadic difficulties), 20.0%, 61-70 (some difficulties), 17.5%, and 81-90 (good functioning), 17.5%, were greater than the placebo-treated group, 20.9%, 16.3%, 16.3% and 14.0%, respectively, for those levels of functioning. In the 31-40 (major impairment) and 91-100 (superior functioning) categories, the percentage placebo-treated subjects, 7.0% and 4.7%, respectively, was greater than the Remeron®-treated group, 2.5% in each of those categories. In Study 2 the results for the CGAS general level of functioning were that at Week 8/Endpoint, a higher percentage of placebo-treated subjects were functioning at a level of 41-50, 33.0%, 51-60,17.9%, 81-90, 15.4% and 91-100, 2.6%, compared to the Remeron®-treated group, 24.1%, 15.2%, 13.9% and 1.3%, respectively.

The SCARED results for total and associated factors – Week 4 and Week 8/Endpoint scores – for Study 1 showed a trend of reduction of mean scores at Week 4 and Week8/Endpoint in total SCARED and associated factors (somatic/panic, general anxiety, separation anxiety and social phobia) in both the Remeron®-treated and placebo-treated groups. At Week 8/Endpoint, the total SCARED mean scores were comparable in both treatment groups: 18.85±1.51(SE) in the Remeron®-treated group and 19.09±2.05(SE) in the placebo-treated group. No statistically significant difference was observed between treatment groups at any time point for the SCARED total scores or any of the factors of the SCARED. The SCARED results for Study 2 were that at Week 8/Endpoint, the total SCARED mean scores were comparable in both treatment groups: 18.86±1.36(SE) in the Remeron®-treated group and 18.77±1.93(SE) in the placebo-treated group. No statistically significant difference was observed between treatments groups at any time point for the SCARED total scores or any of the factors of the SCARED.

The Conners' Global Index Scale results for the teacher version – mean scores at Week 8/Endpoint for Study 1, where the teacher version of this scale is a list of 10 behaviors to be rated from 0 (not true at all, never, seldom) to 3 (very much true, very often, very frequent), were that in the Remeron®-treated group the Week 8/Endpoint mean change from baseline was 0.3±0.87(SE), and -1.3±1.08(SE) in the placebo-treated group. No meaningful changes in scores were observed for both treatment groups and no statistically significant difference was observed between treatment groups at any time point. The Conners' Global Index Scale results for the parents version – mean scores Week 8/Endpoint for Study 1, where the parent version of this scale is a list of 10 behaviors to be rated from 0 (not true at all, never, seldom) to 3 (very much true, very often, very frequent) were that in the Remeron®-treated group the Week 8/Endpoint mean change from baseline was 6.94±0.71(SE), and 4.62±0.97(SE) in the placebo-treated group. No statistically significant difference was observed between treatment groups at any time point. The results for the Conners' Global Index Scale for Study 2 for the teacher version were that in Remeron®-treated group the Week 8Endpoint mean change from baseline was .51±1.27(SE), and 1.12±1.56(SE) in the placebo-treated group. In the parent version, in the Remeron-treated group the Week 8/Endpoint mean change from baseline was 5.3±0.71(SE), and 4.09±1.02(SE) in the placebo-treated group. No statistically significant difference was observed between treatment groups at any point.

Safety

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 71, NUMBER 2

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MOII-C-3

CYP2A6 POLYMORPHISM AND NICOTINE METABOLISM. N.L. Benowitz, MD, R. Tyndale, PhD, P. Jacob, III, PhD, G.E. Swan, PhD, University of California, San Francisco, University of Toronto, SRI International, San Francisco, CA.

Nicotine (N) metabolism is catalyzed primarily by hepatic CYP2A6. Published research suggests that CYP2A6 genotype is a determinant of cigarette consumption and addiction risk. However, the relationship between CYP2A6 genotype and the rate of N metabolism has not been established. As part of a study of the genetics of N metabolism, we infused deuterium-labeled N and cotinine (C) into 188 twins (94 pairs), whose blood was also genotyped. The genotype distribution was 155 – *1/*1 (wild type), 12 –*1/*4 (deletion), 8 –*1/*2 (point mutation), 8 –*1/*1x2 (duplication), 2 –*2/*1x2, and 2 –*2/*4. The average clearances and half-lives for the most frequent genotypes were as follows:

Genotype	N	Cl-Nic (ml/min/kg)	Half-life Nic (min)	Cl-Cot (ml/min/kg)	Half-life Cot (min)
*1/*1	155	17.3	114	0.68	1111
*1/*4	12	13.0*	176*	0.57	1331
*1/*2	8	15.0	141*	0.70	1147
*1/*1x2	8	21.4*	105	0.67	998

* p<0.05 compared to *1/*1.

We conclude that compared to *1/*1, the clearance of N is substantially slower with the *1/*4, moderately slower with the *1/*2 and considerably faster with the *1/*1x2 genotype. The clearance of C is minimally affected by CYP2A6 gene mutations, suggesting that other enzymes are more important for C metabolism.

MOII-C-4

FUNCTIONAL CHARACTERIZATION OF THE 5'-FLANKING REGION OF CYP2A6 AND ITS GENETIC POLYMORPHISMS. M. Pitarque, O. von Richter, M. Oscarson, M. Ingelman-Sundberg, Institute of Environmental Medicine, Karolinska Institutet, Biozentrum of the University of Basel, Stockholm, Sweden.

CYP2A6 is the major nicotine-oxydase in humans. The enzyme activates some tobacco-related precarcinogens and it also contributes, to a larger or smaller extent, to the metabolism of a few drugs. Expression of CYP2A6 predominantly occurs in the liver and 100-fold interindividual variability in both mRNA and protein levels has been reported.

To increase our knowledge on the regulation of the CYP2A6 gene and to uncover the existence of promoter polymorphisms that might modulate CYP2A6 expression, we conducted a functional analysis of its 5'-flanking region. Using a luciferase reporter assay, a series of 5'-deleted promoter constructs were transfected into the human hepatoma B16A2 cells, allowing the transcriptional mapping up to -1 kb. Both up- and down-regulating elements were potentially identified, and the binding ability of the related transcription factors (e.g., HNF-4, C/EBP, CAR-RXR, Oct-1, NF-Y, GATA) was investigated by EMSAs. A mutational analysis confirmed the importance of CAR-RXR site for both basal and induced expression. Regarding, NF-Y and GATA, further cotransfection experiments were carried out to evaluate the functional significance of the polymorphic CCAAT (-745 A>G) and GATA (-1013 G>A) boxes, respectively. These two novel SNPs, along with *CYP2A6*9* (-48 T>G) previously described by our group, constitute the largest pool of *CYP2A6* genetic variability among Caucasians (allele frequencies: 26 % for -1013 G>A, 7-9 % for -745 A>G, and 6 % for *CYP2A6*9*).

TPII-1

SINGLE-DOSE PHARMACOKINETICS (PK) OF MIRTAZAPINE (M) AND ITS DEMETHYL METABOLITE (MET) IN DEPRESSED CHILDREN AND ADOLESCENTS. M.D. Reed, PharmD, R. Findling, K. Boyle, M. van den Heuvel, J. Blumer, Case Western Reserve University, Cleveland, OH.

Depression is a common, debilitating condition in children (C) & adolescents (AD). Numerous drugs encompassing variable receptor targets have been used; M is a noradrenergic & specific serotonergic antidepressant & may show promise in these patients. We determined the single dose PK of M & it's demethyl (ORG3838) MET in 16 subjects (8C & 8AD) with major depression. Fifteen blood samples were obtained over 72 hours following an oral 15 mg M tablet; M & MET were determined in plasma by LC. PK parameters were estimated non-compartmentally. Apart from a significantly longer t1/2 of MET in females, no sex related differences in M or MET PK were observed. M Cmax was higher in C vs AD (58.5 vs 34.6 ng/mL) & t1/2 shorter in C (23.1 hr) vs AD (33.5 hr) with no apparent differences observed in CL/F (0.81 C vs 0.54 L/hr/kg AD) Vd/F (26.7 C vs 23.4 L/Kg AD) or AUC (506 C vs 479 ng*hr/ml AD). For MET, Cmax was higher in C (11.2 ng/mL) vs AD (6.0 ng/mL), whereas AUC tended to be greater in C, 256 ng/mL hr for C vs 186 ng*hr/ml for AD & t1/2 tended to be shorter in C (20.2 hr) vs 31.2 hr in AD. Overall, the disposition characteristics of M & MET in AD appear similar to values reported in adults. Differences in M t1/2 & Cmax & MET Cmax between C & AD may reflect differences in overall absorption and/or clearance rate. However, similarity in the extent of systemic exposure (AUC) for the two age groups of the primary active moiety suggest similar initial M dosing could be employed for C & AD.

TPII-2

NEWBORN HEARING SCREENING: TOBRAMYCIN AND VANCOMYCIN AS RISK FACTORS FOR HEARING LOSS. J.N. van den Anker, PhD, B.A. van Zanten, PhD, W.C. Hop, PhD, M. de Hoog, PhD, Division of Pediatric Clinical Pharmacology and Medical Toxicology, Sophia Childrens Hospital, Erasmus University, Columbus, OH.

Objective: Investigate the relation between hearing loss detected by neonatal hearing screening (A-ABR screening) and exposure to tobramycin and vancomycin.

Methods: A-ABR hearing screening was performed in all neonates with at least one risk factor for hearing loss. Exposure to tobramycin and vancomycin was quantitated in terms of total dose, duration of therapy and serum concentrations and related to the result of hearing screening using logistic regression. In patients failing hearing screening, exposure to ototoxic medication was assessed in the light of other risk factors for hearing loss.

Results: A total of 625 patients were analyzed. 45 neonates failed hearing screening. Tobramycin, vancomycin and furosemide were used in 508, 130 and 174 patients, respectively. Exposure to vancomycin and tobramycin in terms described above, was not related to failure to pass A-ABR screening. Exposure to both antibiotics in the same patient, as well as combination with furosemide, was also not related to hearing loss. In none of the patients with serum concentrations outside the therapeutic range, exposure to ototoxic medication was the most likely risk factor for hearing loss.

Conclusion: No quantitative or qualitative relation between exposure to tobramycin or vancomycin and a failure to pass hearing screening was found. Routine TDM of vancomycin and tobramycin in neonates for ototoxicity reasons is not helpful in detecting patients at risk for clinically important hearing loss.

FINAL STUDY REPORT: SERTRALINE PROTOCOL A0501001

A MULTICENTER 10-WEEK RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED FLEXIBLE DOSE OUTPATIENT STUDY OF SERTRALINE IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

See next page

PHASE OF DEVELOPMENT: Phase 3

STUDY DATES: 22 December 1999 – 17 May 2001

REPORT DATE: 03 October 2001

SPONSOR'S SIGNATORIES:

This study was conducted according to local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
USA		

India

* Investigational sites that received study drug but did not randomize any subjects.

† Principal investigator (PI) changed during the course of the study. Most recent PI is listed first

PROTOCOL A0501001: **A Multicenter 10-Week Randomized Double-blind Placebo-controlled Flexible Dose Outpatient Study of Sertraline in Children and Adolescents With Major Depressive Disorder**

Principal Investigators:

USA

India

* Investigational sites that received study drug but did not randomize any subjects.

Study Publication: None

Study Dates: 22 December 1999 – 17 May 2001

Phase of Development: Phase 3

Study Objectives: To evaluate the safety and efficacy of sertraline compared with placebo in children and adolescents (6 to 17 years of age) who are outpatients with major depressive disorder (MDD).

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, flexible dose outpatient trial of sertraline in children (6 to 11 years of age) and adolescents (12 to 17 years of age) with MDD. Following a two-week screening period, eligible subjects were randomized to either sertraline or placebo in a 1:1 ratio with a 1:1 stratification of children to adolescents. Approximately 160 subjects were to be treated (80 sertraline; 80 placebo). The double-blind treatment phase was of 10 weeks duration.

Evaluation Groups: One hundred eighty-eight subjects (97 sertraline; 91 placebo) were randomized to double-blind treatment and treated with study drug. Of the 188 randomized subjects, 65 subjects (67.0%) in the sertraline group and 77 subjects (84.6%) in the placebo group completed treatment. The following table shows the number of subjects evaluable for efficacy and safety analyses by treatment group.

Subject Evaluation Groups	Sertraline N (%)	Placebo N (%)
Randomized	97	91
Treated	97	91
Completed Study	65 (67.0)	77 (84.6)
Discontinued Study	32 (33.0)	14 (15.4)
Analyzed for Efficacy		
Intent-to-Treat	93 (95.9)	88 (96.7)
Efficacy Evaluable	81 (83.5)	82 (90.1)
Analyzed for Safety		
Adverse Events	97 (100.0)	91 (100.0)
Laboratory Data	85 (87.6)	86 (94.5)

Diagnoses and Criteria for Inclusion of Subjects: Children (6 to 11 years of age) and adolescents (12 to 17 years of age) diagnosed with a current episode of MDD, whose Children's Depression Rating Scale-Revised (CDRS-R) score was ≥45 and Clinical Global Impression of Severity (CGI-S) score was ≥4 at Screening Day 1, 7, and 14 (baseline), and who met all of the inclusion and none of the exclusion criteria were enrolled in this study.

Drug Administration:

Dosage Form	25-mg sertraline tablets, FID No. QC2186 50-mg sertraline tablets, FID No. QC1457 Placebo tablets, FID Nos. G00308AA and QC1458
Dosing	25 mg/day for the first 3 days followed by 50 mg/day through the first 2 weeks. Thereafter, the dose could be increased in increments of 50 mg/day in intervals of two weeks up to a maximum of 200 mg/day, depending on clinical response and dose-limiting side effects.
Duration	10 weeks of double-blind treatment

Efficacy and Safety Evaluations: Efficacy assessments were done at the screening visits (Day 1 and 7), baseline (Day 14 of screening), and at end-of-week (EOW) visits 1, 2, 3, 4, 6, 8, and 10. Several efficacy-rating scales were used to rate the subject's progress during the study. The primary efficacy rating scale specified by the protocol was the Children's Depression Rating Scale Revised (CDRS-R). The secondary efficacy rating scales were: 1) Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I) scales, 2) the Children's Global Assessment Scale (CGAS), 3) the

Multidimensional Anxiety Scale for Children (MASC), and 4) the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q). Safety assessments included review of adverse events, clinical laboratory data, physical examinations, ECGs, body weight, and vital signs.

Statistical Methods: Changes from baseline to endpoint (Last Observation Carried Forward or LOCF) in the CDRS-R total score, CDRS-R sub-factor scores, CGI-S, CGAS score, MASC score, and PQ-LES-Q score were examined and compared between treatment groups using analysis of covariance (ANCOVA) model. The ANCOVA model contained treatment, age group (child and adolescent strata are used in this model) and baseline effects. The LOCF values of the CGI-I score were examined using analysis of variance (ANOVA) model with treatment and age group effects. Changes from baseline to each of the follow-up visits in the CDRS-R total score and the CGI-S were analyzed by a repeated-measures mixed model. The model included the baseline effect, the random subject effect and the fixed effects of site, treatment, age group, week and week by treatment interaction. The same mixed model (without the baseline effect) was used to analyze the CGI-I scores at each follow-up visit. Treatment comparisons of CDRS-R response rates, CGI-I response rates, remitters, and remitted responders were performed using the Cochran-Mantel-Haenzel (CHM) methods with centers as strata. All statistical tests were two-sided and performed at 0.05 significance level.

Efficacy Results: One hundred eighty-one (93 sertraline; 88 placebo) subjects were included in the ITT analyses. The mixed model analysis showed a statistically significant difference in favor of the sertraline group in the change in CDRS-R averaged over the follow-up visits and, in particular, at the final visit at week 10. There was no statistically significant difference between the treatment groups in the change in CDRS-R total score from baseline to endpoint due to a difference between treatment groups in the rate of discontinuation from the study. Significantly greater improvement ($p<0.01$) was seen in the sertraline group compared to the placebo group as measured by the CGI-S and CGI-I scores averaged over the follow-up visits and at week 10. Sertraline-treated subjects completing 10 weeks of therapy had significantly better CGI-S and CGI-I scores compared with placebo-treated subjects. Again, due to the differential discontinuation rate no significant difference was noted in the endpoint scores for these two rating scales between treatment groups.

For subjects completing 10 weeks of therapy, the proportion of CGI-I Responders (percentage of subjects who had a CGI-I score of 1 or 2 at endpoint) was statistically significantly higher in the sertraline group than in the placebo group. No statistically significant difference was noted in treatment groups at Endpoint (LOCF) in any of the responder analyses.

The adjusted scores for the MASC were significantly higher for sertraline treated subjects than for placebo treated subjects. Adolescents treated with sertraline scored

significantly higher on the PQ-LES-Q than did placebo-treated adolescents, but statistical significance was not reached for the entire ITT population on this rating scale.

Safety Results: The safety results are summarized in the following table.

Summary of Safety Results

	Number of Subjects Evaluated; (With Event); [Discontinued due to Event]	
	Sertraline	Placebo
	N	N
TEAE (all causality)[1]	97 (87)[10]	91 (73) [0]
TEAE (treatment-related)	97 (66) [5]	91 (49) [0]
Serious Adverse Events	97 (5) [4]	91 (1) [0]
Serious Adverse Events (treatment-related)	97 (0) [0]	91 (0) [0]
Clinically Significant Laboratory Test Abnormalities	85 (25) [0]	86 (23) [0]

TEAE = treatment emergent adverse event

TEAEs reported in ≥2% of sertraline-treated subjects and at least twice the incidence of the placebo group included mouth dry, hyperkinesia, stools loose, vomiting, arthralgia, aggressive reaction, agitation, anorexia, depression aggravated, suicidal ideation, sinusitis, vision abnormal, migraine, micturition frequency, tremor, and urinary incontinence. The majority of the adverse events in both treatment groups were mild or moderate in severity.

Children in the placebo group had a higher incidence (5% or greater difference between age or treatment groups) of abdominal pain and pharyngitis than did subjects in any of the other groups. In both treatment groups, the incidence of upper respiratory tract infection, abdominal pain, agitation, and accidental injury was higher in children than in adolescents, whereas the incidence of headache, and nausea was higher in adolescents than in children.

There were no deaths reported in this study. Five sertraline-treated subjects and 1 placebo-treated subject experienced serious adverse events. Suicidal ideation was the only serious adverse events that occurred in more than 1 subject. Suicidal ideation occurred in 3 subjects (3 sertraline; 0 placebo). None of the serious adverse events were considered treatment-related.

The incidence of clinically significant laboratory abnormalities was comparable between the two treatment groups. No subject discontinued prematurely from the study as a result of clinically significant laboratory abnormalities.

Incidences of clinically significant changes in vital signs, ECGs, and changes in physical examination findings from baseline were comparable between the two treatment groups.

A statistically significant increase in weight for placebo-treated subjects compared to sertraline-treated subjects was observed.

Conclusions: The sertraline group showed significantly more improvement than the placebo group as measured by the primary efficacy variable, CDRS-R, and the CGI-S and CGI-I averaged over the follow-up visits and, in particular at the final follow-up visit at week 10.

Sertraline was generally well tolerated in both children and adolescents with major depressive disorder, although there was a notable difference in study discontinuation rate between the two groups with 32 subjects treated with sertaline discontinuing prematurely from the study compared to 14 placebo-treated subjects. The reported reasons for discontinuation were multifactorial in the sertraline group, though the most commonly reported reasons were either adverse event or subject defaulted. The incidence of adverse events reported in this study was similar to that previously reported for pediatric obsessive-compulsive disorder and incorported into the Zoloft® package insert.

Sertraline was shown to be safe and effective in the treatment of MDD when administered for 10 weeks at a dose of 50 to 200 mg/day in subjects 6 to 17 years of age.

FINAL STUDY REPORT: SERTRALINE PROTOCOL A0501017

A MULTICENTER 10-WEEK RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED FLEXIBLE DOSE OUTPATIENT STUDY OF SERTRALINE IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

COUNTRY	PRINCIPAL INVESTIGATOR
See next page	

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PHASE OF DEVELOPMENT: Phase 3

STUDY DATES: 08 February 2000 – 26 March 2001

REPORT DATE: 10 October 2001

SPONSOR'S SIGNATORIES:

This study was conducted according to local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
USA		
		, MD
		MD
Canada		
Costa Rica		
Mexico		
Brazil		
India		

*Investigational sites that received study drug but did not randomize any subjects.
†Principal investigator (PI) changed during the course of the study. Most recent PI is listed first.

PROTOCOL A0501017: **A Multicenter 10-Week Randomized Double-blind Placebo-controlled Flexible Dose Outpatient Study of Sertraline in Children and Adolescents With Major Depressive Disorder**

Principal Investigators:

USA

Canada

Costa Rica

Mexico

Brazil

India

*Investigational sites that received study drug but did not randomize any subjects.

Study Publication: None

Study Dates: 08 February 2000 – 26 March 2001

Phase of Development: Phase 3

Study Objectives: To evaluate the safety and efficacy of sertraline compared with placebo in children and adolescents (6 to 17 years of age) who were outpatients with major depressive disorder (MDD).

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, flexible dose outpatient trial of sertraline in children (6 to 11 years of age) and adolescents (12 to 17 years of age) with MDD. Following a two-week screening period, eligible subjects were randomized to either sertraline or placebo in a 1:1 ratio with a 1:1 stratification of children to adolescents. Approximately 160 subjects were to be treated (80 sertraline; 80 placebo). The double-blind treatment phase was of 10 weeks duration.

Evaluation Groups: One hundred eighty-eight subjects (92 sertraline; 96 placebo) were randomized to double-blind treatment. One hundred eighty-five subjects (92 sertraline; 93 placebo) were treated with study drug. Of the 188 randomized subjects, 78 subjects (84.8%) in the sertraline group and 79 subjects (84.9%) in the placebo group completed treatment. The following table shows the number of subjects evaluable for efficacy and safety analyses by treatment group.

Subject Evaluation Groups

	Sertraline N (%)	Placebo N (%)
Randomized	92	96
Treated	92	93
Completed study	78 (84.8)	79 (84.9)
Discontinued study	14 (15.2)	14 (15.1)
Analyzed for efficacy		
Intent-to-treat	92 (100.0)	91 (97.8)
Efficacy evaluable	82 (89.1)	78 (83.9)
Analyzed for safety		
Adverse events	92 (100.0)	93 (100.0)
Laboratory data	90 (97.8)	88 (94.6)

Diagnoses and Criteria for Inclusion of Subjects: Children (6 to 11 years of age) and adolescents (12 to 17 years of age) diagnosed with a current episode of MDD, whose Children's Depression Rating Scale-Revised (CDRS-R) score was ≥45 and Clinical Global Impression Severity of Illness (CGI-S) score was ≥4, and who met all of the inclusion and none of the exclusion criteria were enrolled in this study.

Drug Administration:

Dosage Form	25 mg sertraline tablets, FID No. QC2186 50 mg sertraline tablets, FID No. QC1457 Placebo tablets, FID Nos. G00308AA and QC1458
Dosing	25 mg/day for the first 3 days followed by 50 mg/day through the first 2 weeks. Thereafter, the dose could be increased in increments of 50 mg/day in intervals of two weeks up to a maximum of 200 mg/day, depending on clinical response and dose-limiting side effects.
Duration	10 weeks of double-blind treatment

Efficacy and Safety Evaluations: Efficacy assessments were done at the screening visits (Day 1 and 7), baseline (Day 14 of screening), and at end-of-week (EOW) visits 1,

2, 3, 4, 6, 8, and 10. Several efficacy-rating scales were used to rate the subject's progress during the study. The primary efficacy rating scale specified by the protocol was the Children's Depression Rating Scale Revised (CDRS-R). The secondary efficacy rating scales were: 1) Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I) scales, 2) the Children's Global Assessment Scale (CGAS), 3) the Multidimensional Anxiety Scale for Children (MASC), and 4) the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q). Safety assessments included review of adverse events, clinical laboratory data, physical examinations, ECGs, body weight, and vital signs.

Statistical Methods: Changes from baseline to endpoint (Last Observation Carried Forward or LOCF) in the CDRS-R total score, CDRS-R sub-factor scores, CGI-S, CGAS score, MASC score, and PQ-LES-Q score were examined and compared between treatment groups using analysis of covariance (ANCOVA) model. The ANCOVA model contained treatment, age group (child and adolescent strata are used in this model) and baseline effects. The LOCF values of the CGI-I score were examined using analysis of variance (ANOVA) model with treatment and age group effects. Changes from baseline to each of the post-baseline visits in the CDRS-R total score and the CGI-S were analyzed by a repeated-measures mixed-model. The model included the baseline effect, the random subject effect, and the fixed effects of center, treatment, age group, week and week by treatment interaction. The same mixed-model (without the baseline effect) was used to analyze the CGI-I scores at each post-baseline visit. Treatment comparisons of CDRS-R response rates, CGI-I response rates, remitters, and remitted responders were performed using the Cochran-Mantel-Haenzel (CHM) methods with centers as strata. All statistical tests were two-sided and performed at 0.05 significance level.

Efficacy Results: One hundred eighty-three (92 sertraline; 91 placebo) subjects were included in the ITT analyses. There were no statistically significant differences between the two treatment groups in the adjusted mean change in CDRS-R total score from baseline to endpoint. With respect to the adjusted mean change from baseline to endpoint in CDRS-R individual items, sertraline-treated subjects showed a significant improvement over placebo-treated subjects in listless speech (p=0.011), irritability (p=0.014), and hypoactivity (p=0.014).

The proportion of CDRS-R responders (percentage of subjects who had a 40% decrease in the adjusted CDRS-R total score from baseline to endpoint) at Endpoint was statistically significantly higher in the sertraline group than in the placebo group.

The adjusted scores for CGI-S, CGI-I, and MASC were lower for sertraline-treated subjects than for placebo-treated subjects. For PQ-LES-Q and CGAS scores, sertraline-treated subjects had higher adjusted mean changes from baseline when compared with placebo-treated subjects. However, the superior responses in the sertraline group did not reach statistical significance.

Safety Results: The safety results are summarized in the following table.

Summary of Safety Results

	Number of Subjects Evaluated; (With Event); [Discontinued due to Event]	
	Sertraline	Placebo
	N	N
TEAE (all causality)	92 (83) [7]	93 (78) [4]
TEAE (treatment-related)	92 (60) [5]	93 (45) [0]
Serious Adverse Events	92 (2) [2]	93 (5) [2]
Serious Adverse Events (treatment-related)	92 (1) [1]	93 (0) [0]
Clinically significant laboratory test abnormalities	90 (30) [0]	88 (28) [1]

The most frequently occurring treatment emergent adverse events (TEAEs) reported in ≥2% of sertraline-treated subjects and with an incidence rate of at least twice that in the placebo group included diarrhea, anorexia, agitation, fever, urinary incontinence, dysuria, tremor, epistaxis, and rhinitis. Diarrhea, fever, and anorexia were reported in ≥5% of subjects and at a 5% or higher rate in the sertraline group than in the placebo group. Upper respiratory tract infection occurred at a higher rate in the placebo group than in the sertraline group. The majority of the adverse events in both treatment groups were mild or moderate in severity. Seven (7.6%) sertraline-treated subjects and 4 (4.3%) placebo-treated subjects were discontinued prematurely due to adverse events and laboratory test abnormalities (1 subject in each treatment group for laboratory test abnormalities).

Children in the sertraline group had a higher incidence of diarrhea, anorexia, epistaxis, and urinary incontinence than did subjects in any of the other groups (children treated with placebo, adolescents treated with sertraline or placebo). In both treatment groups, of the TEAEs that occurred in more than 2 subjects, the incidence of vomiting, influenza-like symptoms, anorexia, and gastroenteritis was higher in children than in adolescents, whereas the incidence of nausea, dyspepsia, back pain, pain, upper respiratory tract infection, and dizziness was higher in adolescents than in children.

There were no deaths reported in this study. Two sertraline-treated subjects and 5 placebo-treated subjects experienced serious adverse events. Suicide attempt and appendicitis were the only serious adverse events that occurred in more than 1 subject. Suicide attempt occurred in 4 subjects (2 sertraline; 2 placebo) and appendicitis occurred in 2 placebo-treated subjects. Suicide attempt by one sertraline-treated subject was the only serious adverse event that was considered by the investigator to be related to study drug. The sponsor concluded that the suicide attempt was related to the disease under study.

The incidence of clinically significant laboratory abnormalities was comparable between the two treatment groups. One placebo-treated subject discontinued from the study due to a clinically significant elevation in total bilirubin levels. One sertraline-treated subject discontinued due to elevated SGOT (ALT) levels. However, this elevation in SGOT (ALT) levels was not clinically significant.

Incidences of clinically significant changes in vital signs, ECGs, and changes in physical examination findings from baseline were comparable between the two treatment groups. A statistically significant increase in weight for placebo-treated subjects was observed.

Conclusions: In general, sertraline was numerically superior to placebo on efficacy measures. However, for the primary endpoint, the CDRS-R change from baseline to endpoint, as well as some of the secondary endpoints, these changes did not reach statistical significance. Sertraline was superior to placebo in CDRS-R individual item scores for listless speech, irritability, and hypoactivity. The proportion of CDRS-R responders (percentage of subjects who had a 40% decrease in the adjusted CDRS-R total score from baseline to endpoint) at Endpoint was statistically significantly higher in the sertraline group than in the placebo group. Sertraline was shown to be safe in the treatment of MDD when administered for 10 weeks at a dose of 25 to 200 mg/day to children and adolescents 6 to 17 years of age.

ORIGINAL CONTRIBUTION

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Efficacy of Sertraline in the Treatment of Children and Adolescents With Major Depressive Disorder

Two Randomized Controlled Trials

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Context The efficacy, safety, and tolerability of selective serotonin reuptake inhibitors (SSRIs) in the treatment of adults with major depressive disorder (MDD) are well established. Comparatively few data are available on the effects of SSRIs in depressed children and adolescents.

Objective To evaluate the efficacy and safety of sertraline compared with placebo in treatment of pediatric patients with MDD.

Design and Setting Two multicenter randomized, double-blind, placebo-controlled trials were conducted at 53 hospital, general practice, and academic centers in the United States, India, Canada, Costa Rica, and Mexico between December 1999 and May 2001 and were pooled a priori.

Participants Three hundred seventy-six children and adolescents aged 6 to 17 years with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*–defined MDD of at least moderate severity.

Intervention Patients were randomly assigned to receive a flexible dosage (50-200 mg/d) of sertraline (n=189) or matching placebo tablets (n=187) for 10 weeks.

Main Outcome Measures Change from baseline in the Children's Depression Rating Scale–Revised (CDRS-R) Best Description of Child total score and reported adverse events.

Results Sertraline-treated patients experienced statistically significantly greater improvement than placebo patients on the CDRS-R total score (mean change at week 10, −30.24 vs −25.83, respectively; $P=.001$; overall mean change, −22.84 vs −20.19, respectively; $P=.007$). Based on a 40% decrease in the adjusted CDRS-R total score at study end point, 69% of sertraline-treated patients compared with 59% of placebo patients were considered responders ($P=.05$). Sertraline treatment was generally well tolerated. Seventeen sertraline-treated patients (9%) and 5 placebo patients (3%) prematurely discontinued the study because of adverse events. Adverse events that occurred in at least 5% of sertraline-treated patients and with an incidence of at least twice that in placebo patients included diarrhea, vomiting, anorexia, and agitation.

Conclusion The results of this pooled analysis demonstrate that sertraline is an effective and well-tolerated short-term treatment for children and adolescents with MDD.

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MAJOR DEPRESSIVE DISORder (MDD) occurs not only in adults but also in children and adolescents.[1-11] Prevalence rates of up to 3% in children and 8% in adolescents have been reported,[3] and the lifetime prevalence rate for depression in youths aged 15 to 18 years has been estimated at 14% to 15%,[12] which is comparable with that in adults.[13] In general, the clinical course of the disease is similar in pediatric and adult patients, although there is some evidence that early-onset MDD may represent a more pernicious form of the disease.[4,14] Patients diagnosed as having MDD during childhood or adolescence face a 2- to 4-fold greater risk of developing depression as young adults than do children or adolescents without MDD.[14-16]

For editorial comment see p 1091.

The social and economic costs associated with pediatric MDD are high and may carry over into adulthood, including more frequent hospitalizations and lower educational and earning potential.[14,15,17] In addition, a quarter of adolescents with MDD develop substance

Author Affiliations, Financial Disclosures, and the Sertraline Pediatric Depression Study Group Investigators are listed at the end of this article.
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abuse disorders[3] and approximately half attempt suicide at some time during their lives. Among children with MDD, there is a 4- to 5-fold higher lifetime risk of suicide attempt than in healthy controls.[14,15,18]

Despite the costs and prevalence of the disorder, MDD is frequently underdiagnosed and inadequately treated.[19] For pediatric patients, this problem has been compounded by the discouraging results of early psychopharmacological studies, in which tricyclic antidepressants were consistently found to be no more effective than placebo in treating depressed youths.[20] On the basis of their good safety profile and established efficacy in treatment of adults with MDD, selective serotonin reuptake inhibitors (SSRIs) are routinely cited as the best available treatment option for depressed children and adolescents.[21,22] Empirical evidence of the effectiveness of SSRIs in this patient population has been limited, however. Several small uncontrolled trials of SSRIs[23-28] and a single-center (N=96) placebo-controlled trial of fluoxetine[29] have suggested efficacy. Published reports of 2 large multicenter, placebo-controlled studies of fluoxetine[30] and paroxetine[31] also reported favorable results, but statistical significance was not achieved for their primary end points.

Encouraging results have been reported in 3 small, open-label studies of sertraline in adolescents with MDD[32-34] and in a retrospective chart review of pediatric patients.[35] Herein, we report the pooled results of 2 identically designed, concurrently conducted 10-week international, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials of sertraline vs placebo in children and adolescents with MDD.

METHODS

Study Participants

Participants were outpatients aged 6 to 17 years who met the diagnostic criteria for MDD, as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)[1] and as determined by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL).[36] For study entry eligibility, these diagnostic criteria had to be met at the first and third visits during a 2-week screening period and the current episode of major depression had to be of at least 6 weeks' duration. At all 3 visits during the screening period, patients were required to have a Children's Depression Rating Scale–Revised (CDRS-R) score of at least 45[37,38] and a Clinical Global Impression of Severity of Illness (CGI-S) rating of at least 4,[39] indicating at least moderate severity of illness. Exclusion criteria included current, primary, *DSM-IV*–defined diagnosis of attention-deficit/hyperactivity disorder, conduct disorder, obsessive-compulsive disorder, or panic disorder; history of bipolar disorder; any current psychotic features; and history of psychotic disorders or autistic spectrum disorders. Patients who had previously attempted suicide or who were judged to pose a significant suicidal or homicidal risk were also excluded. Patients were also excluded if screening electrocardiographic or laboratory test results, vital signs, or body weight were clinically significantly outside the normal range. Other exclusion criteria included a positive serum β-human chorionic gonadotropin pregnancy test (among girls aged 12-17 years) at the second screening visit, previous enrollment in a sertraline study, medical contraindications to treatment with SSRIs, and history of failure to respond to a clinically adequate dosing regimen of an SSRI. Patients were required to be free of psychotropic medication (with the exception of diphenhydramine or chloral hydrate as sleep aids) for at least 2 weeks (at least 4 weeks for fluoxetine) prior to initiation of double-blind study drug treatment.

Study Design

The 2 trials, developed in response to a US Food and Drug Administration (FDA) written request, were identically designed and were conducted at 53 hospital, general practice, and academic centers in the United States, India, Canada, Costa Rica, and Mexico. Participation in the study was based on inspection of the study site by 1 of the authors (C.W.) or a designate. Criteria for investigator participation included but was not limited to previous experience with multicenter research trials, expertise in pediatric psychiatry, and a clear understanding of Good Clinical Practices, as outlined in the US Code of Federal Regulations. Additionally, study conduct was reviewed at investigators' meetings, and all investigators who conducted interviews using the CDRS-R were required to first pass a certification test. During the study, all sites were regularly monitored. When necessary, additional training regarding completion of study documents, retention of source documents, and conduct of ratings was provided on a personal level. All data collected were reviewed for errors in formatting and for inconsistency.

Enrollment began in December 1999 and follow-up ended in May 2001. Both trials were approved by institutional review boards or ethics committees for each study center. Informed assent or written permission of the child or adolescent and written informed consent of at least 1 parent or legal guardian were obtained.

The trials began with the 2-week pretreatment screening period. During these screening visits, diagnosis of MDD was confirmed using the K-SADS-PL and clinical history and symptom severity was assessed using the CDRS-R and CGI-S. Physical and laboratory evaluations were performed at the second screening visit. At the third screening visit (baseline), patients who remained eligible for study entry were randomly assigned to double-blind receipt of either sertraline or matching placebo for 10 weeks in a 1:1 ratio using a computer-generated randomization code. To ensure that each treatment group included similar numbers

of younger and older children, patients were stratified into 2 age groups: children (aged 6-11 years) and adolescents (aged 12-17 years). Study drug was packaged in identical blister packs containing 25-mg and/or 50-mg sertraline tablets or matching placebo. For all patients, treatment was initiated at a dosage of 25 mg/d for the first 3 days and was continued at a dosage of 50 mg/d through the end of the second week. Thereafter, in the absence of dose-limiting adverse events, the dosage could be flexibly titrated upward in increments of 50 mg/d every 2 weeks to a maximum of 200 mg/d until a satisfactory clinical response was achieved. Both patients and clinicians were blinded to group assignment.

With the exception of diphenhydramine and chloral hydrate, which could be used intermittently as sleep aids, concomitant treatment with a psychotropic drug was not permitted. Patients were not permitted to receive cognitive behavioral therapy during the study. Other types of psychotherapy were permitted, provided that they did not specifically address issues of depression and had been under way for at least 2 months prior to the initial screening visit. Patients could be discontinued from the study at an investigator's discretion for reasons such as adverse events and failure to improve despite increases in the study drug dosage.

Outcome Measures, Schedule of Assessments, and Sample Size

The primary efficacy rating scale was the CDRS-R, a validated 17-item, clinician-rated instrument that measures the severity of a patient's depressive symptoms, with total possible scores ranging from 17 to 113. Fourteen of the 17 items are rated on a scale from 1 to 7, with an item score of 3 suggestive of mild, 4 or 5 moderate, and 6 or 7 severe symptoms. The other 3 items are rated on a scale from 1 to 5. Both children and their parents provide input into the first 14 items of the scale. A child's nonverbal behavior is rated by the observer for items 15 through 17. The prospectively defined primary efficacy outcome measure was the CDRS-R Best Description of the Child total score, which is based on the highest (most severe) rating provided for each item by a valid, reliable source, in the judgment of the investigator; sources included the child, parent or legal guardian, and other available sources.[37,38] Secondary efficacy measures included the proportion of CDRS-R responders, defined a priori as patients who had at least a 40% decrease in the adjusted CDRS-R total score (CDRS-R total minus 17, the minimum possible total score); scores on the CGI-S and the Clinical Global Impression of Improvement (CGI-I) scales, clinician-rated instruments that assess a patient's severity of illness and global improvement, respectively[39]; and the proportion of CGI-I responders, defined as patients with a CGI-I score of 2 or lower ("very much" or "much" improved). The CDRS-R and CGI-S measurements were collected at all 3 screening visits and, along with the CGI-I, at the end of weeks 1, 2, 3, 4, 6, 8, and 10 of double-blind treatment (or at the time of early discontinuation).

Patient-rated secondary efficacy measures included the Multidimensional Anxiety Scale for Children (MASC), which is used to assess symptoms of anxiety[40]; the Children's Global Assessment Scale (CGAS), which measures a patient's social functioning[41]; and the total score on the 15-item Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q), a measure of a patient's quality of life (Jean Endicott, PhD, unpublished data, 2002). This scale was adapted from the Q-LES-Q, a validated instrument that assesses quality of life in adults and that has been shown to be sensitive to drug-placebo differences in mood and anxiety.[42] These assessments were made at baseline and at the end of week 10 of double-blind treatment (or at the time of early discontinuation).

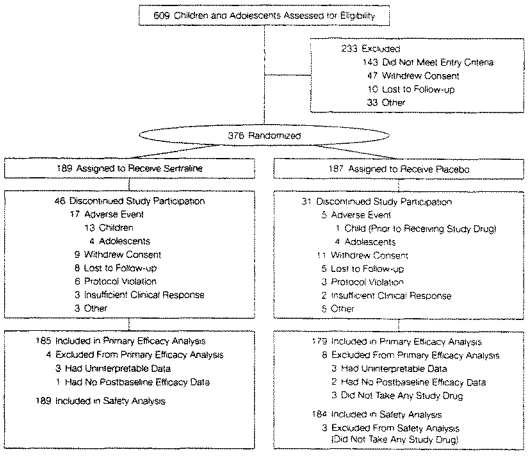
Safety data were collected from the first day of double-blind study drug receipt through 7 days after the last dose of double-blind study drug was taken and included vital signs (blood pressure and pulse), body weight, and all adverse events reported by patients or observed by investigators. A serious adverse event was defined, according to established criteria, as any event that resulted in death or was life-threatening or that resulted in inpatient hospitalization or prolongation of a hospital stay, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Blood samples for routine hematologic and serum chemistry studies and urine samples for routine urinalysis and drug testing were obtained at screening and the end of weeks 4 and 10 (or at the time of early discontinuation). Thyroid function was tested at screening and the pregnancy test was repeated at the end of weeks 4 and 10. A 12-lead electrocardiogram was obtained and a physical examination was performed at screening and the end of week 10 (or at the time of early discontinuation).

Based on the single-center study reported by Emslie et al,[29] a sample size for each trial of 160 patients, with 80 patients per treatment group, was calculated to provide 88% power for a 2-sided test at an α level of .05 to detect differences between treatment groups. The studies were not powered to detect differences between treatment groups within age groups.

Statistical Analyses

Data from both studies were pooled in a prospectively defined combined analysis. Using a repeated-measures mixed-model analysis, the mean changes from baseline to each postbaseline visit in the CDRS-R total and the CGI-S score were compared between treatment groups. For each measure, the mean changes from baseline to each postbaseline visit week were then averaged to give a mean overall change from baseline, and the mean overall changes from baseline were compared between treatment groups. The model included the baseline effect as covariate, the random subject effect, and the fixed effects of site, treatment, age group, week, and week-by-treatment interaction. The same mixed model (without the baseline

Figure 1. Flow of Patients Through the 2 Trials



effect) was used to compare the CGI-I scores at each postbaseline visit as well as the mean overall CGI-I score in each treatment group. Categorical variables (proportions of CDRS-R responders and CGI-I responders at study end point) were compared between treatment groups using Cochran-Mantel-Haenszel methods with centers as strata. Changes from baseline to study end point in the MASC, CGAS, and PQ-LES-Q total scores (using the last-observation-carried-forward method) were compared between treatment groups using an analysis of covariance model that contained study treatment group, age group, and baseline effects. As described in the statistical analysis plan, centers with fewer than 4 patients were combined to form 1 pooled center within each trial, and an additional pooled center was generated from centers with exactly 4 patients. This "sort and pool" procedure was chosen as the most objective and conservative way to pool because selective factors such as location and language/culture were not used. For all statistical tests, a 2-sided $P \leq .05$ was considered significant. Assumptions regarding the linearity of data were made in the analysis plan and were tested following database release. No gross violation of linear model assumptions was detected; therefore, nonparametric analyses were not performed. Descriptive statistics were used to summarize safety results. SAS version 8.2 (SAS Institute Inc, Cary, NC) was used for the efficacy analysis and SAS version 6.12 was used for safety data.

RESULTS

Patient Disposition

As shown in FIGURE 1, 376 patients were randomly assigned to double-blind treatment with either sertraline (n = 189) or placebo (n = 187). All 189 patients randomized to sertraline and 184 of the patients randomized to placebo received at least 1 dose of double-blind study drug and were included in the safety evaluation. Patients were randomized by the following countries: United States, 297; India, 44; Costa Rica, 16; Canada, 14; and Mexico, 5. The intention-to-treat population was modified as follows: 1 sertraline-treated and 2 placebo patients were excluded from the efficacy analysis because no postrandomization efficacy data were collected, and 3 sertraline-treated and 3 placebo patients, all from 1 US site, were excluded because of problems with data collection. Thus, 185 sertraline-treated patients (98%) and 179 placebo patients (97%) were included in the efficacy analysis. Forty-six sertraline-treated patients (24%) and 31 placebo patients (17%) discontinued the study early. Among patients treated with sertraline, the most common reasons for discontinuation were adverse events (n = 17; 9%), withdrawal of consent (n = 9; 5%), and loss to follow-up (n = 8; 4%). Similar proportions of placebo patients discontinued from the study because they withdrew consent (n = 11; 6%) or were lost to follow-up (n = 5; 3%); fewer placebo patients (n = 5, 1 of whom had not received study drug; 3%) discontinued because of adverse events. This difference was more apparent in children, among whom 13 sertraline-treated patients but no placebo patients discontinued because of adverse events.

Demographic and Background Characteristics

The 2 treatment groups were evenly balanced with respect to race, weight, clinical characteristics, and psychosocial stressors at baseline (TABLE 1). There was a statistically significant between-group difference in sex (57% of sertraline-treated and 45% of placebo patients were female; $P = .02$) but no significant interaction by age group for the primary and secondary efficacy variables. The majority of patients in both treatment groups (≥86%) were in their first lifetime MDD episode, whereas the others (<14%) were having a recurrent episode. In both subsets of patients, onset of illness occurred at approximately 10 years of age. There were no statistically significant differences in mean baseline CDRS-R or CGI-S scores between

treatment groups. Nearly 40% of patients had at least 1 comorbid psychiatric disorder, with the most common (occurring in ≥5% of patients) being oppositional defiant disorder, anxiety, adjustment reaction, and phobic disorders. More than half of patients had a family history of MDD. The most common stressors included parental divorce or separation and death of a relative or friend. Only about half of patients were living with their biological father.

Table 1. Baseline Demographic, Clinical, and Psychosocial Characteristics of Patients by Treatment Group*

Characteristics	Sertraline (n = 189)	Placebo (n = 187)
Demographic characteristics		
Sex		
Male	81 (42.9)	103 (55.1)
Female	108 (57.1)	84 (44.9)
Age group, y		
6-11 (Children)	86 (45.5)	91 (48.7)
12-17 (Adolescents)	103 (54.5)	96 (51.3)
Race		
White	135 (71.4)	130 (69.5)
Asian	26 (13.8)	23 (12.3)
Hispanic	15 (7.9)	19 (10.2)
Black	7 (3.7)	9 (4.8)
Other	6 (3.2)	6 (3.2)
Clinical characteristics		
Patients with single-episode MDD, mean (range)†		
Age at onset of illness, y	10.0 (1.3-16.8)	10.1 (1.2-16.9)
Duration of illness, mo	22.1 (1.5-107.6)	19.1 (1.1-119.3)
Patients with recurrent MDD, mean (range)†		
Age at onset of illness, y	9.6 (3.0-15.8)	10.3 (4.0-14.5)
Duration of illness, mo	43.7 (3.0-132.0)	39.8 (6.0-108.0)
CDRS-R score, mean (SD)‡	64.3 (11.0)	64.6 (11.0)
CGI-S score, mean (SD)§	4.6 (0.6)	4.5 (0.7)
Psychosocial characteristics		
≥1 Other psychiatric disorder	73 (38.6)	71 (38.0)
Family history of MDD	97 (51.3)	104 (55.6)
Parents were divorced or separated	80 (42.3)	86 (45.9)
Experienced death of close family member/friend	73 (38.6)	64 (34.2)
Biological mother living in same household	164 (86.7)	168 (89.8)
Biological father living in same household	92 (48.6)	98 (52.4)

Abbreviations: CDRS-R, Children's Depression Rating Scale–Revised; Best Description of Child total score; CGI-S, Clinical Global Impression of Severity of Illness scale; MDD, major depressive disorder.
*Data are expressed as No. (%) unless otherwise indicated.
†For sertraline, n = 171 with single episodes and n = 18 with recurrent episodes; for placebo, n = 161 with single episodes and n = 26 with recurrent episodes.
‡For sertraline, n = 185 and for placebo, n = 179 patients in efficacy analysis.
§For sertraline, n = 185 and for placebo, n = 178 patients in efficacy analysis.

Efficacy

As can be seen in FIGURE 2 and TABLE 2, sertraline-treated patients exhibited significantly greater improvement over the course of the study than those receiving placebo on the CDRS-R (mean change in scores of −22.84 vs −20.19, respectively; $P = .007$), as well as on the CGI-S and CGI-I. Similar outcomes favoring sertraline were observed among patients who completed all 10 weeks of double-blind treatment (mean changes in the CDRS-R total score of −30.24 vs −25.83, respectively, $P = .001$; and in the CGI-S of −1.99 vs −1.58, respectively, $P = .001$; and mean CGI-I scores of 2.02 and 2.30, respectively, $P = .009$). Week-by-week analyses showed that significant differences in favor of sertraline were apparent as early as week 1 on the CGI-I and week 3 on the CDRS-R and the CGI-S ($P < .05$).

The adjusted mean change from baseline to study end was assessed for the individual items of the CDRS-R. Statistically significantly greater improvement was noted with sertraline treatment for 5 of the 17 items, including irritability ($P < .001$), low self-esteem ($P = .02$), excessive weeping ($P = .003$), listless speech ($P = .005$), and hypoactivity ($P = .03$). The change in depressed feelings was of borderline significance ($P = .05$), as was difficulty having fun ($P = .09$). No statistically significant difference was noted between treatment groups for suicidal ideation ($P = .78$), and the mean change was of similar magnitude between sertraline (−0.58) and placebo (−0.60).

Although the study was not powered to detect differences between age groups, a slightly greater difference in the CDRS-R mean change between treatment groups was noted in adolescents (sertraline, −21.55 vs placebo, −18.20; $P = .01$) than in children (sertraline, −24.05 vs placebo, −22.20; $P = .19$). Following 10 weeks of treatment, the difference in CDRS-R scores was of borderline significance in children (sertraline, −31.44 vs placebo, −27.56; $P = .05$) and remained significant in adolescents (sertraline, −28.95 vs placebo, −24.11; $P = .01$).

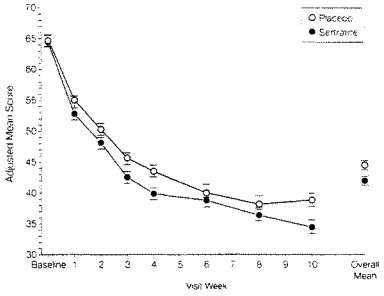
At study end point, using the last observations carried forward and the Cochran-Mantel-Haenszel method of analysis between treatment groups, 69% of sertraline-treated patients and 59% of placebo patients met the CDRS-R responder criteria ($P = .05$), and 63% of sertraline-treated patients compared with 53% of placebo patients met the CGI-I responder criteria ($P = .05$). In addition, significantly more sertraline-treated patients than placebo patients met the CDRS-R responder criteria at the end of weeks 1, 3, and 10 and the CGI-I responder criteria at the end of weeks 1, 2, 3, 4, and 10 ($P < .05$). With a 10% difference in responder rates for both the CDRS-R and CGI-I, the number needed to treat to expect a difference in response between sertraline and placebo would be 10 using either criterion. Patients treated with sertraline also had numerically better scores at study end point compared with placebo patients on the MASC,

PQ-LES-Q, and CGAS (Table 2). However, the differences between treatment groups did not reach statistical significance.

Tolerability

The mean dosage of study drug administered to patients who completed 10 weeks of double-blind treatment was 131 mg/d of sertraline and 144 mg/d of placebo equivalent, and the median duration of exposure to study drug was the same in both treatment groups (68 days). Sertraline in the dosage range of 50 to 200 mg/d was generally well tolerated. In the majority (>90%) of patients, adverse events were mild or moderate in intensity. There were 4 adverse events that occurred in at least 5% of sertraline-treated patients and with an incidence of at least twice that in placebo patients: diarrhea, vomiting, anorexia, and agitation (TABLE 3). Seventeen sertraline-treated patients (9%) discontinued the study because of adverse events; 13 of these patients were children. Seven sertraline-treated patients and 6 placebo patients had adverse events that met the established criteria for a "serious" adverse event, including suicide attempt (2 sertraline and 2 placebo), suicidal ideation (3 sertraline), and aggressive reaction (1 sertraline), as well as medical hospitalizations (1 sertraline and 4 placebo). There were no clinically important differences between the 2 treatment groups with respect to laboratory test, vital sign, physical examination, or electrocardiographic findings. The mean change in body weight from baseline to the final visit was −0.38 kg among patients treated with sertraline and +0.78 kg among placebo patients ($P = .001$).

Figure 2. Weekly and Overall Adjusted Mean CDRS-R Scores



CDRS-R indicates Children's Depression Rating Scale–Revised Best Description of Child total score. Data are least square means at each visit week, with mean scores averaged to give the overall mean, from a repeated-measures mixed-model analysis with age category, site, treatment, week, and week-by-treatment interaction used as fixed effects, subject as a random effect, and baseline effect as a covariate. Error bars indicate SE of the adjusted means, derived from the repeated-measures mixed-model procedure. *P* values are as follows: week 1, $P = .09$; week 2, $P = .08$; week 3, $P = .01$; week 4, $P = .008$; week 6, $P = .37$; week 8, $P = .18$; week 10, $P = .001$; and mean response, $P = .007$.

COMMENT

In the trials reported here, sertraline was found to be more effective than placebo for treatment of pediatric MDD, with statistically greater improvement occurring as early as week 3. Of the 3 randomized, double-blind, placebo-controlled trials of an SSRI in pediatric MDD that have been published to date,[30,31] only 1, the study by Emslie et al[31] of fluoxetine, reported statistically significantly better results for the prospectively defined primary end point, and this was a comparatively small (n = 96) single-center trial. Thus, our trials describe the largest positive psychopharmacological study of pediatric MDD, using an international multicenter study design.

The significance of the results is clinically as well as statistically relevant.

Table 2. Secondary End Point Measures

Measures	Baseline Score, Mean (SD)		Adjusted Overall Score, Mean (SE)*		Adjusted Change in Score From Baseline, Mean (SE)*		*P* Value†
	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo	
CGI-I	NA	NA	2.56 (0.06)	2.75 (0.06)	NA	NA	.009
CGI-S	4.57 (0.64)	4.54 (0.66)	3.33 (0.05)	3.55 (0.05)	−1.22 (0.05)	−1.01 (0.05)	.005
CGAS	50.21 (7.07)	49.71 (7.17)	66.00 (1.04)	64.69 (1.04)	16.04 (1.04)	14.74 (1.04)	.38
MASC	51.06 (19.0)	51.85 (20.09)	45.90 (1.17)	48.35 (1.16)	−5.56 (1.17)	−3.11 (1.16)	.14
PQ-LES-Q	49.43 (10.82)	48.92 (10.94)	55.63 (0.68)	53.85 (0.68)	6.46 (0.68)	4.68 (0.68)	.07

Abbreviations: CGAS, Children's Global Assessment Scale; CGI-I, Clinical Global Impression of Improvement scale; CGI-S, Clinical Global Impression of Severity of Illness scale; MASC, Multidimensional Anxiety Scale for Children; NA, not applicable; PQ-LES-Q, Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

*For the CGI-I and CGI-S, least square means and SEs are provided from a repeated-measures, mixed-model analysis with age category, site, treatment, week, and week-by-treatment interaction used as fixed effects in the model and subject used as a random effect. Baseline CGI-S score was used as a covariate for the analysis of CGI-S. Change from baseline of CGI-S and observed value of CGI-I were analyzed. For the CGAS, MASC, and PQ-LES-Q, last-observation-carried-forward least square means and SEs are provided from analysis of covariance, including protocol number, treatment, age, and baseline effects. Repeated-measures analysis was not used for these end points because values were collected only at baseline and study end.

†*P* values were derived from *t* tests and are the same for both adjusted overall scores and adjusted changes in scores.

Variability of response is typical in pediatric trials and was clearly evident in our study, as demonstrated by the high placebo response rates.[43] Larger variation in response is expected with greater numbers of participating sites because random errors from subject and measurement variation (particularly with subjective measurements) increase with a larger number of investigators with different degrees of experience.[44,45] We used a large number of sites (53) compared with a relatively small number of sites in the fluoxetine studies (15 and 1).[29,30] Additionally, the multinational nature of this study possibly contributed to the variability seen. While no statistically significant treatment-by-center, study, sex, or age interactions were noted, this does not entirely preclude an effect of variability, as long as the effect size from center to center was similar. The fact that no placebo-controlled study of tricyclic antidepressants in children has ever shown significant difference from placebo[20] suggests that even though the differences observed in this study were numerically small, they are nonetheless important.

Mean baseline levels of symptom severity were moderate to severe, as judged by the CDRS-R total scores, and these levels were mild following 10 weeks of treatment. Additionally, the degree of drug-placebo difference was similar to that observed with fluoxetine,[30] which was recently approved by the FDA for treatment of pediatric MDD. In fact, the magnitude of response was greater for sertraline (the mean change from baseline to study end point in CDRS-R total score was −22.0 for fluoxetine vs −14.9 for placebo; mean change from baseline to study end point in CDRS-R total score was −27.31 for sertraline vs −23.89 for placebo). A larger-than-expected percentage of patients in the fluoxetine study had self-rated depression scores that were in the lower range of severity, and approximately one third of those patients had comorbid attention-deficit/hyperactivity disorder, while less than 10% (36/376) of our patients did. It is unknown, however, whether these differences account for the differential treatment responses observed between the fluoxetine study results and ours.

The treatment effect size observed in these studies was modest in comparison with that typically observed in adult studies.[46] In part, this appears to be related to the relatively high rate of response to placebo in our patient sample (53%, CGI-I response rate). High placebo response rates have been a consistent feature of psychopharmacological studies of depressed adults,[46] and although studies of depressed youths are comparatively small in number, the data suggest that the placebo response rate is at least as high in this age population.[20,21,29,31] In our study, the exact nature of the high placebo response rate is unclear, but possible factors include frequent follow-up visits, the relatively large number of centers involved (increased variability), and language/cultural factors. Increased visit frequency and the attention associated with these visits may have an intrinsic component of therapy and is different than a "waiting period" control, in which there is no interaction. Furthermore, 8 placebo patients (4.3%) were receiving some form of psychotherapy during the course of the study and 29 (15.7%) had received psychotherapy prior to enrollment, potentially providing these patients with access to previously learned exercises. Thus, randomization to receipt of placebo does not imply complete lack of treatment.

Suicidality is an important concern in depressed patients. [Recently, regulators in the United States and the United Kingdom have issued advisories about the use of paroxetine, another SSRI, in the treatment of children and adolescents with MDD. The FDA is currently reviewing these data and a final determination regarding paroxetine and suicide risk has not yet been reached.] In our sertraline study, the number of suicide attempts was the same in each treatment group (2 for sertraline and 2 for placebo). Our trials showed a lack of significant difference in suicidal ideation between sertraline-treated and placebo patients, as measured by the CDRS-R. In patients who continued into the 24-week open-label extension study, only 1 episode of suicidal ideation was reported, and the investigator attributed this event to teasing by classmates. Additionally, the Best Pharmaceuticals for Children Act requires a review of adverse events for a period of 1 year after a drug is granted pediatric exclusivity. This review of sertraline's safety data was recently conducted by the FDA. The agency concluded: "These reports do not provide any safety signals that indicate that the Agency needs to do anything except continue to actively assess the evolving benefit-risk profile of these products [sertraline]."[47] Regardless, it is important to carefully supervise and assess the potential for suicidality in all patients with MDD, and larger studies on this issue should be conducted.

Table 3. Treatment-Emergent Adverse Events in Patients Analyzed for Safety*

Adverse Events	Sertraline	Placebo
Children†		
Insomnia	17 (19.8)	7 (8.0)
Diarrhea	13 (15.1)	4 (4.5)
Anorexia	9 (10.5)	2 (2.3)
Vomiting	8 (9.3)	4 (4.5)
Agitation	7 (8.1)	2 (2.3)
Urinary incontinence	6 (7.0)	0
Purpura	5 (5.8)	1 (1.1)
Adolescents‡		
Vomiting	8 (7.8)	3 (3.1)
Diarrhea	7 (6.8)	3 (3.1)

*Data are expressed as No. (%) for events occurring in at least 5% of sertraline-treated patients and with an incidence of at least 2 times that seen in placebo patients.
†For sertraline, n = 86 and for placebo, n = 86.
‡For sertraline, n = 103 and for placebo, n = 96.

Although our trials were not powered to detect differences by age group, there was some suggestion that sertraline may be more effective in adolescents. Further studies may be helpful to determine whether both age groups respond equally well to drug therapy.

Sertraline appears to be generally well tolerated, although these trials were powered only for efficacy. Patients treated with sertraline more frequently experienced agitation, anorexia, diarrhea, nausea, purpura, urinary incontinence, and vomiting. Although the incidence of dis-

continuations due to adverse events was similar between treatment groups in adolescents, a higher proportion of sertraline-treated children discontinued because of adverse events. The nature of this difference is unclear, although identical dosing regimens were used for both age groups and it is possible that the higher serum levels of sertraline in children[48] resulted in the greater incidence of adverse events. This may suggest a need for reduced initial doses or slower titration of sertraline in children compared with adolescents in an effort to improve tolerability. Regardless of age, careful symptomatic monitoring is warranted in all patients with MDD.

Discontinuation of sertraline was not associated with withdrawal symptoms in either the 10-week double-blind trials or the 24-week open-label extension study. All patients entering the extension study began open-label treatment with 50 mg/d of sertraline, regardless of their dosage in the double-blind study, and no significant untoward reactions were noted as a result of this dosage change.

The clinical importance of the weight difference noted in the 10-week trials is unclear, but in a subset of patients (n=226) who continued into the 24-week open-label extension study, this pattern was reversed and patients previously treated with sertraline displayed a mean weight gain (+2.98 kg) that was greater than in patients previously randomized to placebo (+1.22 kg).[49] Because appetite and weight changes are common in MDD, it is advisable for practitioners to monitor weight patterns in all patients with depression.

Acute studies such as reported here are limited by several factors, including the subjective nature of rating scales and the relatively short duration of treatment exposure. The applicability of these scales to younger patients with less developed insight and ability to form abstract thought is unclear. In addition, most patients were treated with doses of study drug lower than the maximum allowed by the protocol, and it is possible that in a longer-term study, investigators would have titrated the dosage to higher levels. Although no dose-response relationship for sertraline has been demonstrated, patients who do not respond initially to lower dosages may respond to dosage escalation, up to a maximum of 200 mg/d.

Major depressive disorder is a serious public health problem that is frequently underdiagnosed and inadequately treated.[1a] Given the paucity of empirical data available to guide physicians in the psychopharmacological treatment of pediatric MDD, further research is needed. Whether lower initial dosages in children would improve tolerability or long-term sertraline treatment in children and adolescents would result in maintenance of effect and an improvement of quality of life deserves study. Nonetheless, the results reported here support the conclusion that sertraline is an effective, safe, and well-tolerated short-term treatment for children and adolescents with MDD.

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Psychopharmacological Treatment of Major Depressive Disorder in Children and Adolescents

Christopher K. Varley, MD

THE REPORT BY WAGNER AND COLLEAGUES[1] IN THIS ISSUE of THE JOURNAL, a pooled analysis of 2 multicenter, double-blind, randomized placebo-controlled trials evaluating the effect of the selective serotonin reuptake inhibitor (SSRI) sertraline on children and adolescents aged 6 to 17 years with major depressive disorder (MDD), constitutes the largest positive psychopharmacological study of MDD in this age group reported to date. The primary outcome was change from baseline in the Children's Depression Rating Scale–Revised (CDRS-R), with a prospectively determined primary efficacy measure of the CDRS-R Best Description of Child total score; secondary efficacy measures included the proportion of CDRS-R responders, defined as patients who had at least a 40% decrease in the adjusted CDRS-R total score. The results indicate a statistically significant improvement for patients receiving active drug vs those receiving placebo.

An increasing body of knowledge confirms that depression is a common and serious illness in youth, affecting 3% to 8% of children and adolescents.[2] Moreover, rates of depression increase dramatically as children move into adolescence.[3] An estimated 20% of adolescents have had at least 1 episode of MDD by age 18 years, while 65% report transient, less severe depressive symptoms.[4,5] Depression compromises the developmental process; feelings of worthlessness, low self-esteem, and thoughts of suicide are common, as are difficulties with concentration and motivation.[6] As many as 20% of adolescents each year have suicide ideation and 5% to 8% attempt suicide.[7] While the majority of attempts are not lethal, suicide is a leading cause of death in adolescents and is a major health care concern. One of the major risk factors associated with suicide is depression.

Depressive disorders in children and adolescents can be chronic and recurrent. The mean length of a major depressive episode in youth aged 6 to 17 years is 7 to 9 months, with remittance commonly occurring over a 1½- to 2-year period.[8] Longitudinal studies suggest a strong potential for recurrence; 48% to 60% of this age group have recurrence of major depression after an initial MDD episode within 5 years.[6,8]

See also p 1033.

Although depression in youth is now recognized as a significant health concern, identification of safe and effective treatment has been challenging. The study by Wagner et al in this issue of THE JOURNAL is the fourth published double-blind, placebo-controlled study demonstrating efficacy in the treatment of MDD in children and adolescents; all studies included SSRIs. In 1997, Emslie et al[9] reported the first randomized controlled trial examining the efficacy of an antidepressant (fluoxetine) in the treatment of MDD. In 2001, Keller et al[10] reported a trial showing the efficacy of paroxetine. In 2002, Emslie et al[11] reported another positive study with fluoxetine. In 2001, Wagner et al[12] presented data from a positive double-blind, placebo-controlled trial of citalopram, but to date, the results have not been published in a peer-reviewed journal.

A number of psychotropic medications established as safe and effective in the treatment of MDD in adults have been investigated in youth but may not be effective, including tricyclic antidepressants, monoamine oxidase inhibitors, and venlafaxine.[13,14] There are also safety concerns regarding the use of tricyclic antidepressants in children and adolescents, including lethality in overdose and cardiac conduction delays (and possibly increased risk of sudden death) in therapeutic dosages.[15]

On the basis of the 2 positive studies,[9,11] fluoxetine has received US Food and Drug Administration (FDA) labeling as safe and effective for the treatment of MDD in children and adolescents. However, the SSRI findings are not without controversy. The beneficial effects in both fluoxetine studies were modest,[9,11] and in the second, larger multicenter study,[11] not all of the prospectively identified primary outcome measures were significantly different than with placebo.

Similarly, in the study by Keller et al,[10] the response rate for patients receiving paroxetine was 63% compared with 50% for imipramine and 46% for placebo. Only 1 of 2 prospectively identified primary outcome measures achieved statistical significance. Two other large placebo-controlled trials of paroxetine in MDD were negative (written com-

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munication, Philip Perera, MD, Medical Information Department, GlaxoSmithKline, July 9, 2003).[16]

In the current study by Wagner et al, 69% of the patients receiving sertraline were considered responders compared with 59% of those receiving placebo, a difference of only 10%.[1] These findings suggest that children may be more responsive than adults to nonspecific measures of support that are included in the placebo response, possibly because children and adolescents are in a more dependent and reactive developmental state.

Despite this limited evidence base, prescription of psychotropic medications for the treatment of depression in children and adolescents has increased dramatically.[17] In a study of almost 900 000 youths enrolled in 3 large health care systems, antidepressant medication prevalence increased in the period 1987-1996 by a factor of 3.6 at one site, 6.2 at a second, and 10.4 at a third.[17]

One attractive feature of the SSRIs has been their relative safety profile. Previous concerns regarding a possible association with suicidal ideation and attempts in adults led to scientific review, as well as congressional hearings, ultimately revealing no causal link.[18]

Recent reports by regulatory agencies have expressed concern regarding the use of paroxetine in children and adolescents. On June 10, 2003, Gordon Duff, chairman of the Committee on Safety in Medicines in Great Britain, wrote that paroxetine was now contraindicated and "should not be used in children and adolescents under the age of 18 years to treat depressive illness."[19] This message came 2 weeks after new data from clinical trials sponsored by the manufacturer of paroxetine were received by the Medicines and Health Care Products Regulatory Agency (MHRA). These trials of paroxetine included more than 1000 patients aged 7 to 17 years (written communication, Philip Perera, MD, Medical Information Department, GlaxoSmithKline, July 9, 2003). There were no deaths due to suicide, although the rates of suicidal thinking and suicide attempt were higher among those receiving paroxetine compared with placebo. An expert working group reviewed the data and concluded that paroxetine did not demonstrate efficacy in depressive illness in this age group. In addition, the risk of harmful outcomes, including episodes of self-harm and potentially suicidal behavior, was estimated to be between 1.5 and 3.2 times higher with paroxetine than with placebo. The balance of risks and benefits with paroxetine was assessed to be "unfavourable when used to treat depressive illness in this age group."[19]

On June 19, 2003, the FDA posted a talk paper indicating that the possible increased risk of suicidal thinking and suicide attempts in youth younger than 18 years who were treated with paroxetine for MDD was being reviewed.[20] The FDA recommended that paroxetine not be used in children and adolescents with MDD while this issue was under review. Both the FDA and the MHRA suggest that there is no evidence that paroxetine is effective in children or adolescents with MDD,[19,20] even though the study by Keller et al[10] reported some benefit.

In addition, in the study by Keller et al,[10] serious adverse events were defined as those that resulted in hospitalization, were associated with suicidal gestures, or were described by the treating physician as serious. Serious adverse events occurred in 11 patients treated with paroxetine, 5 with imipramine, and 2 with placebo. The serious adverse events in the paroxetine group included 10 patients with various psychiatric events, including worsening of depression (n=2), emotional lability, which included suicidal ideation and gestures (n=5), conduct problems or hostility, including aggressiveness (n=2), and euphoric mood or expansiveness (n=1). Seven patients in the paroxetine group were hospitalized because of worsening depression (n=2), emotional lability (n=2), conduct problems (n=1), or euphoria (n=1). In the placebo group, 1 patient had emotional lability and 1 patient had worsening depression; both were considered serious adverse events.

In the study by Wagner and colleagues, sertraline was reported as generally well tolerated, although more patients receiving the active drug (9%) than receiving placebo (3%) discontinued medication because of adverse events, most commonly reported as abdominal pain, diarrhea, and nausea.[1] Serious adverse events included suicide attempts in 2 patients in the sertraline group and 2 patients in the placebo group; 3 patients receiving sertraline had suicidal ideation and 1 receiving sertraline had an aggressive reaction.

In contrast, the fluoxetine studies do not report higher rates of adverse events, including mood symptoms or suicidal ideation, with active drug compared with placebo.[9-11]

Depression is an illness associated with agitation, despair, self-loathing, and suicide. Suicide attempts may occur as depression is lifting and an individual is energized enough to act on thoughts of self-harm. Since suicide is rare in children and adolescents, ascertaining whether there is a meaningful increased risk of suicidal ideation, suicide attempts, or suicide completion associated with any medication used to treat depression will require review of large numbers of patients.

Until this issue is resolved, prudent practice in the treatment of depressive illnesses in children and adolescents must include careful attention to the decision to treat a child or adolescent with medication for MDD; clinical expertise with mental health assessment, consideration of varied treatment modes including cognitive behavioral or interpersonal psychotherapy, partnership with patients and their parents, and careful attention to symptom course, particularly emotional lability and the assessment of suicidal ideation in youth who are treated with antidepressant medications (specifically, SSRIs, and more particularly, paroxetine). Current evidence continues to support the use of SSRIs, particularly fluoxetine and sertraline, in the treatment of MDD in children and adolescents. Caution is indicated at this time regarding the use of paroxetine in children and adoles-

cents with MDD, and a clinician would be ill-advised to begin treatment with paroxetine for a patient younger than 18 years with MDD. In patients who have been identified as having a robust response to paroxetine, it does not appear prudent to switch to another SSRI based on current data.

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Principles of Medical Research
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- **Effective date:** Implementation of these standards will begin with all clinical trials of marketed products that are completed after July 1, 2004. In addition, the registry will be populated retrospectively with results of core efficacy and safety registration trials of marketed compounds with first approval after July 1, 1994.

- **Verification of disclosure**: An independent third party will audit and verify adherence by Lilly to these standards on results disclosure.

Lilly

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Date: August 3, 2004

For Release: Immediately
Refer to: 317-433-9899 – Edward Sagebiel
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Lilly To Disclose Results of All Clinical Trials For Marketed Products Via A Publicly Available Registry

Company also to post initiation of all Phase III and Phase IV clinical trials

Eli Lilly and Company (NYSE: LLY) announced today that it would disclose the results of all clinical trials for which Lilly is a sponsor via a publicly available registry, beginning in the fourth quarter of this year. Consistent with the company's policy of open disclosure, the registry will include results of all Phase I through Phase IV clinical trials of Lilly's marketed products conducted anywhere in the world. Additionally, the company will begin posting the initiation of all Phase III and Phase IV clinical trials via the registry.

"Lilly understands that patients, customers, and critics are looking for transparent answers that provide value to the health care decision-making process," said Sidney Taurel, Lilly's chairman, president and chief executive officer. "Our announcement today represents a comprehensive effort to publicly disclose Lilly's clinical trial information. These actions should prove to be invaluable for patients and the medical community as they seek to make informed decisions about Lilly medicines."

What results Lilly will disclose

For each clinical trial of its marketed products, the company will disclose publicly the results corresponding to the study's predefined primary and secondary outcome measures that are specified in the study protocol, as well as additional safety and efficacy results that impact patient care and the clinical use of Lilly products. Results that do not support the hypothesis being tested or that are contrary to the expected outcome will be disclosed. Additionally, Lilly will post a comprehensive description of the trial design and methodology for each study.

Posting initiation of trials

Additionally, the company will publicly report the initiation of all Phase III and Phase IV clinical trials, with an identifier assigned to each trial. When the trial is completed and the drug is commercially available, the results of the trial will be appended to its identifier.

When Lilly will disclose results

For Phase I, II and III studies, Lilly will disclose clinical trial results when a drug's indication is approved and it is commercially available. Phase III trial results for secondary indications of marketed drugs that fail to achieve approval will also be posted. For Phase IV studies, Lilly will disclose clinical trial results as soon as possible after the data analysis is completed but no later than one year after the trial's completion. For studies that are under review by a peer-reviewed journal that prohibits pre-publication disclosure of results, the results will be posted on the registry at the time of the publication.

How Lilly will disclose results

In all cases, Lilly will disclose clinical trial results on a publicly available, on-line registry. Lilly also will seek to disclose results through a peer-reviewed medical journal, subject to the discretion of the journal editors. The company will commit to providing a reference in the clinical trial registry for study results that are disclosed in a peer-reviewed journal. In addition, Lilly's clinical trial results may be disclosed through presentations or abstract submissions at professional scientific meetings.

"Our support of a publicly available clinical trial registry is a natural extension of Lilly's commitment to disclose data from Lilly-sponsored clinical trial data," said Dr. Alan Breier, vice president and chief medical officer at Eli Lilly and Company. "A publicly available clinical trial registry, which provides results from all industry-sponsored clinical trials of marketed products, could prove useful to both physicians and patients seeking information on a broad range of illnesses – from serious and potentially life-threatening diseases to chronic and debilitating conditions including depression, osteoporosis, and diabetes."

Breier noted that the registry information would be made publicly available beginning in the fourth quarter of this year via www.lillytrials.com. Additionally, the company reaffirms its

commitment to continue posting information on the initiation by Lilly of clinical trials for serious and life-threatening diseases via the U.S. government web site, www.clinicaltrials.gov.

Timeline and audit

Implementation of these standards will begin with all clinical trials of marketed products that are completed after July 1, 2004. In addition, the registry will be populated retrospectively with results of core efficacy and safety registration trials of marketed compounds approved since July 1, 1994.

The company will assign an independent third party to audit and verify adherence by Lilly to these standards for results disclosure.

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers – through medicines and information – for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

# # #

Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression

Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial

Treatment for Adolescents With Depression Study (TADS) Team

JAMA. 2004;292:807-820.

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ABSTRACT

Context Initial treatment of major depressive disorder in adolescents may include cognitive-behavioral therapy (CBT) or a selective serotonin reuptake inhibitor (SSRI). However, little is known about their relative or combined effectiveness.

Objective To evaluate the effectiveness of 4 treatments among adolescents with major depressive disorder.

Design, Setting, and Participants Randomized controlled trial of a volunteer sample of 439 patients between the ages of 12 to 17 years with a primary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnosis of major depressive disorder. The trial was conducted at 13 US academic and community clinics between spring 2000 and summer 2003.

Interventions Twelve weeks of (1) fluoxetine alone (10 to 40 mg/d), (2) CBT alone, (3) CBT with fluoxetine (10 to 40 mg/d), or (4) placebo (equivalent to 10 to 40 mg/d). Placebo and fluoxetine alone were administered double-blind; CBT alone and CBT with fluoxetine were administered unblinded.

Main Outcome Measures Children's Depression Rating Scale-Revised total score and, for responder analysis, a (dichotomized) Clinical Global Impressions improvement score.

Results Compared with placebo, the combination of fluoxetine with CBT was statistically significant (P = .001) on the Children's Depression Rating Scale-Revised. Compared with fluoxetine alone (P = .02) and CBT alone (P = .01), treatment of fluoxetine with CBT was superior. Fluoxetine alone is a superior treatment to CBT alone (P = .01). Rates of response for fluoxetine with CBT were 71.0% (95% confidence interval [CI], 62%-80%); fluoxetine alone, 60.6% (95% CI, 51%-70%); CBT alone, 43.2% (95% CI, 34%-52%); and placebo, 34.8% (95% CI, 26%-44%). On the Clinical Global Impressions improvement responder analysis, the 2 fluoxetine-containing conditions were statistically superior to CBT and to placebo. Clinically significant suicidal thinking, which was present in 29% of the sample at baseline, improved significantly in all 4 treatment groups. Fluoxetine with CBT showed the

greatest reduction (P = .02). Seven (1.6%) of 439 patients attempted suicide; there were no completed suicides.

Conclusion The combination of fluoxetine with CBT offered the most favorable tradeoff between benefit and risk for adolescents with major depressive disorder.

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Major depressive disorder (MDD) in adolescence is common—the point prevalence is 1 in 20—and is associated with significant morbidity and family burden.[1-2] Depression also is an important contributor to adolescent suicidal behavior and to completed suicide,[3-4] which is the third leading cause of death among adolescents.[5] Furthermore, depression in adolescence is a major risk factor for MDD, suicide, and long-term psychosocial impairment in adulthood.[6] Thus, improvements in the treatment of MDD among adolescents should positively affect public health.

When the Treatment for Adolescents With Depression Study (TADS) was designed in 1998, empirical literature supported cognitive-behavioral therapy (CBT) as a treatment for MDD in youth,[7] with both behavioral[8] and cognitive[9] approaches well represented.[10] In contrast, Emslie et al's[11] randomized controlled trial comparing fluoxetine with placebo, along with the lack of favorable efficacy data for the tricyclic antidepressants,[12] formed the sole empirical basis for the TADS pharmacotherapy condition. Although the fluoxetine results were subsequently replicated,[13] which lead to approval from the Food and Drug Administration of fluoxetine for MDD in youth—the only medication so recognized—meta-analyses of antidepressant trials for MDD in children and adolescents tell a mixed story regarding benefits and risks of medication management.[14-15] Given that antidepressants are widely used as first-line treatments for depressed youth,[16] it seemed critical then (and even more so now) that rapid replication of the efficacy studies of CBT and fluoxetine be performed in an effectiveness sample of depressed adolescents.

Response rates for CBT and medication in previous studies are approximately 60%, leaving substantial room for improvement in treatment outcomes. In adults, the combination of CBT with medication may lead to greater improvement in depression

than monotherapy with either treatment.[17-19] Although combined treatment is frequently recommended by experts, especially for more severely ill patients,[20-21] the relative efficacy of CBT and medication, alone and in combination, for depressed adolescents is unknown. It also is not clear which patients might benefit most from combined treatment.

TADS is a multicenter, randomized, clinical trial designed to evaluate the effectiveness of treatments for adolescents with MDD.[22] Stage 1 compares randomly assigned groups receiving 12-week treatment with (1) fluoxetine alone, (2) CBT alone, (3) fluoxetine with CBT, or (4) placebo. Placebo and fluoxetine alone were administered double-blind, while CBT alone and fluoxetine with CBT were administered unblinded. Blinding for the primary dependent measures was maintained by means of an independent evaluator.

The specific aims of the study, the design, and the rationale for choices made, the required sample size calculations, and the methods used are detailed elsewhere.[22] The demographic and clinical characteristics of the sample and the external validity relative to epidemiological and treatment-seeking samples have also been published.[23] The intent-to-treat effectiveness and safety outcomes for stage 1 of TADS are presented herein.

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Participants

A volunteer sample of 439 patients with a primary *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[24] *(DSM-IV)*, diagnosis of MDD entered the study between spring 2000 and summer 2003. Patients were recruited without regard to sex, race, or ethnicity from (1) clinics; (2) paid and public service advertisements in newspapers and on the radio and TV; (3) primary care physicians; (4) other mental health clinicians; and (5) schools and juvenile justice facilities at 13 academic and community clinics. All patients and at least one of their parents provided written informed consent. The Duke University Medical Center (Durham, NC) and the institutional review boards at each site approved and monitored the protocol; TADS was monitored quarterly by the data safety and monitoring board of the National Institute of Mental Health (Bethesda, Md).

Inclusion criterion were age of 12 to 17 years (inclusive); ability to receive care as an outpatient; a *DSM-IV* diagnosis of MDD at consent and again at baseline; a Children's Depression Rating Scale-Revised[25] (CDRS-R) total score of 45 or higher at baseline; a full-scale IQ of 80 or higher; and not taking antidepressant(s) prior to consent. Depressive mood had to have been present in at least 2 of 3 contexts (home, school, among peers) for at least 6 weeks prior to consent. Concurrent stable psychostimulant treatment (eg, methylphenidate or mixed amphetamine salts) for attention-deficit/hyperactivity disorder was permitted.

Exclusion criterion were current or past diagnosis of bipolar disorder, severe conduct disorder, current substance abuse or dependence, pervasive developmental disorder(s), thought disorder, concurrent treatment with psychotropic medication or psychotherapy outside the study, 2 failed selective serotonin reuptake inhibitor (SSRI) trials, a poor response to clinical treatment containing CBT for depression, intolerance to fluoxetine, confounding medical condition, non-English speaking patient or parent, and/or pregnancy or refusal to use birth control. No patients were asked or required to discontinue other forms of psychiatric treatment to enter the study.

Patients were excluded for dangerousness to self or others if they had been hospitalized for dangerousness within 3 months of consent or were deemed by a cross-site panel to be "high risk" because of a suicide attempt requiring medical attention within 6 months, clear intent or an active plan to commit suicide, or suicidal ideation with a disorganized family unable to guarantee adequate safety monitoring.

Randomization and Blinding

Eligible patients were randomly assigned to fluoxetine alone, CBT alone, fluoxetine with CBT, or placebo using a computerized stratified randomization, a 1:1:1:1 treatment allocation ratio, permuted blocking (first block size = 4, with subsequent random block sizes of 4 and 8) within each stratum, and site and sex as stratification variables. Except in emergencies, participants and clinicians remained blind in the fluoxetine alone and placebo treatment groups. Patients and clinicians were aware that participants in the fluoxetine with CBT group received active medicine and that participants in the CBT alone group did not receive medication. As is necessary in efficacy studies comparing psychosocial and pharmacological interventions, masking was maintained for the primary dependent measures by means of independent evaluators blind to treatment assignment. Except at assessments, independent evaluators were physically isolated from patients, data, and treating clinicians. Specific instructions were provided to the parents, participants, and the independent evaluator not to disclose treatment assignment.

Interventions

Treatments were designed to meet best practice standards and were performed according to instruction manuals to allow ready dissemination (if warranted) in clinical practice at the conclusion of the trial.[22]

Patients had only one pharmacotherapist throughout the study. In addition to monitoring clinical status and medication effects during six 20- to 30-minute medication visits spread across 12 weeks of treatment, the pharmacotherapist offered general encouragement about the effectiveness of pharmacotherapy for MDD.

Using a flexible dosing schedule dependent on pharmacotherapist-assigned Clinical Global Impressions[26] (CGI) severity score and the ascertainment of clinically significant adverse events, doses of placebo and fluoxetine began at a starting dose of 10 mg/d, which was then increased to 20 mg/d at week 1 and, if necessary, to a maximum of 40 mg/d by week 8.

In TADS, CBT is a skills-oriented treatment based on the assumption that depression is either caused by or maintained by depressive thought patterns and a lack of active, positively reinforcing behavioral patterns; treatment included 15 sessions, which lasted between 50 and 60 minutes, over the first 12 weeks.[27-28] In this context, the approach taken for CBT required skill-building and optional or modular sessions, which allowed flexible tailoring of the treatment to the adolescent's needs in a developmentally sensitive fashion and integrated parent and family sessions with individual sessions. The required aspects of treatment (weeks 1-6 or longer if necessary) included psychoeducation about depression and its causes, goal-setting with the adolescent, mood monitoring, increasing pleasant activities, social problem-solving, and cognitive restructuring. Subsequently, modules chosen jointly by the therapist and adolescent during weeks 7 through 12 addressed relevant social skill deficits of the adolescent, such as problems in social engagement, communication, negotiation, compromise, or assertion. Two parent-only sessions provided psychoeducation about depression and, depending on need, 1 to 3 conjoint parent and adolescent sessions focused on addressing parent and adolescent concerns.

Treatment combining fluoxetine with CBT contained all of the components from both the medication alone and CBT alone groups. To allow limited integration between CBT and medication management, CBT was functionally independent of medication management (ie, no decisions regarding the CBT protocol depended on decisions about medication management). Second, the protocols for administering medication and CBT were functionally independent for all medication increases other than those depending on the presence of partial response. Third, when partial response was present, the pharmacotherapist in consultation with the CBT therapist evaluated compliance with CBT, the overall change trajectory, and the adverse event profile when considering whether to adjust the dose of fluoxetine.

Diagnostic and Outcome Measures

The diagnosis of MDD and associated comorbidities at baseline were established using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version,[29] which was administered by the same independent evaluator who rated the primary dependent measures.

Two primary outcome measures were chosen a priori: the scalar CDRS-R total score, which is based on a synthesis of information collected from interviewing both the adolescent and the parent,[25] and an end-of-treatment CGI improvement score[26] (defined as much improved or very much improved). Both outcome measures were assessed by the independent evaluator at baseline, week 6, and week 12. Data is also presented herein from the Reynolds Adolescent Depression Scale (RADS),[30] which is an adolescent self-report measure of depression that was included because of the prominent place accorded adolescent self-report in the CBT literature.[7] The Suicidal Ideation Questionnaire-Junior High School Version (SIQ-Jr),[31] which is a self-reported measure of suicidal ideation, also was included to clarify the ratio of benefit

to harm. Psychometric properties and intercorrelations for all measures are presented elsewhere.[23]

Independent evaluators were clinicians with either master or doctorate degrees, with experience administering research-related structured clinical interviews with depressed patients or adolescent psychiatric patients or, in most cases, both. Quality assurance procedures and reliability of the baseline assessments are documented elsewhere.[22-23] For the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version diagnostic criteria of the *DSM-IV* for MDD, 94.1% of the reviewed interviews met the criterion of at least 80% agreement between the 2 raters. The intraclass correlation coefficient for the total number of MDD symptoms present was 0.80. The intraclass correlation coefficient for the 14-item CDRS-R total score at baseline was 0.95, suggesting excellent interrater reliability for both measures. The intraclass correlation coefficient for the 14-item CDRS-R total score during stage 1 of treatment was 0.95, again suggesting excellent interrater reliability on the primary dependent measure.

Safety Assessments

To ensure patient safety, evaluate the tolerability of treatment, and to minimize the potential for cross-site differences in protocol delivery, integrated procedures were used for adverse event monitoring and adjunctive services and attrition prevention.[22] An *adverse event* was defined as any unfavorable medical change occurring postrandomization that was accompanied by functional or clinical impairment. An adverse event may or may not be related to or caused by the study drug or CBT treatment. A functional threshold on adverse event reporting was imposed, specifying that an adverse event must (1) cause clinically significant interference with functioning, (2) require medical attention, or (3) be associated with any impairment in functioning and cause the patient to take a concomitant medication. A *harm-related adverse event* was defined as involving harm to self, which can include a nonsuicidal event, such as cutting for relief of dysphoric affects, worsening of suicidal ideation without self-harm, or a suicide attempt of any lethality; or harm to others, which includes aggressive or violent ideation or action against another person or property. A *suicide-related adverse event* requires that the patient exhibit either worsening suicidal ideation or make a suicide attempt, or both. Harmful behaviors without suicidal ideation or intent, such as some instances of cutting, are not included in the definition of a suicide-related adverse event. Reporting of an adverse event does not include preexisting conditions or illnesses that do not worsen in severity or increase in frequency during the study period.

Sample Size and Power Estimates

The primary end point used in the sample size estimate was treatment response rate, which was defined as a CGI improvement score of 1 (very much improved) or 2 (much improved), assigned by the independent evaluator. Using a χ^2 statistic, power estimates for detecting differences in treatment response in the 4 groups were then computed using the following assumptions: (1) H_a:$P_{(fluoxetine)}$ = .60, $P_{(CBT)}$= .60, $P_{(fluoxetine\ with\ CBT)}$ = .80, and $P_{(placebo)}$ = .40; (2) no adjustment for loss to follow-up; (3) no adjustment for multiple comparisons; and (4) αlevel of .05 for a 2-tailed test. Under these assumptions, 108 patients per treatment group (N = 432) were needed to achieve 80% or greater power to detect a difference of .20 in response rates between any 2 treatment groups.

Statistical Methods

Data entry and verification, data transfer, confidentiality and security, back-up and storage, and data analyses were conducted under the direction of the principal investigator and the principal statistician. All effectiveness and safety analyses were conducted using an intent-to-treat principle in which the analysis included all randomized patients in the treatment groups to which they were randomly assigned, regardless of their protocol adherence, actual treatment received, and/or subsequent withdrawal from treatment, assessments, or deviations from protocol.[32]

Statistical analyses on the primary outcome measure using CDRS-R scores were conducted using a linear random coefficient regression model.[33-35] Consistent with an intent-to-treat approach, random regression permits estimation of changes in continuous repeated measures in the presence of missing data on both a population and participant-specific level without necessitating last observation carried forward or exclusion of participants with missing data.[33-35] Specifically, the impact of treatment on outcome was modeled as a linear function of fixed effects for treatment, time (defined as the natural log of days since baseline + 1), and treatment-by-time interaction and random effects for participant and clinical site, including all 2- and 3-way interactions in the initial model. Clinical site and its interaction effects were fitted in the model as random effects. Although site was retained in the model, the site interaction terms were omitted because they accounted for a minimal amount of the overall variance and their omission did not alter the outcome.[35] Under the assumption of random intercepts and slopes for each patient, the overall and treatment group-specific rate of change for the 4 treatment groups for the primary CDRS-R outcome were examined. Pairwise comparisons on treatment slopes (linear trends with time) were then conducted. Supplemental between-treatment contrast analyses also were conducted on the adjusted week 12 means. Identical analyses were performed on secondary measures assessing self-reported adolescent depression (RADS) and suicidal ideation (SIQ-Jr).

Responder rates based on the dichotomized end-of-treatment CGI improvement score for each treatment group were compared using a logistic regression model for the last available assessment point (last observation carried forward) with site as a covariate. The Wald χ^2 test results and adjusted odds ratios (ORs) derived from the regression analysis provided pairwise comparisons of the treatment effects. Generalized linear models and tests for differences in proportions (χ^2 and Fisher exact tests) were performed to evaluate differences across treatment groups at baseline. The rate of harm- and suicide-related adverse events in each treatment group were compared using χ^2 and Fisher exact tests, with ORs calculated to provide an indicator of relative risk of active treatment to the placebo or a control condition.

For hypotheses stipulated in the statistical plan for the 2 primary outcomes, the nominal significance level was set a priori at a 2-tailed type I error rate of .05 for the omnibus tests designed to compare all 4 treatment groups. If the treatment or treatment-by-time interaction term was significant, then pairwise comparisons were conducted using a closed test procedure with an αlevel of .05 for each test. In the event of a nonsignificant omnibus result, a sequential rejective approach was planned to safeguard against type I error.[36] Because adverse events were rare and the study was not powered for their detection, the sequential rejective method was not applied to adverse event reporting.

To evaluate the clinical significance of the impact of treatment on outcome, effect sizes (Hedge g) were calculated as $M_E - M_C/SD_{pooled}$, where M_E represents the adjusted mean of experimental treatment, $M_C$represents the adjusted mean of the comparison treatment, and SD_{pooled} represents pooling of the SDs from within both groups.[37] The *number needed to treat* was defined as the number of patients who need to be treated to bring about one additional good outcome and was calculated according to methods outlined by Sackett et al.[38]

Analyses were conducted using SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC) with PROC MIXED used for the random regression analyses.[39]

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Patient Disposition

A total of 2804 patients were screened by telephone (Figure 1). Of these, 1088 signed consent for evaluation of inclusion and exclusion criteria and 439 were randomized to treatment and baseline assessment. Of those randomized, 56% learned of the study via an advertisement; the remainder were recruited via clinical or self-referral. The most frequent reasons for exclusion were prohibited psychotropic medication use (8.8%), did not meet criteria for MDD (17.5%), MDD not stable and pervasive (11.7%), or missed more than 25% of school days in previous 2 months (13.2%). Of those excluded, 1.6% had not improved with clinical treatment during a previous fluoxetine trial or were intolerant to fluoxetine; 1.1% had not improved with clinical treatment during 2 previous SSRI trials; and 0.8% had not improved with clinical treatment during of a CBT trial.

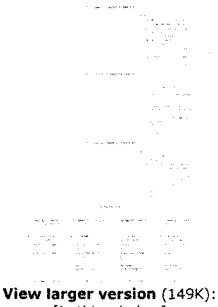

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Figure 1. Flow Diagram of Treatment for Adolescents With Depression Study

CBT indicates cognitive-behavioral therapy; CDRS-R, Children's Depression Rating Scale-Revised; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; MDD, major depressive disorder. The top 5 exclusionary reasons are listed for patients who were screened but were not assessed by diagnostic interview and for patients who underwent baseline assessment but were not randomized. Adolescents may have been included in more than one exclusionary category. The randomization error refers to a patient who was randomized but who should have been excluded according to the specified exclusionary criteria. This person was not included in the analysis, but was treated based on the recommendation by the TADS Scientific Advisory Board.

Of the 439 analyzable patients, 411 (94%) of the sample had at least 1 postbaseline CDRS-R data point. Forty-eight patients (10.9%) withdrew consent prior to week 12. Another 42 patients (9.6%) were terminated prematurely by the TADS team because they required an out-of-protocol treatment in place of or in addition to study treatment. Thus, 359 patients (82%) remained and 351 (80%) were assessed in their assigned treatment group at week 12. Treatment assignment did not influence the probability of dropping out ($P = .18$) or premature termination ($P = .50$).

Of the possible 15 sessions, the mean (median) number of completed CBT sessions was 11 (12) in both the in the CBT alone group and the CBT with fluoxetine group. The mean (SD) highest dose of fluoxetine was 28.4 (8.6) mg/d in the fluoxetine with CBT group; 33.3 (10.8) mg/d for the fluoxetine alone group; and 34.1 (9.5) mg/d for the placebo group.

Demographic and Clinical Characteristics

Participants resemble adolescents with MDD seen in general clinical practice (Table 1). The mean (SD) age was 14.6 (1.5) years; 45.6% of the sample was male; 73.8% was white; 12.5% was black; and 8.9% was Hispanic (includes black and white Hispanics). Race and ethnicity were self-classified. With a range of mild (CDRS-R total score of 45) to severe depression (CDRS-R total score of 98), the mean (SD) CDRS-R raw score at entry was 60 (10.4), which translates to a normed t score (standardized to a mean [SD] of 50 [10]) of 76 (6.43), indicating moderate to moderately severe MDD. This level of depression is consistent with a mean (SD) CGI

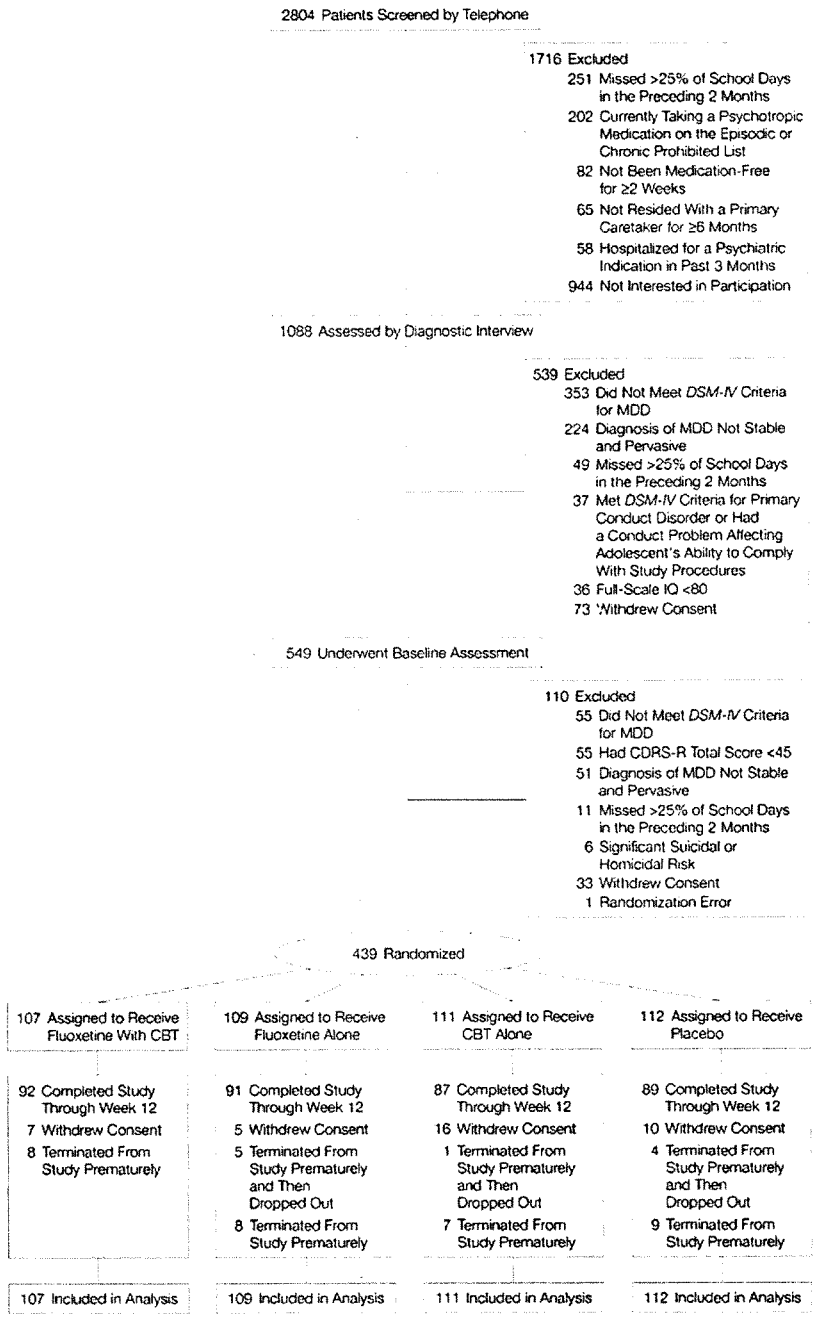
2804 Patients Screened by Telephone
1716 Excluded
251 Missed >25% of School Days in the Preceding 2 Months
202 Currently Taking a Psychotropic Medication on the Episodic or Chronic Prohibited List
82 Not Been Medication-Free for ≥2 Weeks
65 Not Resided With a Primary Caretaker for ≥6 Months
58 Hospitalized for a Psychiatric Indication in Past 3 Months
944 Not Interested in Participation
1088 Assessed by Diagnostic Interview
539 Excluded
353 Did Not Meet DSM-IV Criteria for MDD
224 Diagnosis of MDD Not Stable and Pervasive
49 Missed >25% of School Days in the Preceding 2 Months
37 Met DSM-IV Criteria for Primary Conduct Disorder or Had a Conduct Problem Affecting Adolescent's Ability to Comply With Study Procedures
36 Full-Scale IQ <80
73 Withdrew Consent
549 Underwent Baseline Assessment
110 Excluded
55 Did Not Meet DSM-IV Criteria for MDD
55 Had CDRS-R Total Score <45
51 Diagnosis of MDD Not Stable and Pervasive
11 Missed >25% of School Days in the Preceding 2 Months
6 Significant Suicidal or Homicidal Risk
33 Withdrew Consent
1 Randomization Error
439 Randomized
107 Assigned to Receive Fluoxetine With CBT
109 Assigned to Receive Fluoxetine Alone
111 Assigned to Receive CBT Alone
112 Assigned to Receive Placebo
92 Completed Study Through Week 12
7 Withdrew Consent
8 Terminated From Study Prematurely
91 Completed Study Through Week 12
5 Withdrew Consent
5 Terminated From Study Prematurely and Then Dropped Out
8 Terminated From Study Prematurely
87 Completed Study Through Week 12
16 Withdrew Consent
1 Terminated From Study Prematurely and Then Dropped Out
7 Terminated From Study Prematurely
89 Completed Study Through Week 12
10 Withdrew Consent
4 Terminated From Study Prematurely and Then Dropped Out
9 Terminated From Study Prematurely
107 Included in Analysis
109 Included in Analysis
111 Included in Analysis
112 Included in Analysis

Figure 1. Flow Diagram of Treatment for Adolescents With Depression Study

CBT indicates cognitive-behavioral therapy; CDRS-R, Children's Depression Rating Scale-Revised; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; MDD, major depressive disorder. The top 5 exclusionary reasons are listed for patients who were screened but were not assessed by diagnostic interview and for patients who underwent baseline assessment but were not randomized. Adolescents may have been included in more than one exclusionary category. The randomization error refers to a patient who was randomized but who should have been excluded according to the specified exclusionary criteria. This person was not included in the analysis, but was treated based on the recommendation by the TADS Scientific Advisory Board.

severity score of 4.77 (0.83) and a CGAS score of 49.6 (7.5). Eighty-six percent of patients experienced only 1 episode of depression, with a median (range) duration of 40.0 (3-572) weeks. More than half the sample (52.1%) was comorbid for at least 1 other psychiatric disorder. Sixty (13.67%) of 439 patients met *DSM-IV* criteria for ADHD and, of these, 21 (4.8%) took an approved psychostimulant. The modal family income was between $50 000 and $74 000, with a range of less than $5000 to more than $200 000. Forty-one percent lived in a single-parent home; 27% had been suspended or expelled from school. No statistically significant differences between the 4 treatment groups on any baseline characteristic were noted.

View this table: [in this window] [in a new window]	**Table 1.** Baseline Values by Treatment Group

Effectiveness Outcomes

Table 2 presents the intent-to-treat CDRS-R adjusted mean (SD) total scores by treatment group; CDRS-R adjusted mean scores for site are depicted graphically in Figure 2A. Random regression analyses on longitudinal CDRS-R score identified a statistically significant linear trend with time ($F_{1,382}$= 1066; P = .001) and a time-by-treatment interaction ($F_{3,381}$= 9.08; P = .001). Planned contrasts on the CDRS-R slope coefficients across 12 weeks of treatment produced a statistically significant ordering of outcomes. Specifically, fluoxetine with CBT (P = .001) was statistically significant compared with placebo, whereas treatment with fluoxetine alone (P = .10) and CBT alone (P = .40) were not. Fluoxetine with CBT was superior to fluoxetine alone (P = .02) and to CBT alone (P = .001). Despite failure to separate from placebo, fluoxetine alone also was superior to CBT alone (P = .01). Supportive contrasts performed on the week 12 adjusted means yielded a slightly different result. Specifically, fluoxetine with CBT (P = .001) and fluoxetine alone (P = .002) proved superior to placebo whereas CBT alone did not (P = .97). Fluoxetine with CBT was superior to CBT alone (P = .001), but not to fluoxetine alone (P = .13), whereas fluoxetine alone proved superior to CBT alone (P = .001).

View this table: [in this window] [in a new window]	**Table 2.** Changes in Total Scores Across 12 Weeks of Treatment

Table 1. Baseline Values by Treatment Group

Variable	CBT With Fluoxetine	Fluoxetine Alone	CBT Alone	Placebo	Total	*P* Value
Characteristics for Depression, Suicidality, and Functioning[a]						
No. of persons randomized	107	109	111	112	439	
Children's Depression Rating Scale-Revised						
Raw score[b]	60.75 (11.56)	58.96 (10.16)	59.58 (9.21)	61.11 (10.50)	60.10 (10.39)	.38
T score[c]	75.67 (6.53)	74.73 (6.74)	75.37 (6.32)	76.14 (6.11)	75.48 (6.43)	.43
Clinical Global Impressions severity score[d]	4.79 (0.85)	4.66 (0.85)	4.77 (0.76)	4.84 (0.84)	4.77 (0.83)	.43
Children's Global Assessment Scale score[e]	49.95 (7.52)	49.49 (7.26)	50.01 (7.58)	49.13 (7.59)	49.64 (7.47)	.79
Reynolds Adolescent Depression Scale total score[f]	79.91 (13.68)	77.00 (14.67)	78.83 (14.97)	81.20 (13.94)	79.24 (14.35)	.18
Suicidal Ideation Questionnaire-Junior High School Version total score, median (range)[g]	17.5 (0-89)	17.0 (0-79)	15 (0-85)	16.5 (0-84)	16.0 (0-89)	.57[h]
Current major depressive episode duration, median (range), wk	48.0 (3-456)	38.0 (6-572)	52.0 (4-330)	35.5 (4-357)	40.0 (3-572)	.28[h]
Comorbidity at Baseline by Treatment Group[i]						
Comorbidity						
Any psychiatric, No. (%)[j]	59 (55.66)	47 (43.12)	64 (58.18)	57 (51.35)	227 (52.06)	.13
Amount, median (range)	1.0 (0-5)	0 (0-5)	1.0 (0-5)	1.0 (0-5)	1.0 (0-5)	.50[h]
Dysthymia, No. (%)	11 (10.28)	6 (5.50)	17 (15.45)	12 (10.71)	46 (10.50)	.12
Type of disorder, No. (%)						
Anxiety	30 (28.04)	26 (23.85)	36 (32.43)	28 (25.23)	120 (27.40)	.50
Disruptive behavior	23 (21.50)	25 (22.94)	27 (24.32)	28 (25.00)	103 (23.46)	.93
Obsessive-compulsive/tic	4 (3.74)	2 (1.83)	2 (1.80)	4 (3.57)	12 (2.73)	.73[k]
Substance use	3 (2.80)	3 (2.75)	1 (0.90)	0	7 (1.59)	.23[k]
Attention-deficit/hyperactivity	14 (13.08)	13 (11.93)	14 (12.61)	19 (16.96)	60 (13.67)	.70
Taking medications	4 (3.74)	3 (2.75)	4 (3.60)	10 (8.93)	21 (4.78)	.12[k]

Abbreviation: CBT, cognitive behavioral therapy.

[a] Values are expressed as mean (SD) unless otherwise indicated. For mean (SD) data, *P* values are for 1-way analysis of variance using a general linear model unless otherwise indicated.

[b] The range for possible scores is 17 to 113.

[c] The range for possible scores is 36 to 85.

[d] The range for possible scores is 1 to 7.

[e] The range for possible scores is 1 to 100.

[f] The range for possible scores is 30 to 120.

[g] The range for possible scores is 0 to 90.

[h] Nonparametric Kruskal-Wallis test.

[i] Values are expressed as number (percentage) unless otherwise indicated. For number (percentage) data, *P* values are for the χ^2 test unless otherwise indicated.

[j] Refers to the presence of 1 or more coexisting psychiatric disorder, including dysthymia.

[k] Fisher exact test.

Table 2. Changes in Total Scores Across 12 Weeks of Treatment

	Adjusted Mean (SD)*		
	Baseline	Week 6	Week 12
CBT with fluoxetine			
Children's Depression Rating Scale-Revised clinician total score	60.79 (4.85)	38.10 (7.78)	33.79 (8.24)
Reynolds Adolescent Depression Scale total score	80.12 (9.23)	60.90 (11.59)	56.95 (12.24)
Suicidal Ideation Questionnaire-Junior High School Version total score	27.33 (18.51)	14.31 (12.58)	11.79 (11.69)
Fluoxetine alone			
Children's Depression Rating Scale-Revised clinician total score	58.94 (4.00)	39.80 (7.37)	36.30 (8.18)
Reynolds Adolescent Depression Scale total score	76.96 (9.57)	63.41 (12.44)	60.58 (13.07)
Suicidal Ideation Questionnaire-Junior High School Version total score	21.81 (15.68)	16.20 (12.42)	14.44 (11.13)
CBT alone			
Children's Depression Rating Scale-Revised clinician total score	59.64 (4.52)	44.63 (8.30)	42.06 (9.19)
Reynolds Adolescent Depression Scale total score	78.69 (10.59)	69.10 (13.59)	67.96 (14.18)
Suicidal Ideation Questionnaire-Junior High School Version total score	21.91 (16.28)	13.18 (11.34)	11.40 (10.44)
Placebo			
Children's Depression Rating Scale-Revised clinician total score	61.18 (4.27)	44.90 (7.32)	41.77 (7.99)
Reynolds Adolescent Depression Scale total score	81.26 (9.22)	69.43 (10.94)	66.68 (11.41)
Suicidal Ideation Questionnaire-Junior High School Version total score	24.20 (16.46)	16.85 (11.70)	15.01 (11.05)

Abbreviation: CBT, cognitive behavioral therapy.
*Means are for predicted individual scores that have been adjusted for both fixed (treatment and time) and random (participant and site) effects derived from the linear random coefficient model.

Table 2. Changes in Total Scores Across 12 Weeks of Treatment

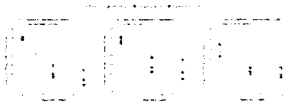

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Figure 2. Adjusted Mean (SE) Scale Scores for Participants in the Treatment for Adolescents With Depression Study

CBT indicates cognitive-behavioral therapy. Means are for predicted individual scores that have been adjusted for both fixed (treatment and time) and random (participant and site) effects derived from the linear random coefficient model.

With a positive response defined as a CGI improvement score of 1 (very much improved) or 2 (much improved), rates of response adjusted for clinical site were 71.0% (95% CI 62%-80%) for fluoxetine with CBT; 60.6% (95% CI, 51%-70%) for fluoxetine alone; 43.2% (95% CI, 34%-52%) for CBT alone; and 34.8% (95% CI, 26%-44%) for placebo. When clinical site and treatment were entered in the logistic regression model, the effect of the clinical site was nonsignificant (Wald χ^2 = .14; P = .71), whereas treatment was statistically significant (Wald χ^2 = 33.9; P = .001). Planned pairwise contrasts indicated that fluoxetine with CBT (P = .001) and fluoxetine alone (P = .001) were superior to placebo whereas CBT alone was not (P = .20). Fluoxetine with CBT and fluoxetine alone did not differ statistically (P = .11). Both fluoxetine with CBT (P = .001) and fluoxetine alone (P = .01) proved superior to CBT alone.

The adjusted mean (SD) total scores on the RADS for the intent-to-treat sample broken out by treatment group are presented in Table 2 and depicted graphically in Figure 2B. Random regression analyses on longitudinal RADS total score identified a statistically significant linear trend with time ($F_{1,380}$= 471.41; P = .001) and a time-by-treatment interaction ($F_{3,380}$= 10.32; P = .001). Planned contrasts on the RADS slope coefficients produced a statistically significant ordering of outcomes that was identical to that found on the CDRS-R. Specifically, fluoxetine with CBT (P = .001) proved statistically superior to placebo whereas fluoxetine alone (P = .34) and CBT alone (P = .21) did not. Fluoxetine with CBT was superior to fluoxetine alone (P = .002) and to CBT alone (P = .001). Despite failure to separate from placebo, fluoxetine alone also was superior to CBT alone (P = .03). Supportive contrasts performed on the week 12 adjusted means also followed the pattern established on the CDRS-R. Specifically, fluoxetine with CBT (P = .001) and fluoxetine alone (P = .003) proved superior to placebo whereas CBT alone did not (P = .94). Fluoxetine with CBT was superior to CBT alone (P = .001), but not to fluoxetine alone (P = .11), whereas fluoxetine alone again proved superior to CBT alone (P = .003).

The clinical significance (magnitude) of the impact of treatment on outcome was evaluated by calculating effect sizes (Hedge g) and the number needed to treat relative to placebo. The effect size on the CDRS-R was 0.98 for fluoxetine with CBT, 0.68 for fluoxetine alone, and −0.03 for CBT alone. Effect sizes derived from the OR for the dichotomized CGI improvement were 0.84 for fluoxetine with CBT, 0.58 for fluoxetine alone, and 0.20 for CBT alone. The number needed to treat for the dichotomized CGI improvement was 3 (95% CI, 2-4) for fluoxetine with CBT, 4 (95%

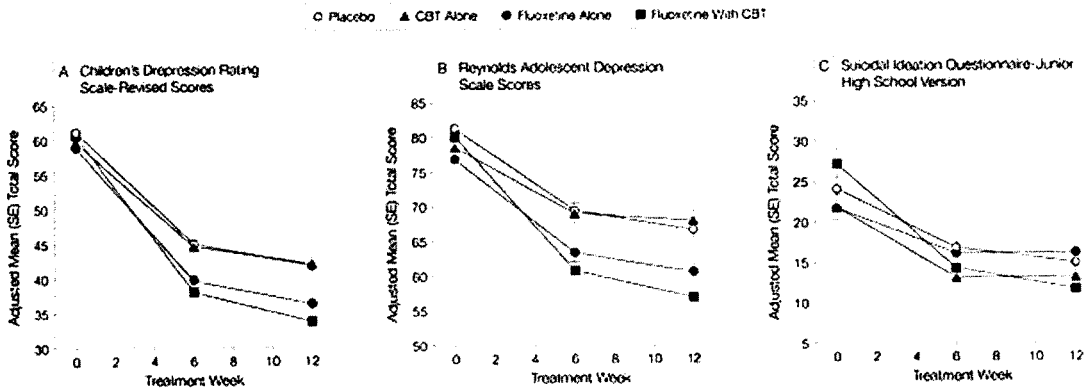

Figure 2. Adjusted Mean (SE) Scale Scores for Participants in the Treatment for Adolescents With Depression Study

CBT indicates cognitive-behavioral therapy. Means are for predicted individual scores that have been adjusted for both fixed (treatment and time) and random (participant and site) effects derived from the linear random coefficient model.

CI, 3-8) for fluoxetine alone, and 12 (95% CI, 5-23) for CBT alone. Taken together, these scalar and categorical indicators of clinical magnitude indicate that combination of fluoxetine with CBT is better than fluoxetine alone, which is better than CBT alone, which is equal to placebo.

Suicidality

Despite the exclusion for high-risk suicidality, a substantial minority of patients endorsed at least some suicidal ideation at baseline. For CDRS-R suicide item No. 13, 27% of patients were defined as having at least minimal suicidal ideation (score of ≥ 2), with 2% endorsing severe ideation (score of ≥6). On the SIQ-Jr, 29% of patients attained a score of 31 or higher, which indicates a level of suicidality requiring prompt clinical attention. By the end of 12 weeks of treatment, the percentage of patients showing an elevated CDRS-R item No. 13 or a SIQ-Jr score had decreased to 9.4% and 10.3%, respectively.

The adjusted mean (SD) total scores on the SIQ-Jr for the intent-to-treat sample are presented in Table 2 and depicted graphically in Figure 2C. Random regression analyses on longitudinal SIQ-Jr total score identified a statistically significant linear trend with time ($F_{3,419}$= 131.34; P = .001) and a time-by-treatment interaction ($F_{3,409}$= 3.59; P = .01). Planned contrasts on the SIQ-Jr slope coefficients across 12 weeks of treatment produced a statistically significant ordering of outcomes different in direction from those identified on the CDRS-R and RADS. Specifically, fluoxetine with CBT (P = .02) proved statistically superior to placebo whereas fluoxetine (P = .36) alone and CBT alone (P = .76) did not. Fluoxetine with CBT was superior to fluoxetine alone (P = .002) and to CBT alone (P = .05) while fluoxetine alone was not significantly different from CBT alone (P = .22). Consistent with substantial improvement across all 4 treatment groups, none of the post-hoc week 12 contrasts was statistically significant. Effect sizes (Hedge g) on the week 12 SIQ-Jr adjusted means were 0.28 for fluoxetine with CBT, 0.33 for CBT alone, and 0.05 for fluoxetine alone, implying a discrete albeit small protective effect for CBT on suicidal ideation.

Harm-Related Adverse Events

Counts, rates, and ORs (95% CI relative to placebo) for harm- and suicide-related adverse events are presented by treatment group in Table 3. Thirty-three (7.5%) of 439 patients experienced a harm-related adverse event. Of these, 23 (69.7%) met the Food and Drug Administrations's definition for a serious adverse event. Twenty-four (5.5%) of 439 patients experienced a suicide-related adverse event. Rates of harm-related adverse events by treatment group were fluoxetine alone (11.9%), fluoxetine with CBT (8.4%), CBT alone (4.5%), and placebo (5.4%). For harm-related adverse events, an omnibus χ^2 test for differences across the 4 treatment groups was not statistically significant (P = .15). Inspection of the ORs indicated little or no increased risk (defined as OR ≤2) in the CBT alone group and intermediate risk for the fluoxetine and CBT combined group, suggesting a protective effect for CBT. However, the ORs (95% CIs) indicated a statistically significant elevated risk for harm-related adverse events only in SSRI-treated participants (fluoxetine alone and fluoxetine with CBT pooled) in contrast to non-SSRI treated patients (CBT only and placebo pooled) (OR, 2.19; 95% CI, 1.03-4.62). While the pattern is the same, none of the ORs for suicide-related events were statistically significant. Seven patients—too small a number (1.6% of the total sample) for statistical comparison—attempted

suicide: 4 were assigned to fluoxetine with CBT, 2 to fluoxetine alone, and 1 to CBT alone. There were no completed suicides.

View this table: [in this window] [in a new window]	**Table 3.** Harm- and Suicide-Related Adverse Events

Psychiatric Adverse Events

Table 4 presents absolute rates for psychiatric-related adverse events, which reflect the broad construct of emotional and behavioral disinhibition. As expected, these adverse events were more common in patients receiving fluoxetine with CBT (16/107; 15%) and fluoxetine alone (23/109; 21%) compared with CBT alone (1/111; 1%) or placebo (11/112; 9.8%). Because overlapping adverse events can occur within the same patient, Table 4 also presents the total number of patients experiencing a psychiatric adverse event. Using the latter figure, the OR for active treatment vs placebo was 1.45 (95% CI, 0.58-3.58; 11.2%) for fluoxetine combined with CBT; 2.57 (95% CI, 1.11, 5.94; 18.5%) for fluoxetine alone; and 0.1 (95% CI, 0.01-0.84; 0.9%) for CBT alone. Thus, treatment with fluoxetine alone shows a statistically significant elevated risk for psychiatric adverse events; fluoxetine combined with CBT shows an intermediate risk between fluoxetine alone and CBT alone. Only 2 events met reporting requirements for a serious adverse event: worsening depression (fluoxetine) and mania (placebo). All patients with reported adverse events responded to dose reduction, treatment modification, addition of an out-of-protocol treatment, or treatment discontinuation.

View this table: [in this window] [in a new window]	**Table 4.** Psychiatric-Related Adverse Events*

Other Adverse Events

Rates of nonpsychiatric adverse events that occurred in at least 2% of patients and at least twice as often in one of the active treatment groups as in the placebo group appear in Table 5. Again, with the caveat that the rate of functionally impairing adverse events was low, they were more common in fluoxetine-treated patients. Headache was the only adverse event that occurred in at least 10% of patients in any single treatment group, but with little difference between fluoxetine combined with CBT (5.6%), fluoxetine alone (12%), and placebo (9%); no patients assigned to

Table 3. Harm- and Suicide-Related Adverse Events

	Total No. of Patients	Intent-to-Treat Cases	
		Harm-Related	Suicide-Related
Active Treatment vs Placebo			
CBT with fluoxetine			
No. (%) of patients	107	9 (8.41)	6 (5.61)
OR (95% CI)		1.62 (0.56-4.72)	1.60 (0.44-5.85)
Fluoxetine alone			
No. (%) of patients	109	13 (11.93)	9 (8.26)
OR (95% CI)		2.39 (0.87 6.54)	2.43 (0.73-8.14)
CBT alone			
No. (%) of patients	111	5 (4.50)	5 (4.50)
OR (95% CI)		0.83 (0.25-2.61)	1.27 (0.33-4.87)
Placebo			
No. (%) of patients	112	6 (5.36)	4 (3.57)
SSRI vs No SSRI			
SSRI			
No. (%) of patients	216	22 (10.19)	15 (6.94)
OR (95% CI)		2.19 (1.03-4.62)	1.77 (0.76-4.15)
No SSRI			
No. (%) of patients	223	11 (4.93)	9 (4.04)
CBT vs No CBT			
CBT			
No. (%) of patients	218	14 (6.42)	11 (5.05)
OR (95% CI)		0.73 (0.36-1.49)	0.85 (0.37-1.94)
No CBT			
No. (%) of patients	221	19 (8.60)	13 (5.88)

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

Table 3. Harm- and Suicide-Related Adverse Events

Table 4. Psychiatric-Related Adverse Events*

Adverse Event	CBT With Fluoxetine	Fluoxetine Alone	CBT Alone	Placebo
Mania/hypomania				
Mania	0	1 (0.92)	0	1 (0.89)
Hypomania	1 (0.93)	2 (1.83)	0	1 (0.89)
Elevated mood	0	1 (0.92)	0	0
Irritable/depressed mood				
Hypersensitivity	0	2 (1.83)	0	0
Irritability	1 (0.93)	1 (0.92)	0	0
Anger	0	1 (0.92)	0	0
Worsening of depression	0	1 (0.92)	0	1 (0.89)
Crying	1 (0.93)	0	0	0
Agitation/restlessness				
Agitation	0	0	0	1 (0.89)
Akathisia	1 (0.93)	0	0	0
Nervousness	0	0	0	1 (0.89)
Restlessness	0	1 (0.92)	0	1 (0.89)
Hyperactivity	0	1 (0.92)	0	0
Anxiety/panic				
Panic attacks	0	1 (0.92)	1 (0.91)	0
Anxiety	0	1 (0.92)	0	0
Sleep				
Somnolence	1 (0.93)	0	0	1 (0.89)
Insomnia	5 (4.67)	3 (2.75)	0	1 (0.89)
Nightmare	1 (0.93)	0	0	0
Night sweats	0	1 (0.92)	0	0
Fatigue/sedation				
Sedation	1 (0.93)	3 (2.75)	0	0
Fatigue	2 (1.87)	1 (0.92)	0	2 (1.79)
Other				
Tremor	1 (0.93)	2 (1.83)	0	0
Behavior abnormal	0	0	0	1 (0.89)
Feeling abnormal	1 (0.93)	0	0	0
Total				
No. of events	16	23	1	11
No. of patients	12	20	1	9

Abbreviation: CBT, cognitive behavioral therapy.

*Values are expressed as number (percentage) except for "Total" values. A patient may experience multiple events, so total number of cases is presented. Events were defined as unique serious and nonserious events. Worsening of depression (fluoxetine) and mania (placebo) were reported as serious. Some patients have multiple unique events. Patients were defined as the number of patients with at least 1 event.

Table 4. Psychiatric-Related Adverse Events*

CBT alone reported headache or any other nonpsychiatric adverse event. As expected, gastrointestinal tract problems, sedation, and insomnia were the other most common complaints.

View this table: [in this window] [in a new window]	**Table 5.** Nonpsychiatric Adverse Events*

COMMENT

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Focused on the initial treatment of MDD in adolescents, TADS was designed to answer clinically important questions concerning the benefit(s) of fluoxetine with CBT relative to medication management with fluoxetine alone or to CBT alone and the benefit(s) of CBT alone and fluoxetine alone relative to placebo. The effectiveness outcomes were clear and the clinical implications straightforward. The combination of fluoxetine with CBT produced the greatest improvement in symptoms of MDD. Fluoxetine alone was effective, but not as effective as fluoxetine with CBT. Treatment of CBT alone was less effective than fluoxetine alone and not significantly more effective than placebo. With respect to risk, suicidality decreased substantially with treatment. Improvement in suicidality was greatest for patients receiving fluoxetine with CBT and least for fluoxetine alone. While fluoxetine did not appear to increase suicidal ideation, harm-related adverse events may occur more frequently in fluoxetine-treated patients and CBT may protect against these events. Taking risks and benefits into account, the combination of fluoxetine with CBT appears superior as a short-term treatment for MDD in adolescents.

Generalizability

Patients exhibited the full range of mild-to-severe MDD, with a mean illness severity on the CDRS-R indicating moderate-to-moderately severe MDD. Given the tendency

Table 5. Nonpsychiatric Adverse Events*

Adverse Event	Active Treatment Frequency (%)	Placebo Frequency (%)	Active to Placebo Ratio
Sedation			
Fluoxetine alone	3 (2.75)	0	3.00
Upper abdominal pain			
Fluoxetine alone	6 (5.50)	2 (1.79)	3.08
Diarrhea			
CBT with fluoxetine	2 (1.87)	1 (0.89)	2.09
Fluoxetine alone	2 (1.83)	1 (0.89)	2.06
Influenza			
Fluoxetine alone	2 (1.83)	1 (0.89)	2.06
Insomnia			
CBT with fluoxetine	5 (4.67)	1 (0.89)	5.23
Fluoxetine alone	3 (2.75)	1 (0.89)	3.08
Sinusitis			
Fluoxetine alone	4 (3.67)	2 (1.79)	2.06
Vomiting			
CBT with fluoxetine	4 (3.74)	1 (0.89)	4.19
Fluoxetine alone	2 (1.83)	1 (0.89)	2.06

Abbreviation: CBT, cognitive behavioral therapy.
*Indicates events occurring in at least 2% of patients in at least 1 treatment group and with an incidence of at least 2 times greater than that seen in placebo-treated patients.

Table 5. Nonpsychiatric Adverse Events*

of industry-funded registration trials to exclude comorbid patients, it is especially noteworthy that more than 50% of the sample exhibited 1 or more comorbid disorders. Thus, while participants likely were more psychiatrically disturbed than participants in previous studies of medication and CBT monotherapy, TADS succeeded in recruiting a sample that includes the full range of treatment-seeking patients with MDD.[23] Accordingly, we conclude that the results of the study should be broadly applicable to youth with MDD seen in clinical practice.[23]

Treatment With Fluoxetine Alone

The response rates for fluoxetine monotherapy in TADS were consistent with those seen previously in pediatric fluoxetine trials. In the first placebo-controlled trial that demonstrated significantly positive effects of an antidepressant over placebo, the response rate for the fluoxetine group was 56% based on a CGI improvement score of 1 or 2.[11] In a multisite replication, fluoxetine had a 52% response rate based on a CGI improvement score of 1 or 2.[40] Thus, we conclude that the TADS response rate of 60.6% effectively replicates previous research demonstrating that fluoxetine monotherapy is an effective treatment for MDD in adolescents.

Treatment With CBT Alone

The 43% response rate for CBT alone in TADS is surprising given previous research showing that approximately 60% of depressed adolescents responded positively to CBT.[7, 10] This lower absolute rate of response could be due to differences in the version of CBT and/or sample composition. Albeit modified for dissemination across multiple sites, the CBT used in TADS was based on models previously shown to be efficacious.[8-9,41] Although unlikely, it is possible that these modifications inadvertently weakened the intervention. Regarding sample composition, patients receiving CBT alone appear to have had more severe and chronic depression and higher rates of comorbidity than participants in previous CBT trials and thus may have faired more poorly with treatment. With respect to comparative effectiveness, it is important to note that this is the first adolescent depression study in which any psychotherapy has been compared with clinical management with either active medication or pill placebo. While it was not hypothesized that CBT monotherapy would fail to separate from pill placebo or prove inferior to fluoxetine monotherapy, CBT did show the specific effect of decreasing suicidality in both the CBT alone group and the CBT combined with fluoxetine group. Subsequent analyses regarding expectancy, treatment fidelity, mediational processes, and compliance with treatment should further explicate the pattern of findings. Finally, in all but one of the adult trials,[42] the comparative strength of CBT has been greater in the follow-up phase than during acute treatment. Examination of postacute treatment response and durability will be critical to a more nuanced understanding of the short- and long-term impact of CBT in this patient population.

Treatment With CBT Combined With Fluoxetine

The effectiveness of combined CBT and fluoxetine for treating clinically depressed youth has not been examined previously in a randomized controlled trial. As has generally been the case in studies of depressed adults,[18-19] CBT incrementally enhanced clinical management with fluoxetine leading to the highest response rate among all treatments. However, because the CBT plus placebo condition was not included in the design (it was deemed both too expensive and too artificial to have

clinical relevance) it is not possible to determine whether this combined effect is additive (more is better) or synergistic (the 2 treatments enhance each other). Conversely, the divergent response patterns for depression and suicidality for participants who received fluoxetine with CBT suggests that the combination may exert a complimentary effect (targeting different domains) that enhances the overall outcome.

Placebo

Placebo response rates in TADS (34%) were consistent with the placebo rates in the 2 fluoxetine trials[11, 40] (33% and 37%, respectively, based on CGI improvement score).[11, 13] In the 2 earlier fluoxetine studies, the placebo response rates were lower than placebo response rates seen in other pediatric antidepressant trials. Because the response to active drug was comparable, it was the placebo response rate that generally determined the effect sizes and, hence, whether a trial was positive or negative.[14]

Why was there a low placebo response rate in TADS? From the point of view of experimental design, TADS was designed to minimize the placebo response rate. The inclusion criteria explicitly required stable depressed mood for at least 6 weeks in at least 2 of 3 contexts (home, school, among peers), making placebo-responsive mood fluctuations less likely. In addition, the primary outcome measures were rated by an independent evaluator blind to treatment assignment and to treatment course. Using an independent evaluator may have introduced a bias for interpreting improvement as being related to assignment to an active treatment.[43] Additionally, in contrast to other trials that included many small clincal sites with little research experience, all 3 fluoxetine studies used fewer clinical sites and the investigators were predominantly from clinical institutions with experience conducting treatment outcome studies with depressed adolescents.

The appropriateness of using a placebo group in randomized controlled trials with adolescent participants remains a subject of debate.[44] In this trial, symptomatic improvement, direct benefit from careful monitoring, high patient retention rate, and low adverse event rate all indicate that including a placebo group did not acutely place patients at unacceptable risk. Inclusion of a placebo group proved critical to documenting the effectiveness and safety outcomes reported herein. Thus, TADS supports the overall conclusion of a recent American Academy of Child and Adolescent Psychiatry report that including a placebo group in randomized controlled trials in pediatric psychopharmacology can be ethical and essential to the scientific aims of the study.[45]

Risk of Suicide

Approximately 500 000 adolescents in the United States attempt suicide each year; almost 2000, one half of whom suffer from major depression, die as a result.[3-5] While the rate of suicide attempts or completed suicide in (treated or untreated) adolescents with MDD is unknown, given the overall improvement in depression and suicidality in TADS it is likely that the rate of harm-related adverse events seen throughout the trial is below what might be expected in an untreated sample of depressed youth.

The separate question of whether SSRI medication is associated with an increased risk of developing suicidal ideation or facilitating suicidal behavior has been under intense scrutiny for years. Initial reports of adult patients developing intense suicidal ideation concurrent with fluoxetine treatment[46] led to investigations of clinical trial databases to assess the possibility of a causal connection.[47-48] In general, investigations with adult patients have failed to provide support for a specific causal association between antidepressant treatment and increased risk of suicidal ideation or behavior. Recently, controversy arose over similar issues among pediatric patients.[15] In June 2003, regulatory agencies in the United States and the United Kingdom issued safety warnings concerning the use of paroxetine in children and adolescents due to at least 1 study identifying increased risk of developing significant suicidality associated with paroxetine treatment. Further examination of this concern in a wide variety of second-generation antidepressants led the regulatory agency of the British Medicines and Healthcare to contraindicate all drugs in this class (except fluoxetine) for use in pediatric patients with MDD due to an unfavorable risk to benefit ratio.[49] The US Food and Drug Administration is continuing to study this issue and has made no definitive statements about risk enhancement specifically in pediatric patients. However, it has requested that stronger warnings be given to prescribing physicians about the need for close monitoring of all patients with second-generation antidepressants for worsening of depression or the development of acute suicidal thinking or behavior.[50]

Data from our study suggest a more complicated risk analysis. It is important to note at the outset that there were no deaths during the first 12 weeks of the study (and none to date of which we are aware for any of the enrolled participants). The number of actual suicide attempts was too small to analyze statistically, and their lethality was low to moderate. The impact of treatment with fluoxetine on reduction of suicidal ideation was identical to that of placebo, suggesting that fluoxetine on average does not increase suicidal ideation. On the other hand, as expected in this population, suicidal crises and nonsuicidal self-harming behaviors were not uncommon and, with the caveat that the numbers were so small as to make statistical comparisons suspect,[51] seemed possibly to be associated with fluoxetine treatment. When considered in light of the SIQ-Jr results, which showed no exacerbation of suicidal ideation in fluoxetine-treated compared with placebo-treated patients, this finding may indicate that self-harm is not driven solely or even primarily by suicidal ideation. Recent research in this area suggests that the movement from ideation to attempt is facilitated by stressful psychosocial events, substance abuse, agitation, irritability, or disinhibition.[4, 52] TADS findings are consistent with work suggesting that CBT has a specific beneficial effect on suicidal ideation[53] and, importantly, that CBT combined with fluoxetine may confer a protective effect not only against suicidal ideation, but also on harm-related behaviors.

Given the clear superiority of fluoxetine combined with CBT in reducing depression and suicidal ideation, the excess of suicide attempts in the fluoxetine with CBT group is perplexing. Reflecting a trend ($P = .06$) toward higher SIQ-Jr scores in the fluoxetine with CBT group, all but 1 of the 7 participants who attempted suicide met SIQ-Jr criteria for clinically significant suicidal ideation at baseline, suggesting that this finding might be related to an imbalance across treatment groups in risk for suicide at baseline. Of note, the TADS fluoxetine and placebo data will be included in the Food and Drug Administration reanalysis of suicide risk, which because of greater power associated with a much larger sample size should allow for stronger conclusions using a covariate-adjusted statistical model.

Other Adverse Events

The imposition of a functional impairment threshold presumably exerted a downward effect on the rates of adverse events. Nevertheless, with few patients ceasing treatment due to adverse events, treatment in TADS appeared to be reasonably well tolerated. As expected, gastrointestinal tract adverse events, sedation, and insomnia were more often reported in fluoxetine-treated patients. Mania/hypomania, irritability, agitation/restlessness, and anxiety, although more common in fluoxetine-treated patients, were rare and patients generally responded well to dose reduction or drug discontinuation. Mania was associated with a harm-related adverse event in only 1 of the 33 harm-related adverse events. Incident narratives indicate that irritability, agitation/restlessness, and anxiety were not commonly reported in association with harm-related adverse events, suggesting that other factors, such as substance use and psychosocial stressors, may be more important in mediating the risk of harm-related adverse events.

Limitations

The limitations of this study are inherent to the research questions, design, and methods that were selected. In the process of selecting the design, we discarded several alternatives, including a balanced fully factorial design, which was deemed better suited to a strict efficacy trial; a fifth placebo plus CBT group, which was not elected because of concerns about ecological validity and cost; psychosocial alternatives to a pill placebo group, such as educational support, which if credible are active and if truly inactive lack credibility; and a community-based treatment as a usual comparison group, which was discarded because of concerns about cross-site variability in quality of and access to treatment. In the end, there was unanimous agreement among the study investigators and the TADS Scientific Advisory Board that the final design represented the best compromise between scientific rigor and credibility, ethical considerations, stakeholder concerns, feasibility of implementation, and cost.

Three specific limitations merit comment. First, the patient's knowledge of the treatment he/she received varied across the 4 groups and across the 2 treatment modalities. Psychotherapeutic interventions cannot be masked at the participant level for experimental purposes, and the provision of CBT was not masked in any treatment group. Regarding pharmacotherapy, provision of fluoxetine was masked in 2 of the 4 groups. Blinding patients in the placebo and fluoxetine alone groups but not in the CBT alone group (participants knew they would not be receiving fluoxetine) and the fluoxetine combined with CBT group (participants knew that they would be receiving fluoxetine) may have interacted with expectancy effects regarding improvement and acceptability of treatment assignment. Second, contact time with the treatment clinicians and expectancy effects were not equated across treatment conditions, so the "active ingredient" in improvement cannot be specified. Third, patients deemed at high risk for suicidal behavior because of recent attempts or pervasive suicidal thoughts were excluded from this outpatient study. Given potentiation of suicidality among patients with substance abuse, exclusion for primary substance abuse or substance dependence also likely reduced the risk for self-harm among TADS patients. Methods for ascertaining suicidality, while more intensive than typical for industry trials, were less than ideal for a trial in which suicide is a primary end point. Specifically, suicide per se is too rare an event to be a primary end point

in a 3-month effectiveness trial targeting MDD, and even suicide attempts are too rare to offer adequate statistical power in the TADS framework.

Conclusion

TADS is based on a best practice model that connects disorder (MDD), empirically supported treatment components (fluoxetine and CBT), and outcome (reduced MDD and collateral symptoms), which should make the treatment procedures widely applicable in a variety of mental health settings. In this context, the remarkably strong and consistent findings reported herein lead us to make the following recommendations for health care decision makers at all levels. First, given the high prevalence, morbidity, and significant mortality associated with MDD, the identification of depressed adolescents and provision of evidence-based treatment should be mandatory in health care systems. Second, despite calls to restrict access to medications, medical management of MDD with fluoxetine, including careful monitoring for adverse events, should be made widely available, not discouraged. Third, given incremental improvement in outcome when CBT is combined with medication and, as importantly, increased protection from suicidality, CBT also should be readily available as part of comprehensive treatment for depressed adolescents.

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PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results **52**

PhRMA has released a statement on principles that govern its members' relationships with others involved in the clinical-research process. While many of the principles reflect current practice, others are new commitments on the part of the companies to ensure the integrity of research.

- All PhRMA members' clinical trials are conducted in accordance with applicable laws and regulations, as well as recognized principles of Good Clinical Practice (GCP), wherever in the world trials are conducted. All clinical trials are monitored for safety purposes, and significant safety information is shared promptly with appropriate persons and authorities.
- The independence of clinical investigators and others involved in clinical research is respected so they can exercise their own decision-making authority to protect research participants. Compensation to clinical investigators will be reasonable and based on their work. Compensation will not paid in the stock or stock options of the sponsor and sponsors will not hire investigators to conduct clinical trials who have proprietary interests in the compound being studied.
- Before trials begin at an investigative site, they are reviewed by Institutional Review Boards (IRBs) or Ethics Committees (ECs) that have the right to disapprove, require changes, or approve the study. All participation in a clinical trial is based on informed consent, freely given without coercion. Any proposed payments to research participants should be reviewed by an independent IRB/EC. The privacy rights of research participants and the confidentiality of medical information is safeguarded.

- There will be timely communication of meaningful study results, regardless of the outcome of the study. The results must be reported in an objective, accurate, balanced, and complete manner, with a discussion of the limitations of the study. Study sponsors will respond in a timely manner to requests for use of their data and will not suppress or veto publications. Where differences of opinion or data exist, the parties should try to resolve the disputes through honest scientific debate.
- Any investigator who participated in the conduct of a multi-site clinical trial will be able to review relevant statistical tables, figures, and reports for the entire study at the sponsor's facilities, or other mutually agreeable location.
- Consistent with the International Committee of Medical Journal Editors and major journal guidelines for authorship, the principles clarify that only those who make substantial contributions to a publication should receive acknowledgement as an author of or contributor to the publication.

Updated Principles For Conduct Of Clinical Trials And Communication Of Clinical Trial Results

June 30, 2004

Washington, D.C. – The Executive Committee of the Pharmaceutical Research and Manufacturers (PhRMA) unanimously adopted a set of principles for the conduct of clinical trials and the communication of results of clinical trials.

The voluntary principles describe the relationship of PhRMA member companies with others involved in clinical research and set forth the rules companies follow to protect the safety of research participants wherever the companies conduct clinical trials. In the Principles, the PhRMA companies commit to the timely communication of all meaningful results of clinical trials, whether those results are positive or negative. Further, the results are always to be communicated in an objective, accurate, balanced and complete manner.

"These principles reaffirm our members' strong commitment to the safety of research participants to ensure the integrity of research and the timely communication of research results" said Alan F. Holmer, President of PhRMA. "PhRMA members have always been committed, and remain committed, to sponsoring clinical research that fully complies with all legal and regulatory requirements."

The principles, many of which reflect existing practices by the industry, become effective for trials begun after October 1, 2002.

Among other provisions, the PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results provide that:

- Clinical trials are conducted in accordance with all applicable laws and regulations, as well as recognized principles of Good Clinical Practice (GCP), wherever in the world trials are conducted.
- The independence of clinical investigators and others involved in clinical research is respected so they can exercise their own decision-making authority to protect research participants. Compensation to clinical investigators will be reasonable and based on their work. Compensation will not paid in the stock of the sponsor.
- Before trials begin, they are reviewed by Institutional Review Boards (IRBs) or Ethics Committees (ECs) that have the right to disapprove, require changes, or approve the study. All participation in a clinical trial is based on informed consent, freely given without coercion.
- There will be timely communication of meaningful study results, regardless of the outcome of the study. The results must be reported in an objective, accurate, balanced, and complete manner, with a discussion of the limitations of the study. Study sponsors will not suppress or veto publications.
- Any investigator who participated in the conduct of a multi-site clinical trial will be able to review relevant statistical tables, figures, and reports for the

entire study at the sponsor's facilities, or other mutually agreeable location.

- Consistent with the International Committee of Medical Journal Editors and major journal guidelines for authorship, the principles clarify that only those who make substantial contributions to a publication should receive acknowledgement as an author of or contributor to the publication.

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. The industry, which invested more than $30 billion in 2001 in discovering and developing new medicines, is leading the way in the search for new cures.

A Q&A on PhRMA's Principles of Conduct for Clinical Trials and Communication of Clinical Trial Results

Why are you publishing these principles now?

Although pharmaceutical companies have long followed ethical principles for conducting clinical trials – in addition to FDA regulations and standards published by the International Conference on Harmonization and other international bodies – these principles have never been set down by the Pharmaceutical Research and Manufacturers of America (PhRMA) in one place before. In addition, criticisms of clinical trials – not necessarily trials conducted by the pharmaceutical industry – have been published in the media (often in sensationalized fashion) and these criticisms needed to be addressed so confidence can be restored in the clinical trial process. To that end, some higher standards were incorporated into these principles.

What's new in these principles?

The principles spell out long-established practices for conducting clinical trials. They also raise the bar by reducing the possibility of conflicts of interest on the part of researchers conducting the trials, and they make more information available on the results of a trial, whether these results are favorable to the company sponsoring the trial or not.

Are all researchers, including academic researchers, bound by these principles?

The principles are voluntary. Pharmaceutical and biotechnology companies that are members of PhRMA drew up the principles and agree that the principles are important for the quality of research and the protection of research participants. We hope that other researchers, including academic researchers, will join us in abiding by these principles. We expect that the principles will be enforced by public opinion.

What are the benefits of clinical trials? What are the risks?

Without clinical research studies, no new medicines would be made available to patients. The primary goal of a trial is to generate new knowledge about a potential medicine so that regulatory authorities can determine whether the medicine is safe and effective. People who participate in clinical trials have the satisfaction of knowing that they are helping to advance the frontiers of medical knowledge. Often, the participants themselves benefit from the medicine being tested and/or the care received while participating in the clinical trial. But the primary purpose of clinical trials is to advance the knowledge of researchers and regulators so that new treatments and cures can be developed.

The medicines tested in clinical trials have already undergone rigorous safety testing in both the laboratory and animals, but people who participate in clinical trials are, in a sense, pioneers. That's why they have to understand and sign informed consent agreements. The trials are monitored by health care professionals including both company employees and non-company employees, regulatory authorities, and the hospital where the trials are conducted.

Do these principles apply all over the world – including in developing countries?

Yes, the principles apply all over the world. The number of new medicines in development is increasing, and so is the average number of clinical trials required for each potential new medicine. So more and more clinical trials are being conducted each year. The overwhelming number of these trials are conducted in the United States and other developed countries. But, in recent years, companies have increased testing in developing countries. Also, companies are developing an increasing number of medicines for diseases that have a higher prevalence in developing countries and must be tested in the countries where the disease exists.

Trials are conducted in accordance with applicable laws and regulations, as well as locally recognized good clinical practice. Companies that wish to use the clinical trial results to have a medicine approved in the United States, Europe or Japan must comply with standards published by international organizations such as the International Conference on Harmonization (ICH).

What is the effective date for these principles?

The principles, many of which reflect existing practices by the industry, become effective for trials begun after October 1, 2002.

Where can people find information about participating in clinical trials?

There are a number of websites that list information about clinical trials. Following are three places from government and industry that can provide people with important information:

TUESDAY, SEPTEMBER 7, 2004 B1

New Web Site To Offer Results Of Drug Studies [53]

By Anna Wilde Mathews

TODAY, THE DRUG industry will unveil its response to a growing push for fuller disclosure of clinical trials. But its plan may not be enough to satisfy calls for greater openness.

The Pharmaceutical Research and Manufacturers of America, the Washington-based trade group that represents the major drug companies, is expected to announce that it will launch an online database designed to include summary results of most of its members' studies, including those that weren't published in medical journals. The Web site, to be available Oct. 1, goes well beyond the industry's efforts so far because it will include information from a number of companies.

Trial Tracker

A new database of clinical-trials results for FDA-approved drugs will have...

- **Late-stage** trial results
- **Summaries** of unpublished findings

...but not

- Some **early-stage** studies
- **Unfinished** trials

Source: PhRMA

The group wants to "increase the transparency of trial results," says Alan Goldhammer, its associate vice president for regulatory affairs, and it thinks the effort will "fill the gap" seen by advocates of greater disclosure.

Some aspects of the proposal, however, are certain to draw questions because they fall short of what doctors and other groups are requesting. For one thing, participation in the PhRMA effort would be voluntary. In addition, the industry database would feature only summaries of the unpublished trials, without access to full data, and would lack some early-stage studies and unfinished trials.

"Without an enforcement mechanism, we can't be sure that the data will actually get submitted and updated on a timely basis," says David Fassler, a Vermont psychiatrist who has helped spearhead calls for a clinical-trials registry. PhRMA says it expects most, if not all, of its members to take part and adds that it will eventually turn over control of the database to an outside entity such as a medical association.

The matter will come to a head Thursday, when a subcommittee of the House Energy and Commerce Committee holds a high-profile hear-

Please Turn to Page B4, Column 1

New Web Site Will Publish Results of Drug Studies

Continued From Page B1

ing on antidepressant trials done on children and adolescents, which have been at the center of the debate over fuller disclosure. Executives of big drug companies are expected to testify.

Also at the hearing, the American Medical Association is expected to flesh out its proposal for a clinical-trials registry that would go further than the industry plan. For example, it would be overseen by the federal government and include information about drugs, medical devices and possibly other treatments. The group also wants a new federal requirement that trials be registered in the central database as a condition for institutional review-board approval. In addition, the AMA wants results from the trials to be made public, though the organization hasn't settled on the details of what would have to be disclosed.

"You'd have to have an enforcement mechanism that will move this whole enterprise into a comprehensive, single registry," says Ron Davis, an AMA trustee who will testify for the group. "I don't see how that could be done at all, much less on a timely basis, through a voluntary mechanism."

Momentum for disclosure is also coming from other quarters. The National Institutes of Health has proposed requiring researchers whose work is funded by the NIH to submit the resulting studies to the agency, which would make them free of charge to the public six months after their publication. Separately, a group of editors of major medical journals is expected to lay out its position on clinical-trial registries this week. Though details aren't public, the editors are widely expected to require that articles they consider for publication have their clinical trials placed in a public registry.

Individual companies, including Eli Lilly & Co. and GlaxoSmithKline PLC, have also committed to new disclosure policies. Most recently, Merck & Co. has begun voluntarily registering a broad spectrum of late-stage and post-marketing clinical trials in an existing government database, which currently only focuses on the most serious medical conditions.

The new push for fuller disclosure has stemmed largely from concerns about the trials of antidepressant drugs in young people. After regulators began probing evidence of a possible link between the drugs and suicidal tendencies, researchers who examined the studies wrote that some unflattering findings about the drugs hadn't been published, potentially creating an overly positive portrait of some of the drugs.

In June, New York Attorney General Eliot Spitzer sued GlaxoSmithKline, alleging the company had illegally downplayed negative findings about the effects of its antidepressant Paxil on children and adolescents. The company denied his claims and has since settled the case without admitting to any illegal behavior.

On Capitol Hill, the issue has gained some traction, though prospects for a bill are unclear. On the House side, Democratic Rep. Henry Waxman of California and others are working on a bill to create a government registry that would hold clinical-trial results. Sen. Edward M. Kennedy, a Massachusetts Democrat, is developing similar legislation.

The PhRMA database is supposed to include summaries of the unpublished results of all trials its members sponsor that they consider "hypothesis-testing," as well as links to published findings, when possible. It will contain only trials completed after Oct. 1, 2002. According to PhRMA officials, the registry should include tests intended to discover whether drugs work in new, unapproved indications or populations, like the antidepressant trials that involved pediatric patients.

But the database will leave out a number of early-stage trials, which PhRMA says aren't as relevant to doctors, as well as trials that aren't completed. In addition, it will limit its information to drugs that are approved for use in the U.S.

Under the plan, the results of the trials are supposed to become public within a year of their conclusion, and the database won't involve registration of trials as they get under way. The summaries would be presented in a format endorsed by an international standards-setting group, and include the trial's structure, results and major safety concerns, but not all details of the study design or raw data.

"We have to make a decision about what is going to be important to physicians using the products," said PhRMA's Dr. Goldhammer. He says the group is willing to discuss adding more information to the clinical-trial results Web site, as well as possibly a separate registry that could list new trials when they are launched.

If an early-stage trial or an uncompleted trial were to raise a safety issue, it would be up to the company and researchers leading the trial to decide whether the results would go into the PhRMA database. The group's guidelines call for sponsors of trials to work with researchers to publish any finding of "significant medical importance."

The PhRMA proposal in some ways promises less than what some individual drug companies already have agreed to make public. Lilly has pledged to make public summaries of clinical trials for drugs it markets, including the earliest-stage studies, and to rely on a third-party auditor to monitor its adherence to the policies. GlaxoSmithKline, under its settlement with Mr. Spitzer, will divulge summaries of all of its trials conducted after Dec. 27, 2000, as well as some before that date.

The industry plan is likely to draw concern from advocates of greater openness. "This isn't going to happen as a voluntary, pro-bono thing unless it has teeth" mandated by the law, says Drummond Rennie, professor of medicine at the University of California-San Francisco and deputy editor of JAMA, the Journal of the American Medical Association. He adds, "The teeth have to be considerable."

Catherine DeAngelis, editor-in-chief of JAMA, says that any registry on clinical trials should include information about trials that aren't completed. "Once it's started, let's hear about it," she says, adding that she was speaking for herself, not the group of medical-journal editors. "If you stop it after five patients, we want to know why."

REPORT OF THE COUNCIL ON SCIENTIFIC AFFAIRS

CSA Report 10-A-04

Subject: Influence of Funding Source on Outcome, Validity, and Reliability of Pharmaceutical Research
(Resolution 514, A-03)

54

Presented by: J. Chris Hawk, III, MD, Chair

Referred to: Reference Committee E
(Stuart Gitlow, MD, Chair)

Resolution 514 (A-03), introduced by the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry and referred to the Board of Trustees, asked that the: Council on Scientific Affairs (1) study the impact of funding sources on the outcome, validity, and reliability of pharmaceutical research; and (2) develop guidelines to assist physician-researchers in evaluating and preserving the scientific integrity, validity, and reliability of pharmaceutical research, regardless of funding source.

Considerable research has been conducted on the issues raised in Resolution 514, and systematic reviews on the subject have been recently published. This report summarizes the findings of these reviews, updates new information, provides some perspectives on the topic, and offers some recommendations on how our American Medical Association (AMA) can continue to assist in improving the scientific integrity, validity, and reliability of pharmaceutical research. *JAMA* and other major-impact medical journals also have recently taken steps to address the problem of publication bias and to properly identify the conflicts of interest that inevitably emerge with the sponsorship of a market-driven enterprise such as prescription drug approval.

Methods

Literature searches were conducted in the MEDLINE and Lexis-Nexis databases for English-language review articles published between 1985 and 2003 using the search terms "clinical trials," "drug industry," "financing, organized," "publishing," and "research or research support," in combination with "economics" or "standards." This search identified 12 systematic reviews on the relationship between pharmaceutical industry sponsorship and research outcome, quality, or publication bias. Three of these reviews evaluated previously published information on the relationship between industry funding and outcome or quality; more than 2000 original studies were included in the original studies covered by these reviews.[1-3] The findings of these 12 systematic reviews form the basis for discussion in this report. Recently published articles not covered in these systematic reviews and other original studies and editorials relevant to related issues also were analyzed. In addition, the draft report was offered to our AMA's Council on Ethical and Judicial Affairs for its review and contribution to the discussion in the "Potential Remedies" section (see below).

Action of the AMA House of Delegates 2004 Annual Meeting: Council on Scientific Affairs Report 10 Recommendations Adopted as Amended and Remainder of Report Filed.

Introduction

The results (and analysis) of clinical research that are published in peer-reviewed journals inform most treatment decisions, and influence public and private health care policy. A longstanding concern exists about the potential for publication bias in pharmaceutical research. Publication bias is the selective publication of studies based on the direction (positive), magnitude, and statistical significance of the treatment effect. Publication bias is often attributed to decisions made by author/investigators and journal editors, but in fact can intrude during the entire process of planning and conducting the clinical trial and publishing the results, leading to outcome bias.[4]

Studies with positive findings are more likely to be published than studies with negative or null results and an association exists between pharmaceutical industry sponsorship of clinical research and publication of results favoring the sponsor's products.[1-3,5-16] Additionally, the publication of negative results may be delayed compared with the time to publication of studies with positive results. This relative time lag is not limited to industry-sponsored trials.[17]

This pattern of publication distorts the medical literature, thereby affecting the validity and findings of systematic reviews and meta-analyses, the decisions of funding agencies, and ultimately the optimal practice of medicine. However, without pharmaceutical industry sponsorship, important therapeutic advances would not have occurred. Modern drug therapy has changed the clinical landscape and represents a cost-effective intervention for disease prevention and treatment. Productive collaborations between the pharmaceutical industry and academic medicine or other research organizations have flourished over the last 30 years enabling a steady stream of new and innovative treatments to improve patient care. In 2002, total grant spending for clinical trials involving human subjects was approximately $5.6 billion, with more than 70% provided by the biopharmaceutical industry. If device manufacturers are included, the total fraction of grant support rises to 80%, with the remainder ($1.1 billion) supplied primarily by the National Institutes of Health (NIH).[18] In 2002, approximately 50,000 clinical investigators received funding for at least one clinical trial conducted in the United States.[18]

Publication bias involving industry-sponsored trials may be exacerbated because many drug trials are conducted to gain regulatory approval, not to test a novel scientific hypothesis or to examine relative therapeutic efficacy versus another treatment. Much of the clinical trial information is unpublished at the time of marketing. Physicians would like to know how one drug compares with other available therapeutic options, and the health care system wants to take cost utility into account, but such information is usually not available initially and may never become available. These deficiencies raise broader issues related to drug approval and marketing.

Sources of Publication Bias

Investigators and Authors. One direct source of publication bias is the failure of investigators to submit completed research for publication.[19-21] Quantitative studies with significant results are more likely to be submitted, and studies with positive results are submitted more rapidly. Given available time and resources, some investigators are unwilling to submit studies with null or unimportant results because they believe the manuscript will be rejected anyway.

Also, investigators (including academic faculty who receive industry funding) may be subject to prepublication review or restricted access to data. Cross-sectional surveys indicate that industry-sponsored faculty are more likely to report restrictions on the dissemination of their research findings and to be denied access to the entire data.[22-25] Delayed publication may occur because of clinical trial agreements that require information to remain confidential for an extended period to enable patent

protection, protect a corporate "lead" in the field, or resolve disputes over intellectual property.[22-25] Another behavior of academic faculty that is associated with pharmaceutical sponsorship or the presence of commercial agreements is refusal to share information with colleagues.[24,25] Because pharmaceutical companies now exert more direct control and ownership of the clinical trial process, published reports also may contain declared authors who have not participated in the design or interpretation of the study, with only limited access to the original data.

Journal Editors and Reviewers. As mentioned above, authors may fail to submit negative studies because of fear of rejection by journal editors. The ideal articles for journals are those with findings that will affect clinical practice. Indeed, instructions to authors may contain phrases such as the journal "gives priority to reports of original research that are likely to change clinical practice or thinking about a disease."[26] Under this rubric, even confirmatory trials (positive or negative) would achieve lower priority. In terms of external advice received by journal editors, selected referees may demonstrate bias against papers with results that are contrary to their own perspectives. This type of confirmatory bias, in which the referees' judgment is colored by their own preconceptions and experience, contributes to poor interrater reliability.[27] In a study of articles submitted to *JAMA* from 1996-1999 that reported results of controlled trials involving an intervention and comparison group, the odds ratio for publishing studies with positive results was 1.30. This difference in publication rates between those with positive and negative results was not statistically significant, suggesting publication bias was not evident in editorial decision-making.[28]

Clinical Trial Agreements. A large percentage of companies providing support for clinical research obtain patents and market products as a result of this relationship. One survey revealed that 53% of signed clinical trial agreements in a sample of university-industry research centers allowed publication to be delayed, 35% allowed the sponsor to delete information from the publication, and 30% allowed both.[22] Commercial interests and intellectual property are often the main reasons for lack of publication of clinical studies funded by the pharmaceutical industry.[29,30] In the last decade, some high-profile cases of direct interference have been noted.[31-34]

Nevertheless, industry's dependence on academia has lessened in the last decade with a shift to contract research organizations (CROs), site management organizations, and commercial drug trial networks.[34] There are several reasons for this development, including changes in the pharmaceutical industry itself (ie, employment of competent researchers to design, run, and interpret trials) and the fact that CROs have been able to use community physicians as a reliable source of patient enrollees, can run trials less expensively and more efficiently than academic medical centers, and generally impose a less cumbersome trial agreement process.

Outcome Bias. When control lies with the commercial rather than academic or public sector, bias can also envelope the process through the trial design.[4,36] Outcome bias can result from the use of unreliable methods or instruments, as well as inadequate sample size or comparison groups. Favorable results are more likely if: (1) the drug is tested in a healthier population (ie, younger, fewer comorbidities, milder disease) that is not representative of the actual patient population that will take the drug; (2) the drug is compared with an insufficient dose of an alternate product; or (3) multiple surrogate endpoints (which may not correlate with more important clinical endpoints) are studied but only results favoring the product are published. Industry-funded studies are also much more likely to use placebos or inactive controls, a practice that increases the likelihood of achieving positive study results.[7,15]

Funding Source and Outcome

For reasons cited above, growing concern exists about the influence that industry sponsorship exerts on clinical trial design and outcome, academic freedom, transparency in the research process, and ultimately, the public good. With regard to the *extent of financial relationships*, at least $1.5 billion flows from industry to academia annually, so a significant percentage (at least 25%) of academic investigators receive industry funding for their biomedical research, and at least one-third have personal financial ties with industry sponsors.[26] Correspondingly, many universities may hold equity in the sponsor's business (as well as accept funding).

Because of these financial relationship, questions have been raised about whether such financial relationships could create institutional conflicts of interest involving research integrity and/or the safety and welfare of human subjects. Because of the increasing trend for faculty researchers to be involved in financial relationships with their research sponsors, Boyd and Bero[37] concluded that "guidelines for what constitutes a conflict and how the conflict should be managed are needed if researchers are to have consistent standards of behavior among institutions." In keeping with this recommendation, the American Association of Medical Colleges (AAMC) formed a task force on conflicts of interest in clinical research. In 2002, the task force released a report that provided guidance on addressing the financial interests of faculty, as well as other individuals involved in the clinical research enterprise.[38]

Funding Source and Publication Outcome or Status. Results of 3 recent systematic reviews confirm that industry-sponsored research tends to yield pro-industry conclusions.[1-3] Even among comparison trials, the sponsor's drug is almost always deemed equivalent or superior to the comparator.[12] The favorable relationship between funding source and outcome extends to pharmacoeconomic studies and sponsored meta-analyses.[2] Authors who have financial relationships with pharmaceutical companies may be more likely to produce proindustry conclusions.[39] This fact and other evidence support the notion that conclusions are generally more positive in trials funded by the pharmaceutical industry, in part due to biased interpretation of trial results.[40]

Although lower quality studies lend themselves inherently to biased results, this does not appear to account for the relationship between industry funding and the bias towards positive published outcomes. With one major exception,[41] most authors have concluded that industry-funded studies published in peer-reviewed journals are of equivalent or higher quality than non-industry funded clinical trials.[7,8,41-43] This view does not necessarily apply to industry-sponsored symposia journal supplements. Research funded by drug companies is more likely to be published in the proceedings of symposia than non-industry sponsored research.[44] Some, but not all studies have concluded that randomized controlled trials published in these supplements were generally of lower quality, although the relationship between funding and positive outcome persists.[8,45,46]

Despite these consistent findings over the last 15 years, results of a recent pilot study of randomized controlled trials published in 5 leading medical journals (including *JAMA*) failed to document any association between funding source, trial outcome, and study quality.[47] This could reflect the beneficial effects of more stringent editorial policies that have been adopted by the editors of these journals.

Potential Remedies

Investigators and Authors. In addition to ethical and legal guidelines that are intended to help protect human subjects, individual investigators should be mindful of guidelines developed to prevent or mitigate potential conflicts of interest that could lead to publication bias. In particular, 2 ethical

opinions included in the AMA's Code of Medical Ethics, E-8.031, "Conflicts of Interest: Biomedical Research," and E-8.0315, "Managing Conflicts of Interest in the Conduct of Clinical Trials," (AMA Policy Database), recommend the disclosure of financial compensation from or other material ties to companies whose products they are investigating to various stakeholders, including journals editors. It is also recommended that physicians should not enter into research contracts that permit the sponsoring company to unduly delay or otherwise obstruct the presentation or publication of results.

Uniform Institutional Practices. A 2001 report issued by the U.S. General Accounting Office noted that equity ownership or investment in a research sponsor may "color [an institution's] review, approval, or monitoring of research...or its allocation of equipment, facilities, and staff for research."[48] In response to these concerns, the AAMC task force authored a second report that laid out a conceptual framework for assessing institutional conflicts of interest in human subjects research.[49] As a fundamental principle "institutions should ensure that, in practice, the functions and administrative responsibilities related to human subjects research are separate from those related to investment management and technology licensing." The report also contained a series of recommendations regarding: (1) authority/responsibility of institutional officials; (2) circumstances or other financial relationships that should trigger close scrutiny; (3) an appropriate internal committee structure and review process; (4) institutional behavior within the confines of multi-center or single, primary site trials; (5) use of external institutional review boards (IRBs); (6) conditions where recusal may be warranted; (7) policies applying to IRB members; and (8) disclosure requirements.

Journals and Journal Editors. The publishing community has taken steps to increase the quality of published reports and to reduce publication bias associated with clinical trials and the conflicts of interest that may arise out of industry funding of investigators. The Consolidated Standards for Reporting of Trials Group (CONSORT) developed a statement (http://www.consort-statement.org) intended as an evidence-based approach to improve the quality of reports emanating from randomized controlled trials (RCTs). Originally published in 1996 and revised in 2001, the CONSORT statement comprises a checklist and flow diagram for the reporting of RCTs, primarily those constructed as parallel-group studies.[50] The checklist includes items, based on evidence, that need to be addressed in the report to avoid biased estimates of treatment effect and to properly evaluate the findings. The flow diagram assists readers in analyzing the progress of trial participants from the time they are randomized until the end of their involvement with the trial. Adoption of the CONSORT statement by journals (including *JAMA*) is associated with improvement in the quality of published reports.[51] Companion efforts to increase the quality of meta-analyses of RCTs (QUOROM), observational studies (MOOSE), and assessments of diagnostic tests (STARD) have been drafted or are under way.

Journal editors also have taken steps to reduce publication bias by revising the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication." This document (http://www.icmje.org) was developed by the International Committee of Medical Journal Editors (ICMJE) and is widely used as the basis for editorial policy. The revision established more rigorous criteria for the acceptance of research sponsored by the pharmaceutical industry, particularly regarding declaration of potential conflicts of interest related to individual authors' commitments or project support. Among the salient points are:

- researchers should not enter into agreements that interfere with their access to the data or their ability to analyze the data independently, to prepare manuscripts, and to publish them.
- authors should describe the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the report for publication.

These tenets hold that the sponsor must impose no impediment, direct or indirect, on the publication of the study's full results, including data perceived to be detrimental to marketing of the drug. Journals adhering to this approach will not review or publish articles based on studies that are conducted under conditions that allow the sponsor to have sole control of the data or withhold publication.[52] Accordingly, journals should encourage a culture of transparency in research and reporting by publishing study protocols and publishing all data from drug studies, including negative results, in concert with a comprehensive trials registry (see below) and development of accessible electronic databases.

Voluntary Industry Guidances. In recognition of the need for proactive involvement of the pharmaceutical industry in addressing publication bias, the Pharmaceutical and Research Manufacturers of America adopted voluntary principles on its members' relationships with those involved in the clinical research process.[53] While these principles "commit to timely communication of meaningful results of controlled trials...that are approved for marketing regardless of outcome," they do not commit "to mak[ing] the designs of clinical trial protocols available publicly at inception, as in a clinical trials registry."

Staff from a small cadre of pharmaceutical companies have also developed guidelines for good publication practices, which they have offered for voluntary use by sponsors when they seek to publish results from their clinical trials.[54] The *Good Publication Practice for Pharmaceutical Companies* is intended for use in conjunction with the ICMJE-derived "Uniform Requirements" and the CONSORT statement. The guidelines cover publication standards, including a commitment to publish results from all clinical trials; premature, duplicate, or redundant publication; contractual relationships between sponsors and investigators; study tags or identification; and authorship, including the role of professional medical writers. The guidelines and a list of pharmaceutical companies and CROs that have endorsed their use can be found at www.gpp-guidelines.org.

Other Recommendations to Reduce Publication Bias. A number of other steps have been recommended to address the problem of publication bias, to improve the quality and reliability of published drug studies, and to assist physicians in accessing, summarizing, and applying information on new drug treatments.

1. Register all clinical trials at inception.[55] Over the last 30 years there have been a number of events and initiatives related to the goal of trial registration. Industry, government, and certain collaborative registers have been formed (see Table), but no comprehensive system for tracking, organizing, and disseminating information about ongoing clinical trials currently exists. This could be implemented by having the Department of Health and Human Services, the parent agency that encompasses the NIH and the Food and Drug Administration, take responsibility for ensuring trial registration in the United States. A recent example of such collaborative action is the GemCRIS system for registration of gene-transfer studies and facilitated reporting of adverse events.

   Institutional review boards could make registration a condition of approval. Industry compliance would also be enhanced if both the researcher and the individual patient insist that the trial be registered before enrollment, with explicit language to that effect in the informed consent document. Finally, legislation to fund, require, and enforce public registration of all trials involving human subjects (regardless of funding source) could be sought. While clinical trial registers address some problems, their effects on patient care will be limited unless they are backed by sound publication policies.

2. Reduce bias in study design[36] by conducting studies of comparative effectiveness and requiring data comparing new drugs with available alternatives for effectiveness and cost as part of the regulatory approval process. Alternatively, to provide physicians with the kind of information needed for optimal treatment decisions, establish a center for the assessment of pharmaceutical effectiveness funded by subscription fees on third-party payers, contributions by payers to address specific research questions, user fees, or taxes on pharmaceutical products.

3. Reduce bias in study conduct[36] by leaving the planning and monitoring of the research design completely to the funded investigators.

Summary and Comment

When an investigator has a financial interest in or funding from a company with activities related to his or her research, the research is more likely to favor the sponsor's product, less likely to be published, and more likely to have delayed publication. Investigators and academic institutions can help ensure the integrity of clinical research by negotiating ethically acceptable contracts that allow full access to data and control of publication rights. Publication bias involving drug studies hasbeen reduced by journal editors who have adopted the revised CONSORT statement, and via revision of the "Uniform Requirements" by the ICMJE. Adoption of these guidelines helps readers make informed judgments about clinical trials and potential biases involving authors, data analyses, and publication/interpretation of results. Thus, guidelines are already established that "assist physician researchers in evaluating and preserving the scientific integrity, validity and reliability of pharmaceutical research, regardless of funding source" as requested by Resolution 514 (A-03).

Additionally, some progress has been made in registering clinical trials at inception. Development of a comprehensive trials registry will require a cooperative venture among all participants. Development of a registry will not guarantee publication of results, but would assist authors conducting systematic reviews and meta-analyses in identifying relevant studies for inclusion. Electronic databases that can serve as a repository of published results are needed to accommodate all trial results. Absent legislative action, IRBs and patient advocates form a potentially powerful coalition in requiring clinical trials involving human subjects to be registered as a condition for approval.

RECOMMENDATIONS

The Council on Scientific Affairs recommends that the following statements be adopted in lieu of Resolution 514 (A-03) and that the remainder of this report be filed:

1. That our American Medical Association establish policy that all medical journal editors and authors should adhere to the revised CONSORT Statement and Uniform Requirements for Manuscripts Submitted to Biomedical Journals. **(New HOD Policy)**

2. That our AMA recommend that (a) the Department of Health and Human Services ~~consider~~ establish~~ing~~ a comprehensive registry for all clinical trials conducted in the United States; (b) every clinical trial should have a unique identifier; and (c) all results from registered clinical trials be made publicly available through either publication or an electronic data repository. **(New HOD Policy)**

3. That our AMA urge that Institutional Review Boards consider registration of clinical trials to an existing registry as condition of approval. **(New HOD Policy)**

~~4. That our AMA refer the issue of a comprehensive clinical trials registry to the Clinical Research Roundtable for further review and action.~~ **(Directive to Take Action)**

Fiscal Note: $534

Table. Clinical Trials Registers

Register	Description/Comment	Information
Government		
National Institute of Mental Health	Trials of pharmacologic agents (1967-1972)	
National Institutes of Health (NIH)	Years 1975-1979 Year 2000-present HIV/AIDS trials	 www.ClinicalTrials.gov www.aidsinfo.nih.gov
NIH and the Food and Drug Administration	GemCRIS. Gene therapy trials from 1989-present	www.gemcris.od.nih.gov
United Kingdom	National Health Service Research Medical Research Council Trials	www.doh.gov.uk/research www.controlledtrials.com
Collaborative Efforts		
Oxford Database of Perinatal Trials	Comprehensive register of published trials (1986-1993)	Oxford University Press
Cochrane Central Register of Controlled Trials	Comprehensive register of controlled clinical trials identified by the Cochrane Collaboration	www.cochrane.org
TrialsCentral	Online register of >200 US-based trials registers	www.trialscentral.org
Current Controlled Trials	Meta register compilation of individual registers	www.controlled-trails.com
Industry Register		
CenterWatch	Compilation of >41,000 active industry and government-sponsored trials	www.centerwatch.com

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American Medical Association
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FOR IMMEDIATE RELEASE **June 15, 2004**

AMA RECOMMENDS THAT DHHS ESTABLISH A REGISTRY FOR ALL U.S. CLINICAL TRIALS

CHICAGO – In response to concerns about the impact of pharmaceutical industry sponsorship on research outcome, quality and publication bias, the American Medical Association House of Delegates called for the Department of Health and Human Services to establish a comprehensive registry for all clinical trials conducted in the United States.

The new registry would ensure that trials with negative as well as positive results are publicly available, by providing every clinical trial with a unique identification and ensuring publication or placement on an electronic database of all results from registered trials.

The new policy, approved at the AMA's annual meeting, also calls for the AMA to urge institutional review boards (at hospitals, universities and medical centers) that must approve any research involving human subjects to consider registration of clinical trials as a condition for approval.

"Studies with positive findings are more likely to be published than studies with negative or null results," said AMA Trustee Joseph M. Heyman, M.D. "We are concerned that this pattern of publication distorts the medical literature, affecting the validity and findings of systematic reviews, the decisions of funding agencies and, ultimately, the best practice of medicine."

The AMA cited growing concern about the influence commercial support of drug trials may have on this publication bias. There are potential problems arising from clinical trial agreements that may delay publication or delete information from publications. There may be outcome bias resulting from the use of unreliable methods and inadequate sample size or comparison groups. Industry-funded studies may be more likely to use placebos or inactive controls, increasing the likelihood of achieving positive study results.

In studying this issue, the AMA also found direct sources of publication bias. Investigators and authors are reluctant to submit studies unless the results are positive or significant, believing that journals will not publish them. Journals are more interested in publishing studies that are likely to affect clinical practice. As a result, confirmatory trials, trials with negative results, and trials that show no significant result are less likely to be published.

The new policies were based on recommendations put forth in a report from the AMA's Council on Scientific Affairs (CSA). Authors of the study reviewed the available scientific literature on the relationship between pharmaceutical sponsorship and research outcome, quality or publication bias, including 12 systematic reviews of thousands of original studies.

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American Medical Association
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For Immediate Release June 18, 2004

AMA ENCOURAGED BY EARLY SIGNS OF INDUSTRY SUPPORT FOR NATIONAL CLINICAL TRIALS REGISTRY

Statement Attributable to: Joseph M. Heyman, MD
AMA Trustee

"The American Medical Association is encouraged by early signs of support from the pharmaceutical industry for a national clinical trials registry, following action taken by the AMA House of Delegates earlier this week.

The AMA announced Tuesday that it would call on the Department of Health and Human Services to create a comprehensive, centralized clinical trials registry so that scientists, investigators and clinicians could easily find information on trials. Posting the results of such trials would address growing concerns over publication and outcome bias in clinical trials. The AMA further called on all institutional review boards to make registration in this database a condition of approval.

We hope that all pharmaceutical companies will follow Merck's lead in deciding to support the AMA's call for a national registry.

The AMA also welcomes the recent news that the International Committee of Medical Journal Editors (which includes representatives from leading medical journals such as ***The Journal of the American Medical Association, The New England Journal of Medicine*** and ***The Lancet)*** may be considering a proposal that would require trials to be listed in a registry before the results would be considered for publication.

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Contact:

Lori Bolas
Media Manager
AMA Dept. of News & Information
(312) 464-4418

One Hundred Seventh Congress of the United States of America 57

Begun and held at the City of Washington on Wednesday,

the third day of January, two thousand and one

An Act

To amend the Federal Food, Drug, and Cosmetic Act to improve the safety and efficacy of pharmaceuticals for children.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the `Best Pharmaceuticals for Children Act'.

SEC. 2. PEDIATRIC STUDIES OF ALREADY-MARKETED DRUGS.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended--

(1) by striking subsection (b); and

(2) in subsection (c)--

(A) by inserting after `the Secretary' the following: `determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and'; and

(B) by striking `concerning a drug identified in the list described in subsection (b)'.

SEC. 3. RESEARCH FUND FOR THE STUDY OF DRUGS.

Part B of title IV of the Public Health Service Act (42 U.S.C. 284 et seq.) is amended--

(1) by redesignating the second section 409C, relating to clinical research (42 U.S.C. 284k), as section 409G;

(2) by redesignating the second section 409D, relating to enhancement awards (42 U.S.C. 284l), as section 409H; and

(3) by adding at the end the following:

`SEC. 409I. PROGRAM FOR PEDIATRIC STUDIES OF DRUGS.

`(a) LIST OF DRUGS FOR WHICH PEDIATRIC STUDIES ARE NEEDED-

`(1) IN GENERAL- Not later than one year after the date of enactment of this section, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs and experts in pediatric research, shall develop, prioritize, and publish an annual list of approved drugs for which--

`(A)(i) there is an approved application under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

`(ii) there is a submitted application that could be approved under the criteria of section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j));

`(iii) there is no patent protection or market exclusivity protection under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.); or

`(iv) there is a referral for inclusion on the list under section 505A(d)(4)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(C)); and

`(B) in the case of a drug referred to in clause (i), (ii), or (iii) of subparagraph (A), additional studies are needed to assess the safety and effectiveness of the use of the drug in the pediatric population.

`(2) CONSIDERATION OF AVAILABLE INFORMATION- In developing and prioritizing the list under paragraph (1), the Secretary shall consider, for each drug on the list--

`(A) the availability of information concerning the safe and effective use of the drug in the pediatric population;

`(B) whether additional information is needed;

`(C) whether new pediatric studies concerning the drug may produce health benefits in the pediatric population; and

`(D) whether reformulation of the drug is necessary.

`(b) CONTRACTS FOR PEDIATRIC STUDIES- The Secretary shall award contracts to entities that have the expertise to conduct pediatric clinical trials (including qualified universities, hospitals, laboratories, contract research organizations, federally funded programs such as pediatric pharmacology

research units, other public or private institutions, or individuals) to enable the entities to conduct pediatric studies concerning one or more drugs identified in the list described in subsection (a).

`(c) PROCESS FOR CONTRACTS AND LABELING CHANGES-

`(1) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS LACKING EXCLUSIVITY- The Commissioner of Food and Drugs, in consultation with the Director of the National Institutes of Health, may issue a written request (which shall include a timeframe for negotiations for an agreement) for pediatric studies concerning a drug identified in the list described in subsection (a)(1)(A) (except clause (iv)) to all holders of an approved application for the drug under section 505 of the Federal Food, Drug, and Cosmetic Act. Such a written request shall be made in a manner equivalent to the manner in which a written request is made under subsection (a) or (b) of section 505A of the Federal Food, Drug, and Cosmetic Act, including with respect to information provided on the pediatric studies to be conducted pursuant to the request.

`(2) REQUESTS FOR CONTRACT PROPOSALS- If the Commissioner of Food and Drugs does not receive a response to a written request issued under paragraph (1) within 30 days of the date on which a request was issued, or if a referral described in subsection (a)(1)(A)(iv) is made, the Secretary, acting through the Director of the National Institutes of Health and in consultation with the Commissioner of Food and Drugs, shall publish a request for contract proposals to conduct the pediatric studies described in the written request.

`(3) DISQUALIFICATION- A holder that receives a first right of refusal shall not be entitled to respond to a request for contract proposals under paragraph (2).

`(4) GUIDANCE- Not later than 270 days after the date of enactment of this section, the Commissioner of Food and Drugs shall promulgate guidance to establish the process for the submission of responses to written requests under paragraph (1).

`(5) CONTRACTS- A contract under this section may be awarded only if a proposal for the contract is submitted to the Secretary in such form and manner, and containing such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section.

`(6) REPORTING OF STUDIES-

`(A) IN GENERAL- On completion of a pediatric study in accordance with a contract awarded under this section, a report concerning the study shall be submitted to the Director of the National Institutes of Health and the Commissioner of Food and Drugs. The report shall include all data generated in connection with the study.

`(B) AVAILABILITY OF REPORTS- Each report

submitted under subparagraph (A) shall be considered to be in the public domain (subject to section 505A(d)(4)(D) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(D)) and shall be assigned a docket number by the Commissioner of Food and Drugs. An interested person may submit written comments concerning such pediatric studies to the Commissioner of Food and Drugs, and the written comments shall become part of the docket file with respect to each of the drugs.

`(C) ACTION BY COMMISSIONER- The Commissioner of Food and Drugs shall take appropriate action in response to the reports submitted under subparagraph (A) in accordance with paragraph (7).

`(7) REQUESTS FOR LABELING CHANGE- During the 180-day period after the date on which a report is submitted under paragraph (6)(A), the Commissioner of Food and Drugs shall--

`(A) review the report and such other data as are available concerning the safe and effective use in the pediatric population of the drug studied;

`(B) negotiate with the holders of approved applications for the drug studied for any labeling changes that the Commissioner of Food and Drugs determines to be appropriate and requests the holders to make; and

`(C)(i) place in the public docket file a copy of the report and of any requested labeling changes; and

`(ii) publish in the Federal Register a summary of the report and a copy of any requested labeling changes.

`(8) DISPUTE RESOLUTION-

`(A) REFERRAL TO PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE- If, not later than the end of the 180-day period specified in paragraph (7), the holder of an approved application for the drug involved does not agree to any labeling change requested by the Commissioner of Food and Drugs under that paragraph, the Commissioner of Food and Drugs shall refer the request to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

`(B) ACTION BY THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE- Not later than 90 days after receiving a referral under

subparagraph (A), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall--

`(i) review the available information on the safe and effective use of the drug in the pediatric population, including study reports submitted under this section; and

`(ii) make a recommendation to the Commissioner of Food and Drugs as to appropriate labeling changes, if any.

`(9) FDA DETERMINATION- Not later than 30 days after receiving a recommendation from the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee under paragraph (8)(B)(ii) with respect to a drug, the Commissioner of Food and Drugs shall consider the recommendation and, if appropriate, make a request to the holders of approved applications for the drug to make any labeling change that the Commissioner of Food and Drugs determines to be appropriate.

`(10) FAILURE TO AGREE- If a holder of an approved application for a drug, within 30 days after receiving a request to make a labeling change under paragraph (9), does not agree to make a requested labeling change, the Commissioner may deem the drug to be misbranded under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

`(11) NO EFFECT ON AUTHORITY- Nothing in this subsection limits the authority of the United States to bring an enforcement action under the Federal Food, Drug, and Cosmetic Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.

`(12) RECOMMENDATION FOR FORMULATION CHANGES- If a pediatric study completed under public contract indicates that a formulation change is necessary and the Secretary agrees, the Secretary shall send a nonbinding letter of recommendation regarding that change to each holder of an approved application.

`(d) AUTHORIZATION OF APPROPRIATIONS-

`(1) IN GENERAL- There are authorized to be appropriated to carry out this section--

`(A) $200,000,000 for fiscal year 2002; and

`(B) such sums as are necessary for each of the five succeeding fiscal years.

`(2) AVAILABILITY- Any amount appropriated under paragraph (1) shall remain available to carry out this section until expended.'.

SEC. 4. WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS THAT HAVE MARKET EXCLUSIVITY.

Section 505A(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)) is amended by adding at the end the following:

`(4) WRITTEN REQUEST TO HOLDERS OF APPROVED APPLICATIONS FOR DRUGS THAT HAVE MARKET EXCLUSIVITY-

`(A) REQUEST AND RESPONSE- If the Secretary makes a written request for pediatric studies (including neonates, as appropriate) under subsection (c) to the holder of an application approved under section 505(b)(1), the holder, not later than 180 days after receiving the written request, shall respond to the Secretary as to the intention of the holder to act on the request by--

`(i) indicating when the pediatric studies will be initiated, if the holder agrees to the request; or

`(ii) indicating that the holder does not agree to the request.

`(B) NO AGREEMENT TO REQUEST-

`(i) REFERRAL- If the holder does not agree to a written request within the time period specified in subparagraph (A), and if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall refer the drug to the Foundation for the National Institutes of Health established under section 499 of the Public Health Service Act (42 U.S.C. 290b) (referred to in this paragraph as the `Foundation') for the conduct of the pediatric studies described in the written request.

`(ii) PUBLIC NOTICE- The Secretary shall give public notice of the name of the drug, the name of the manufacturer, and the indications to be studied made in a referral under clause (i).

`(C) LACK OF FUNDS- On referral of a drug under subparagraph (B)(i), the Foundation shall

issue a proposal to award a grant to conduct the requested studies unless the Foundation certifies to the Secretary, within a timeframe that the Secretary determines is appropriate through guidance, that the Foundation does not have funds available under section 499(j)(9)(B)(i) to conduct the requested studies. If the Foundation so certifies, the Secretary shall refer the drug for inclusion on the list established under section 409I of the Public Health Service Act for the conduct of the studies.

`(D) EFFECT OF SUBSECTION- Nothing in this subsection (including with respect to referrals from the Secretary to the Foundation) alters or amends section 301(j) of this Act or section 552 of title 5 or section 1905 of title 18, United States Code.

`(E) NO REQUIREMENT TO REFER- Nothing in this subsection shall be construed to require that every declined written request shall be referred to the Foundation.

`(F) WRITTEN REQUESTS UNDER SUBSECTION (b)- For drugs under subsection (b) for which written requests have not been accepted, if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall issue a written request under subsection (c) after the date of approval of the drug.'.

SEC. 5. TIMELY LABELING CHANGES FOR DRUGS GRANTED EXCLUSIVITY; DRUG FEES.

(a) ELIMINATION OF USER FEE WAIVER FOR PEDIATRIC SUPPLEMENTS- Section 736(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379h(a)(1)) is amended--

(1) by striking subparagraph (F); and

(2) by redesignating subparagraph (G) as subparagraph (F).

(b) LABELING CHANGES-

(1) DEFINITION OF PRIORITY SUPPLEMENT- Section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321) is amended by adding at the end the following:

`(kk) PRIORITY SUPPLEMENT- The term `priority supplement' means a drug application referred to in section 101(4) of the Food and Drug Administration Modernization Act of 1997 (111 Stat. 2298).'.

(2) TREATMENT AS PRIORITY SUPPLEMENTS- Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended by adding at the end the following:

`(l) LABELING SUPPLEMENTS-

`(1) PRIORITY STATUS FOR PEDIATRIC SUPPLEMENTS- Any supplement to an application under section 505 proposing a labeling change pursuant to a report on a pediatric study under this section--

`(A) shall be considered to be a priority supplement; and

`(B) shall be subject to the performance goals established by the Commissioner for priority drugs.

`(2) DISPUTE RESOLUTION-

`(A) REQUEST FOR LABELING CHANGE AND FAILURE TO AGREE- If the Commissioner determines that an application with respect to which a pediatric study is conducted under this section is approvable and that the only open issue for final action on the application is the reaching of an agreement between the sponsor of the application and the Commissioner on appropriate changes to the labeling for the drug that is the subject of the application, not later than 180 days after the date of submission of the application--

`(i) the Commissioner shall request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and

`(ii) if the sponsor of the application does not agree to make a labeling change requested by the Commissioner, the Commissioner shall refer the matter to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs

Advisory Committee.

`(B) ACTION BY THE PEDIATRIC ADVISORY SUBCOMMITTEE OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE- Not later than 90 days after receiving a referral under subparagraph (A)(ii), the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall--

`(i) review the pediatric study reports; and

`(ii) make a recommendation to the Commissioner concerning appropriate labeling changes, if any.

`(C) CONSIDERATION OF RECOMMENDATIONS- The Commissioner shall consider the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application to make any labeling change that the Commissioner determines to be appropriate.

`(D) MISBRANDING- If the sponsor of the application, within 30 days after receiving a request under subparagraph (C), does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application to be misbranded.

`(E) NO EFFECT ON AUTHORITY- Nothing in this subsection limits the authority of the United States to bring an enforcement action under this Act when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action.'.

SEC. 6. OFFICE OF PEDIATRIC THERAPEUTICS.

(a) ESTABLISHMENT- The Secretary of Health and Human Services shall establish an Office of Pediatric Therapeutics within the Food and Drug Administration.

(b) DUTIES- The Office of Pediatric Therapeutics shall be responsible for coordination and facilitation of all activities of the Food and Drug Administration that may have any effect on a pediatric population or the practice of pediatrics or may in any other way involve pediatric issues.

(c) STAFF- The staff of the Office of Pediatric Therapeutics shall coordinate

with employees of the Department of Health and Human Services who exercise responsibilities relating to pediatric therapeutics and shall include--

(1) one or more additional individuals with expertise concerning ethical issues presented by the conduct of clinical research in the pediatric population; and

(2) one or more additional individuals with expertise in pediatrics as may be necessary to perform the activities described in subsection (b).

SEC. 7. NEONATES.

Section 505A(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(g)) is amended by inserting `(including neonates in appropriate cases)' after `pediatric age groups'.

SEC. 8. SUNSET.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended by striking subsection (j) and inserting the following:

`(j) SUNSET- A drug may not receive any 6-month period under subsection (a) or (c) unless--

`(1) on or before October 1, 2007, the Secretary makes a written request for pediatric studies of the drug;

`(2) on or before October 1, 2007, an application for the drug is accepted for filing under section 505(b); and

`(3) all requirements of this section are met.'.

SEC. 9. DISSEMINATION OF PEDIATRIC INFORMATION.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 5(b)(2)) is amended by adding at the end the following:

`(m) DISSEMINATION OF PEDIATRIC INFORMATION-

`(1) IN GENERAL- Not later than 180 days after the date of submission of a report on a pediatric study under this section, the Commissioner shall make available to the public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted for the supplement, including by publication in the Federal Register.

`(2) EFFECT OF SUBSECTION- Nothing in this subsection alters or amends section 301(j) of this Act or section 552 of title 5 or section 1905 of title 18, United States Code.'.

SEC. 10. CLARIFICATION OF INTERACTION OF PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT AND 180-DAY EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(j) OF THAT ACT.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 9) is amended by adding at the end the following:

`(n) CLARIFICATION OF INTERACTION OF MARKET EXCLUSIVITY UNDER THIS SECTION AND MARKET EXCLUSIVITY AWARDED TO AN APPLICANT FOR APPROVAL OF A DRUG UNDER SECTION 505(j)- If a 180-day period under section 505(j)(5)(B)(iv) overlaps with a 6-month exclusivity period under this section, so that the applicant for approval of a drug under section 505(j) entitled to the 180-day period under that section loses a portion of the 180-day period to which the applicant is entitled for the drug, the 180-day period shall be extended from--

`(1) the date on which the 180-day period would have expired by the number of days of the overlap, if the 180-day period would, but for the application of this subsection, expire after the 6-month exclusivity period; or

`(2) the date on which the 6-month exclusivity period expires, by the number of days of the overlap if the 180-day period would, but for the application of this subsection, expire during the six-month exclusivity period.'.

SEC. 11. PROMPT APPROVAL OF DRUGS UNDER SECTION 505(j) WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING.

(a) IN GENERAL- Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by section 10) is amended by adding at the end the following:

`(o) PROMPT APPROVAL OF DRUGS UNDER SECTION 505(j) WHEN PEDIATRIC INFORMATION IS ADDED TO LABELING-

`(1) GENERAL RULE- A drug for which an application has been submitted or approved under section 505(j) shall not be considered ineligible for approval under that section or misbranded under section 502 on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(D).

`(2) LABELING- Notwithstanding clauses (iii) and (iv) of section 505(j)(5)(D), the Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include--

`(A) a statement that, because of marketing exclusivity for a manufacturer--

`(i) the drug is not labeled for pediatric use; or

`(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and

`(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary.

`(3) PRESERVATION OF PEDIATRIC EXCLUSIVITY AND OTHER PROVISIONS- This subsection does not affect--

`(A) the availability or scope of exclusivity under this section;

`(B) the availability or scope of exclusivity under section 505 for pediatric formulations;

`(C) the question of the eligibility for approval of any application under section 505(j) that omits any other conditions of approval entitled to exclusivity under clause (iii) or (iv) of section 505(j)(5)(D); or

`(D) except as expressly provided in paragraphs (1) and (2), the operation of section 505.'.

(b) EFFECTIVE DATE- The amendment made by subsection (a) takes effect on the date of enactment of this Act, including with respect to applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) that are approved or pending on that date.

SEC. 12. STUDY CONCERNING RESEARCH INVOLVING CHILDREN.

(a) CONTRACT WITH INSTITUTE OF MEDICINE- The Secretary of Health and Human Services shall enter into a contract with the Institute of Medicine for--

(1) the conduct, in accordance with subsection (b), of a review of--

(A) Federal regulations in effect on the date of the enactment of this Act relating to research involving children;

(B) federally prepared or supported reports relating to research involving children; and

(C) federally supported evidence-based research involving children; and

(2) the submission to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives, not later than two years after the date of enactment of this Act, of a report concerning the review conducted under paragraph (1) that includes recommendations on best practices relating to research involving children.

(b) AREAS OF REVIEW- In conducting the review under subsection (a)(1), the Institute of Medicine shall consider the following:

(1) The written and oral process of obtaining and defining `assent', `permission' and `informed consent' with respect to child clinical research participants and the parents, guardians, and the individuals who may serve as the legally authorized representatives of such children (as defined in subpart A of part 46 of title 45, Code of Federal Regulations).

(2) The expectations and comprehension of child research participants and the parents, guardians, or legally authorized representatives of such children, for the direct benefits and risks of the child's research involvement, particularly in terms of research versus therapeutic treatment.

(3) The definition of `minimal risk' with respect to a healthy child or a child with an illness.

(4) The appropriateness of the regulations applicable to children of differing ages and maturity levels, including regulations relating to legal status.

(5) Whether payment (financial or otherwise) may be provided to a child or his or her parent, guardian, or legally authorized representative for the participation of the child in research, and if so, the amount and type of payment that may be made.

(6) Compliance with the regulations referred to in subsection (a)(1)(A), the monitoring of such compliance (including the role of institutional review boards), and the enforcement actions taken for violations of such regulations.

(7) The unique roles and responsibilities of institutional review boards in reviewing research involving children, including composition of membership on institutional review boards.

(c) REQUIREMENTS OF EXPERTISE- The Institute of Medicine shall conduct the review under subsection (a)(1) and make recommendations under subsection (a)(2) in conjunction with experts in pediatric medicine, pediatric research, and the ethical conduct of research involving children.

SEC. 13. FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH.

Section 499 of the Public Health Service Act (42 U.S.C. 290b) is amended--

(1) in subsection (b), by inserting `(including collection of funds for pediatric pharmacologic research)' after `mission';

(2) in subsection (c)(1)--

(A) by redesignating subparagraph (C) as subparagraph (D); and

(B) by inserting after subparagraph (B) the following:

`(C) A program to collect funds for pediatric pharmacologic research and studies listed by the Secretary pursuant to section 409I(a)(1)(A) of this Act and referred under section 505A(d)(4)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(d)(4)(C)).';

(3) in subsection (d)--

(A) in paragraph (1)--

(i) in subparagraph (B)--

(I) in clause (ii), by striking `and' at the end;

(II) in clause (iii), by striking the period and inserting `; and'; and

(III) by adding at the end the following:

`(iv) the Commissioner of Food and Drugs.'; and

(ii) by striking subparagraph (C) and inserting the following:

`(C) The ex officio members of the Board under subparagraph (B) shall appoint to the Board individuals from among a list of candidates to be provided by the National Academy of Science. Such appointed members shall include--

`(i) representatives of the general biomedical field;

`(ii) representatives of experts in pediatric medicine and research;

`(iii) representatives of the general biobehavioral field, which may include experts in biomedical ethics; and

`(iv) representatives of the general public, which may include representatives of affected industries.'; and

(B) in paragraph (2), by realigning the margin of subparagraph (B) to align with subparagraph (A);

(4) in subsection (k)(9)--

(A) by striking `The Foundation' and inserting the following:

`(A) IN GENERAL- The Foundation'; and

(B) by adding at the end the following:

`(B) GIFTS, GRANTS, AND OTHER DONATIONS-

`(i) IN GENERAL- Gifts, grants, and other donations to the Foundation may be designated for pediatric research and studies on drugs, and funds so designated shall be used solely for grants for research and studies under subsection (c)(1)(C).

`(ii) OTHER GIFTS- Other gifts, grants, or donations received by the Foundation and not described in clause (i) may also be used to support such pediatric research and studies.

`(iii) REPORT- The recipient of a grant for research and studies shall agree to provide the Director of the National Institutes of Health and the Commissioner of Food and Drugs, at the conclusion of the research and studies--

`(I) a report describing the results of the research and studies; and

`(II) all data generated in connection with the research and studies.

`(iv) ACTION BY THE COMMISSIONER OF FOOD AND DRUGS- The Commissioner of Food and Drugs shall take appropriate action in response to a report received under clause (iii) in accordance with paragraphs (7) through (12) of section 409I(c), including negotiating with the holders of approved applications for the drugs studied for any labeling changes that the Commissioner determines to be appropriate and requests the holders to make.

`(C) APPLICABILITY- Subparagraph (A) does not apply to the program described in subsection (c)(1)(C).';

(5) by redesignating subsections (f) through (m) as subsections (e) through (l), respectively;

(6) in subsection (h)(11) (as so redesignated), by striking `solicit' and inserting `solicit,'; and

(7) in paragraphs (1) and (2) of subsection (j) (as so redesignated), by striking `(including those developed under subsection (d)(2)(B)(i)(II))' each place it appears.

SEC. 14. PEDIATRIC PHARMACOLOGY ADVISORY COMMITTEE.

(a) IN GENERAL- The Secretary of Health and Human Services shall, under section 222 of the Public Health Service Act (42 U.S.C. 217a), convene and consult an advisory committee on pediatric pharmacology (referred to in this section as the `advisory committee').

(b) PURPOSE-

(1) IN GENERAL- The advisory committee shall advise and make recommendations to the Secretary, through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, on matters relating to pediatric pharmacology.

(2) MATTERS INCLUDED- The matters referred to in paragraph (1) include--

(A) pediatric research conducted under sections 351, 409I, and 499 of the Public Health Service Act and sections 501, 502, 505, and 505A of the Federal Food, Drug, and Cosmetic Act;

(B) identification of research priorities related to pediatric pharmacology and the need for additional treatments of specific pediatric diseases or conditions; and

(C) the ethics, design, and analysis of clinical trials related to pediatric pharmacology.

(c) COMPOSITION- The advisory committee shall include representatives of pediatric health organizations, pediatric researchers, relevant patient and patient-family organizations, and other experts selected by the Secretary.

SEC. 15. PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE.

(a) CLARIFICATION OF AUTHORITIES-

(1) IN GENERAL- The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (referred to in this section as the `Subcommittee'), in carrying out the mission of reviewing and evaluating the data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of pediatric cancers, shall--

(A) evaluate and, to the extent practicable, prioritize new and emerging therapeutic

alternatives available to treat pediatric cancer;

(B) provide recommendations and guidance to help ensure that children with cancer have timely access to the most promising new cancer therapies; and

(C) advise on ways to improve consistency in the availability of new therapeutic agents.

(2) MEMBERSHIP-

(A) IN GENERAL- The Secretary shall appoint not more than 11 voting members to the Pediatric Subcommittee from the membership of the Pediatric Pharmacology Advisory Committee and the Oncologic Drugs Advisory Committee.

(B) REQUEST FOR PARTICIPATION- The Subcommittee shall request participation of the following members in the scientific and ethical consideration of topics of pediatric cancer, as necessary:

(i) At least two pediatric oncology specialists from the National Cancer Institute.

(ii) At least four pediatric oncology specialists from--

(I) the Children's Oncology Group;

(II) other pediatric experts with an established history of conducting clinical trials in children; or

(III) consortia sponsored by the National Cancer Institute, such as the Pediatric Brain Tumor Consortium, the New Approaches to Neuroblastoma Therapy or other pediatric oncology consortia.

(iii) At least two representatives of the pediatric cancer patient and patient-family community.

(iv) One representative of the nursing community.

(v) At least one statistician.

(vi) At least one representative of the pharmaceutical industry.

(b) PRE-CLINICAL MODELS TO EVALUATE PROMISING PEDIATRIC CANCER THERAPIES- Section 413 of the Public Health Service Act (42 U.S.C. 285a-2) is amended by adding at the end the following:

`(c) PRE-CLINICAL MODELS TO EVALUATE PROMISING PEDIATRIC CANCER THERAPIES-

`(1) EXPANSION AND COORDINATION OF ACTIVITIES- The Director of the National Cancer Institute shall expand, intensify, and coordinate the activities of the Institute with respect to research on the development of preclinical models to evaluate which therapies are likely to be effective for treating pediatric cancer.

`(2) COORDINATION WITH OTHER INSTITUTES- The Director of the Institute shall coordinate the activities under paragraph (1) with similar activities conducted by other national research institutes and agencies of the National Institutes of Health to the extent that those Institutes and agencies have responsibilities that are related to pediatric cancer.'.

(c) CLARIFICATION OF AVAILABILITY OF INVESTIGATIONAL NEW DRUGS FOR PEDIATRIC STUDY AND USE-

(1) AMENDMENT OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT- Section 505(i)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(1)) is amended--

(A) in subparagraph (B), by striking `and' at the end;

(B) in subparagraph (C), by striking the period at the end and inserting `; and'; and

(C) by adding at the end the following:

`(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or sponsor has plans for assessing pediatric safety and efficacy.'.

(2) AMENDMENT OF THE PUBLIC HEALTH SERVICE ACT- Section 402(j)(3)(A) of the Public Health Service Act (42 U.S.C. 282(j)(3)(A)) is amended in the first sentence--

(A) by striking `trial sites, and' and inserting `trial sites,'; and

(B) by striking `in the trial,' and inserting `in the trial, and a description of whether, and through what procedure, the manufacturer or sponsor of the investigation of a new drug will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded protocol use of the new drug, particularly in children,'.

(d) REPORT- Not later than January 31, 2003, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs and in consultation with the Director of the National Institutes of Health, shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents.

SEC. 16. REPORT ON PEDIATRIC EXCLUSIVITY PROGRAM.

Not later than October 1, 2006, the Comptroller General of the United States, in consultation with the Secretary of Health and Human Services, shall submit to Congress a report that addresses the following issues, using publicly available data or data otherwise available to the Government that may be used and disclosed under applicable law:

(1) The effectiveness of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act) in ensuring that medicines used by children are tested and properly labeled, including--

(A) the number and importance of drugs for children that are being tested as a result of this legislation and the importance for children, health care providers, parents, and others of labeling changes made as a result of such testing;

(B) the number and importance of drugs for children that are not being tested for their use notwithstanding the provisions of this legislation, and possible reasons for the lack of testing; and

(C) the number of drugs for which testing is being done, exclusivity granted, and labeling changes required, including the date pediatric exclusivity is granted and the date labeling changes are made and which labeling changes required the use of the dispute resolution process established pursuant to the amendments made by this Act, together with a description of the outcomes of such process, including a description of the disputes and the recommendations of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee.

(2) The economic impact of section 505A of the Federal Food, Drug, and Cosmetic Act and section 409I of the Public Health Service Act (as added by this Act), including an estimate of--

(A) the costs to taxpayers in the form of higher expenditures by medicaid and other Government programs;

(B) sales for each drug during the 6-month period for which exclusivity is granted, as attributable to such exclusivity;

(C) costs to consumers and private insurers as a result of any delay in the availability of lower cost generic equivalents of drugs tested and granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), and loss of revenue by the generic drug industry and retail pharmacies as a result of any such delay; and

(D) the benefits to the government, to private insurers, and to consumers resulting from decreased health care costs, including--

(i) decreased hospitalizations and fewer medical errors, due to more appropriate and more effective use of medications in children as a result of testing and re-labeling because of the amendments made by this Act;

(ii) direct and indirect benefits associated with fewer physician visits not related to hospitalization;

(iii) benefits to children from missing less time at school and being less affected by chronic illnesses, thereby allowing a better quality of life;

(iv) benefits to consumers from lower health insurance premiums due to lower treatment costs and hospitalization rates; and

(v) benefits to employers from reduced need for employees to care for family members.

(3) The nature and type of studies in children for each drug granted exclusivity under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.), including--

(A) a description of the complexity of the studies;

(B) the number of study sites necessary to obtain appropriate data;

(C) the number of children involved in any clinical studies; and

(D) the estimated cost of each of the studies.

(4) Any recommendations for modifications to the programs established under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) and section 409I of the Public Health Service Act (as added by section 3) that the Secretary determines to be appropriate, including a detailed rationale for each recommendation.

(5) The increased private and Government-funded pediatric research capability associated with this Act and the amendments made by this Act.

(6) The number of written requests and additional letters of recommendation that the Secretary issues.

(7) The prioritized list of off-patent drugs for which the Secretary issues written requests.

(8)(A) The efforts made by the Secretary to increase the number of studies conducted in the neonate population; and

(B) the results of those efforts, including efforts made to encourage the conduct of appropriate studies in neonates by companies with products that have sufficient safety and other information to make the conduct of studies ethical and safe.

SEC. 17. ADVERSE-EVENT REPORTING.

(a) TOLL-FREE NUMBER IN LABELING- Not later than one year after the date of the enactment of this Act, the Secretary of Health and Human Services shall promulgate a final rule requiring that the labeling of each drug for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act (regardless of the date on which approved) include the toll-free number maintained by the Secretary for the purpose of receiving reports of adverse events regarding drugs and a statement that such number is to be used for reporting purposes only, not to receive medical advice. With respect to the final rule:

(1) The rule shall provide for the implementation of such labeling requirement in a manner that the Secretary considers to be most likely to reach the broadest consumer audience.

(2) In promulgating the rule, the Secretary shall seek to minimize the cost of the rule on the pharmacy profession.

(3) The rule shall take effect not later than 60 days after the date on which the rule is promulgated.

(b) DRUGS WITH PEDIATRIC MARKET EXCLUSIVITY-

(1) IN GENERAL- During the one year beginning on the date on which a drug receives a period of market exclusivity under 505A of the Federal Food, Drug, and Cosmetic Act, any report of an adverse event regarding the drug that the Secretary of Health and Human Services receives shall be referred to the Office of Pediatric Therapeutics established under section 6 of this Act. In considering the report, the Director of such Office shall provide for the review of the report by the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee, including obtaining any recommendations of such subcommittee regarding whether the Secretary should take action under the Federal Food, Drug, and Cosmetic Act in response to the report.

(2) RULE OF CONSTRUCTION- Paragraph (1) may not be construed as restricting the authority of the Secretary of Health and Human Services to continue carrying out the activities described in such paragraph regarding a drug after the one-year period described in such paragraph regarding the drug has expired.

SEC. 18. MINORITY CHILDREN AND PEDIATRIC-EXCLUSIVITY PROGRAM.

(a) PROTOCOLS FOR PEDIATRIC STUDIES- Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) is amended in subsection (d)(2) by inserting after the first sentence the following: 'In reaching an agreement regarding written protocols, the Secretary shall take into account adequate representation of children of ethnic and racial minorities.'.

(b) STUDY BY GENERAL ACCOUNTING OFFICE-

(1) IN GENERAL- The Comptroller General of the United States shall conduct

a study for the purpose of determining the following:

(A) The extent to which children of ethnic and racial minorities are adequately represented in studies under section 505A of the Federal Food, Drug, and Cosmetic Act; and to the extent ethnic and racial minorities are not adequately represented, the reasons for such under representation and recommendations to increase such representation.

(B) Whether the Food and Drug Administration has appropriate management systems to monitor the representation of the children of ethnic and racial minorities in such studies.

(C) Whether drugs used to address diseases that disproportionately affect racial and ethnic minorities are being studied for their safety and effectiveness under section 505A of the Federal Food, Drug, and Cosmetic Act.

(2) DATE CERTAIN FOR COMPLETING STUDY- Not later than January 10, 2003, the Comptroller General shall complete the study required in paragraph (1) and submit to the Congress a report describing the findings of the study.

SEC. 19. TECHNICAL AND CONFORMING AMENDMENTS.

Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a) (as amended by sections 2(1), 5(b)(2), 9, 10, 11, and 17) is amended--

(1)(A) by striking `(j)(4)(D)(ii)' each place it appears and inserting `(j)(5)(D)(ii)';

(B) by striking `(j)(4)(D)' each place it appears and inserting `(j)(5)(D)'; and

(C) by striking `505(j)(4)(D)' each place it appears and inserting `505(j)(5)(D)';

(2) by redesignating subsections (a), (g), (h), (i), (j), (k), (l), (m), (n), and (o) as subsections (b), (a), (g), (h), (n), (m), (i), (j), (k), and (l) respectively;

(3) by moving the subsections so as to appear in alphabetical order;

(4) in paragraphs (1), (2), and (3) of subsection (d), subsection (e), and subsection (m) (as redesignated by paragraph (2)), by striking `subsection (a) or (c)' and inserting `subsection (b) or (c)'; and

(5) in subsection (g) (as redesignated by paragraph (2)), by striking `subsection (a) or (b)' and inserting `subsection (b) or (c)'.

Speaker of the House of Representatives.

Vice President of the United States and

President of the Senate.

END

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MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 5, 2004 **58**

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Background Comments for February 2, 2004 Meeting of Psychopharmacological Drugs Advisory Committee (PDAC) and Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC)

TO: Members of PDAC and Peds AC

Background on Suicidality Associated with Antidepressant Drug Treatment

Longstanding Concern that Antidepressants May be Associated with the Induction of Suicidality Early in Treatment

One of the goals of the February 2, 2004 meeting of the Psychopharmacological Drugs Advisory Committee (PDAC) and the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee (Peds AC) is to give you an update on the current status of our efforts to better understand the suicidality data we have received from various drug development programs involving the use of antidepressant drug products in pediatric patients.

The occurrence of suicidality in the context of treating patients with depression and other psychiatric illnesses has been a concern and a topic of interest and debate for decades. In fact, antidepressant labeling has, for many decades, carried the following standard language under Precautions, alerting clinicians to closely monitor patients during initial drug therapy out of concern for the possible emergence of suicidality:

> "Suicide: The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Drug X should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose."

Of course, this standard Precautions statement does not explicitly warn of the possibility that antidepressant drugs may have a causal role in the emergence of suicidality early in treatment.

While it is likely impossible at this point to trace the history of the addition of this language to antidepressant labeling, I believe that, whether explicit or not, the statement allows for that interpretation. In fact, as early as medical school, many physicians learn of this concern, and it has been part of medical lore for many decades that antidepressants may have an early activating effect that perhaps gives depressed patients the energy to follow through on suicidal impulses before the mood improvement associated with antidepressant treatment takes effect. Following is a statement from a textbook of psychiatry published over 40 years ago that is referring to observations in patients during initial treatment with tricyclic antidepressants [**Slater and Roth's Clinical Psychiatry, by Bailliere, Tindall and Cassell; London, 1960, p. 231**]:

> "With beginning convalescence (following initiation of treatment with tricyclic antidepressants), the risk of suicide once more becomes serious as retardation fades."

In fact, this particular mechanism proposed to explain a possible increase in suicidality early in antidepressant treatment is so well known that it is referred to as the "roll back" phenomenon. However, it is but one of several mechanisms that have been proposed to explain the clinical observation that some patients being treated with antidepressants, particularly early in treatment, may have an increase in suicidality. This topic was discussed at the September, 1991 meeting of the PDAC on this same issue, and Dr. Martin Teicher provided a comprehensive list of the various mechanisms that have been proposed:

- Roll back phenomenon: view that antidepressants with prominent energizing effects may actually increase suicidal behavior in severely depressed patients who are suicidal but also have psychomotor retardation and are thus inhibited from acting on their suicidal thoughts.
- Paradoxical worsening of depression: view that, in rare patients, the depressed mood may actually worsen as a result of antidepressant treatment.
- Akathisia: view that some antidepressants are associated with akathisia, and the belief that akathisia may lead to suicidal behavior in certain depressed patients.
- Induction of anxiety and panic attacks: view that certain antidepressants may induce anxiety and panic attacks, and that these may lead to suicidal behavior in certain depressed patients.
- Stage shifts: view that antidepressants may lead to switch from depression into mixed states in bipolar depressed patients, and this may lead to suicidality.
- Insomnia: view that insomnia associated with certain antidepressants may lead to suicidal behavior in certain depressed patients.

While all of these have some plausibility as mechanisms for explaining the clinical observation of worsening depression or suicidality in depressed patients being treated with antidepressants, proposing a mechanism is quite a different matter from demonstrating empirically that there is a causal association between antidepressant use and induction of suicidality. Of course, this is the key question we hope to be able to address with the suicidality data coming from the studies done with various antidepressant drugs in pediatric patients, i.e., is there a causal link between antidepressant drug use and suicidality in pediatric patients with major depressive disorder or other psychiatric disorders. This is a critically important question to answer, but it is equally important to answer it in a careful, thoughtful manner. Erring in either direction would have

adverse consequences. Missing a signal of increased risk of suicidality would result in greater comfort than is warranted in the safety of these drugs in treating pediatric depression. On the other hand, a premature decision on the strength of the signal could result in the overly conservative use of these drugs, or their lack of availability entirely for the pediatric population. Prematurely reducing therapeutic options for this serious disease with well established morbidity and mortality, quite apart from any role that antidepressant drugs may have, does not seem like a good approach. In any case, the question is obviously timely and important to fully address in order to understand how best to use these drugs in the treatment of pediatric MDD.

If this view that initial antidepressant treatment may be associated with an actual increase in risk of suicidality is in fact empirically established, this would, in a sense, confirm a view that is already widely prevalent in clinical lore, whatever the proposed mechanism. Despite this fairly widely held view, however, the use of antidepressants has obviously increased over the years rather than declined. This fact suggests that, as a group, clinicians may place more weight on their beliefs in the longer-term benefits of antidepressants than their concerns about possible early risks of actually increased suicidal behavior. In fact, the dual findings of an early increase in the risk of suicidality but also a longer-term benefit for this same risk with antidepressant treatment would, if both true, not necessarily be inconsistent. It is quite possible for a drug to have opposite effects over time, even within the same domain.

Debate in Recent Years on the Question of Antidepressant-Induced Suicidality in Adults

The debate on this question with regard to adult depression intensified in 1990, at which time Martin Teicher, a psychiatrist from Harvard Medical School, along with several colleagues, published a paper describing a series of 6 adult patients with depression who, in their view, became suicidal as a result of being treated with Prozac (fluoxetine) **(Teicher, et al, 1990)**. This paper and the ensuing discussion led Lilly, the manufacturer of Prozac, to conduct new analyses of their controlled trials data for Prozac to explore for the emergence of suicidality. This renewed interest in the possible induction of suicidality in association with the use of antidepressant treatment also led FDA to fully re-evaluate its spontaneous reports database to try to detect whether or not a signal of increased risk could be observed. Ultimately, this issue was brought to a PDAC meeting in September, 1991. This one-day meeting consisted of several hours of statements made by family members and others in the open public session, and presentations by representatives from FDA, Lilly, and NIMH. Statements in the open session were made mostly by family members of suicide victims whose deaths the families attributed to their taking Prozac. FDA gave an update on the very substantial number of spontaneous reports of suicidality in association with Prozac use, but also showed how the pattern of reporting was clearly linked to the publication of the Teicher, et al, paper and other publicity about this concern. A representative from NIMH gave that agency's perspective on this issue, essentially making the case that depression is a serious disorder that itself is associated with suicidality, and arguing that the data available to date did not support the view that antidepressants further increase the risks of suicidality in this population. Finally, Lilly presented the results of its analysis of data pooled over its extensive clinical trials, revealing no signal of increased suicidality in association with the use of Prozac **(Beasley, et al, 1991)**. At the end of a long day, a majority of the committee concluded that there was no clear evidence of an increased risk of

suicidality in association with the use of Prozac, and they did not recommend any changes to Prozac labeling with regard to this issue.

Over the next several years, additional data were accumulated as applications for newer antidepressants were submitted and reviewed, and these drugs came to market. Several groups have, in recent years, conducted pooled analyses for adult data on completed or attempted suicides from these programs, in order to continue the search for a possible signal of risk, either by virtue of being assigned to placebo, since the ethics of conducting placebo controlled trials in depression were being challenged, or due to assignment to drug treatment. Arif Khan, a psychiatrist from the Northwest Clinical Research Center, Bellevue, Washington, published a paper in 2000 based on adult data he obtained under FOI from FDA reviews. He concluded that the risk of completed suicide was the same, regardless of treatment assignment **(Khan, et al, 2000)**. Jitschak Storosum, a physician from the Medicines Evaluation Board of the Netherlands, did an analysis of attempted suicides from adult data available to his group, and he reached the same conclusion **(Storosum, et al, 2001)**. FDA has done several analyses on completed suicides for adult data sets provided to us in response to a request for patient level data sets[1] for all relevant studies involving 20 antidepressant drugs studied in 234 randomized controlled trials with MDD. Based on our initial analyses of these data, we have reached a similar conclusion, i.e., that there does not appear to be an increased risk of completed suicide associated with assignment to either active drug or placebo in adults with MDD **(Hammad, et al, 2003)**.

Source of Pediatric Suicidality Data

Regarding pediatric suicidality, it is important first of all to understand how it is that the various pediatric trials happen to have been done. These trials were done largely in response to a change in the Food, Drug and Cosmetic Act that authorized FDA to grant additional marketing exclusivity (referred to as pediatric exclusivity) to pharmaceutical manufacturers who were willing to conduct studies of their drugs as requested by the FDA in pediatric populations. The first law permitting the pediatric exclusivity incentive was the FDA Modernization Act (FDAMA, 1997), and this authority to attach additional marketing exclusivity for such studies was renewed in the Best Pharmaceuticals for Children Act (BCPA, 2001). In order to qualify for pediatric exclusivity, sponsors had to conduct pediatric studies according to the terms of a Written Request from FDA, and submit the results of those studies in a pediatric supplement. We have reviewed 8 pediatric supplements over the past few years for pediatric drug development programs involving antidepressant drugs that were conducted to gain additional marketing exclusivity, and these supplements are the source of the pediatric suicidality data that are at issue for this meeting. For completeness, we have included in our review of pediatric suicidality two studies for a ninth antidepressant drug for which the studies were not done for exclusivity. Our review includes a total of 24 studies for these 9 drugs, involving a total of over

1 I will distinguish between what I will refer to as summary data and patient level data. Summary data will refer to data tables provided by sponsors that include only numbers of events as numerators and either total patients exposed or total accumulated person-time as denominators. Patient level data will refer to data sets provided by sponsors in response to detailed requests made by FDA for electronic data sets structured to include one row per patient participating in each study, with multiple variables for each patient. Patient level data sets permit adjustments for potentially important covariates, while summary data do not.

4000 pediatric patients.

The 9 drugs involved in our review are:

- Prozac (fluoxetine)
- Zoloft (sertraline)
- Paxil (paroxetine)
- Luvox (fluvoxamine)
- Celexa (citalopram)
- Wellbutrin (bupropion)
- Effexor (venlafaxine)
- Serzone (nefazodone)
- Remeron (mirtazapine)

Of the 24 studies for these 9 drugs, 15 were in MDD, 4 in OCD, 2 in GAD, 1 in SAD, and 2 in ADHD.

Effectiveness Data for Antidepressants in Pediatric MDD

While the focus of the discussion at the Feb 2nd PDAC meeting will be on pediatric suicidality data, it is important to consider the effectiveness data for these drugs as part of the overall context for this discussion. Ultimately, this is a risk benefit assessment, so it is important to know where we stand on the benefit side of this issue. Of the 7 programs in pediatric MDD (Prozac; Zoloft; Paxil; Celexa; Effexor; Serzone; Remeron), FDA's reviews of the effectiveness data resulted in only 1 approval for pediatric MDD, i.e., for Prozac. The efficacy results from the 15 studies in pediatric MDD are summarized in **Appendix 1**.

These are sobering findings and certainly raise a question about the benefits of these drugs in pediatric depression, however, the findings need to be considered in the context of several other facts.

(1) In all but one case for the failed programs, there were only 2 studies in MDD; for the remaining failed program, there were 3 MDD studies. Among the failed programs there was one program where 1 of the studies was positive (citalopram), and 2 others where the results, while negative by the usual standards, were at least trending toward positive for 1 of the 2 studies (sertraline and nefazodone). Of note, the published literature gives a somewhat different perspective, suggesting more positivity in 2 of these programs than was the conclusion at FDA. One paper describes one of the Paxil studies as positive on most of the secondary endpoints, while acknowledging that it failed on the primary endpoint **(Keller, et al, 2001)**. Another paper describes the Zoloft program as positive, based on a pooling of 2 similarly designed studies that, when looked at individually, failed **(Wagner, et al, 2003)**.

In adult MDD programs for drugs that are approved for this indication, overall, the failure rate for studies that appear in every respect to be adequate trials is about 50%. Thus, if the failure rate were the same in pediatric MDD, it would not be unexpected to have either 1 or both studies fail. In fact, since the studies can be considered independent of one another, the probability of

having one or both studies fail in the 2-study programs is actually 0.75 [3(0.5 X 0.5)]; the probability of both succeeding would be only 0.25 (0.5 X 0.5). Thus, under the best of circumstances, these very limited programs may have been expected to mostly fail regarding the goal of obtaining 2 positive studies. Nevertheless, the overall success rate for positive studies of 20% (3/15) is clearly a concern.

(2) The history of pediatric MDD studies with the tricyclic antidepressants (TCAs) is uniformly negative. This finding may have several possible explanations, including flaws in design or conduct, or the possibility that TCAs simply do not work in pediatric MDD. It is also possible, however, that there is even greater heterogeneity among pediatric patients who meet criteria for MDD than is true for adults. If true, this would also work against obtaining positive studies in pediatric MDD.

(3) The context in which these studies were conducted was not ideal, in the sense that there was no need to obtain positive results in order to gain exclusivity. The programs simply had to be conducted according to the terms of the Written Requests, and the results submitted to meet deadlines specified in those requests. This is not to suggest that sponsors of these studies did not design and conduct them with good intent and according to high standards, but rather, that the mindset was different than the usual mindset for registration trials. Ordinarily, a failure of a registration trial to show a drug effect is a complete loss. That was not the case here and this reality could have influenced the conduct of the study in subtle ways that might have worked against getting a positive result, e.g., in recruitment of patients.

(4) Finally, there was not the kind of preliminary phase 2 dose finding exploration for these studies that typically precedes definitive trials in adult studies. We are routinely asking for such exploration as part of the Written Requests we are now issuing.

The point I am making is that there are several plausible reasons for all but one of these programs failing, other than the possibility that these drugs may have no benefits in pediatric MDD. It is understandable how some may have reached the conclusion that these studies represent proof that these drugs, with the exception of Prozac, have no benefits in pediatric MDD. We at FDA, however, do not view negative studies as proof of no benefit. In our view, absence of evidence for effectiveness in most of these programs does not constitute evidence of absence of benefit for these drugs in pediatric patients, for all the reasons noted above. Nevertheless, the failure of most of these programs to show a benefit in MDD does heighten the concern about the possibility of certain risks that may be associated with these drugs, in particular the concern about induction of suicidality. In any case, the burden is clearly upon those who believe these drugs do have benefits in pediatric MDD to design and conduct studies that are capable of demonstrating such benefits. I will return later to a possible alternative approach to acute efficacy studies for demonstrating antidepressant benefits of these drugs.

Origins of Present Concern About the Emergence of Pediatric Suicidality in Association with Antidepressant Use; Initial Regulatory Response

Background to May, 2003 Paroxetine Report

After this brief look at the effectiveness issue, I want now to return to the issue of the origins of the present concerns about pediatric suicidality. My approach will be to give a temporal perspective on how this issue has evolved over the past approximately 7 months. The focus will be on certain adverse events that were reported in the pediatric supplements for the various antidepressants, in particular, adverse events considered to represent suicidality.

First, it is important to comment on the approach used to elicit treatment emergent suicidality in these trials. In part, investigators relied on very general prompts, e.g., asking the general question of "how have things been" at each visit. While this approach is perhaps somewhat superior to spontaneous reporting, it is likely a distinctly insensitive approach to eliciting adverse events related to suicidality. Even in adults with MDD, it generally requires a skilled clinician to elicit patient reporting of suicidal ideation or behavior, and this tendency to conceal such ideation and behavior may be even more prominent in adolescents. On the other hand, all of these trials also utilized formal instruments for assessing depressive symptoms, each of them including a suicidality item. However, it is not clear what elicitation approaches were used in completing these instruments, and thus, it is not clear whether or not there was specific elicitation with regard to suicidality. Furthermore, these instruments were not always done at the times that patients were experiencing events of interest, since such events occurred at random times. In order to adequately assess for such emergence of suicidal ideation and/or behaviors, it is important to have methods that are sensitive to detecting such effects.

In any case, verbatim (investigator) adverse events in any drug development program, however they are elicited, are coded by subsuming them under preferred terms in order to capture like events under the same term, even if patients or investigators had used variable language to describe the events. For these pediatric trials, adverse events suggestive of suicidality were coded by the various sponsors for their programs, using approaches unique to each program, and these data were examined, along with numerous other adverse events, in the course of our reviews of the pediatric supplements. FDA's clinical reviews for these supplements, conducted over a several year period prior to our becoming aware of a possible signal for the paroxetine program, did not, overall, suggest a signal for drug treatment-induced suicidality.

The Paxil review, however, did raise a question of data management. The clinical reviewer for the Paxil supplement noticed that events suggestive of possible suicidality were subsumed under the preferred term "emotional lability," rather than under a preferred term more directly suggestive of suicidality. Other verbatim terms were also subsumed under "emotional lability," so one of our requests to GSK in our response letter to their pediatric supplement for Paxil was to ask them to separate out for us the verbatim terms suggestive of suicidality. This request was the basis for the additional work done by GSK on this issue of suicidality that resulted in their

submission of a report on suicidality, first to the UK, and shortly thereafter, to FDA, on May 22, 2003.

This May 22, 2003 report suggested an increased risk (paroxetine vs placebo) of various thoughts and behaviors coded as events considered "possibly suicide related" and also for the subgroup of these events that met the sponsor's criteria for representing "suicide attempts." The signal for increased risk was clearest for 1 of the 3 trials involving pediatric patients with MDD. A summary of the sponsor's findings for the MDD trials in the Paxil program is included in **Appendix 2.**

Initial Regulatory Response to Signal of Increased Risk of Suicidality for Paroxetine

The reaction to this report by the MHRA in the UK was very prompt, resulting in:

- A public statement explicitly stating that paroxetine "should not be used in children and adolescents under the age of 18 years to treat depressive illness," and
- A labeling change contraindicating paroxetine in pediatric MDD.

FDA's response was soon to follow, with:

- A public health advisory, stating that: "Although the FDA has not completed its evaluation of the new safety data, FDA is recommending that Paxil not be used in children and adolescents for the treatment of MDD."
- Despite the strong advisory, we did not take any labeling action, and in fact have not taken any action on labeling as of the date of this memo.

Overview of FDA's Ongoing Review of Antidepressants and Pediatric Suicidality

GSK Approach to Accumulating Paroxetine Summary Data

First, I want to describe in some detail the approach GSK took in evaluating their pediatric clinical trials data for suicidality, since we modeled our request to sponsors of other antidepressants after the GSK approach, in order to ensure that we would have similar data from different programs, for comparative purposes. They focused exclusively on placebo controlled trials (there were 6 such trials in the GSK program), and that has been our focus as well. As noted earlier, in their original pediatric supplement, they had subsumed events suggestive of suicidality under the preferred term "emotional lability," along with various other behavioral events. Subsequent to our request for a separate approach to events suggestive of suicidality, they conducted the following searches to find events of potential interest:

- Electronic searches of their database with text strings of particular relevance for suicidality:
  - Search for all events for which the preferred term was either "overdose" or "intentional overdose" (Note: They did not include any events for which the preferred term was "accidental overdose")
  - Search of verbatim (i.e., investigator) terms for events that had originally been coded with the preferred term "emotional lability," in order to find verbatim

terms including any of the following 15 text strings: "attempt; cut; gas; hang; hung; jump; mutilat; overdos; self damag; self harm; self inflict; self injur; shoot; slash; suic"
    - Search of all verbatim terms containing the text string "overdose" or "suic" (Note: They specifically excluded any events for which the verbatim term selected was a result of the text string occurring in another word that had no relevance to suicidality.)
- They included in their analyses only patients having events that occurred either during randomized treatment or in the +30 days posttherapy window, and only events they judged to represent treatment-emergent events (However, treatment emergent was not well-defined and no information was provided for any cases excluded for not being considered treatment-emergent). All events meeting these criteria were included under the broad category "possibly suicide related."
- GSK then created the subset of patients having events meeting their criteria for "suicide attempt" using the following criteria:
    - A text string suggestive of self-harm
    - Preferred term "overdose" or "intentional overdose"
    - They did exclude certain events judged (blindly) by their own staff not to represent suicidality, however, no details were provided on these patients or for the criteria used in excluding cases

Request for Summary Data for Other Antidepressants

Following our initial review of the Paxil suicidality summary data, we decided to ask for similar data for the other 8 antidepressants. We decided that it would be most efficient to ask other sponsors to use a similar approach to that used by GSK in exploring the Paxil data. Thus, we issued a letter on July 22, 2003, requesting such summary data for the placebo controlled pediatric studies for the 8 other antidepressant products for which such studies had been conducted:

- Prozac (fluoxetine)
- Zoloft (sertraline)
- Luvox (fluvoxamine)
- Celexa (citalopram)
- Wellbutrin (bupropion)
- Effexor (venlafaxine)
- Serzone (nefazodone)
- Remeron (mirtazapine)

In this July 22nd letter, we asked the sponsors for these products to identify "suicide-related events" for their pediatric studies, in a "blinded" manner, using two search strategies. Since our request was modeled after the approach GSK had already used, it included many of the same details provided above:

- Electronic searches of their database with text strings of particular relevance for suicidality:

  - Search of preferred terms for the following 2 text strings: "suic" or "overdos"
    - Note: We indicated that they may exclude instances coded as accidental overdoses, but asked them to provide information on these cases in a separate table.
  - Search of verbatim (i.e., investigator) terms for the following 15 text strings: "attempt; cut; gas; hang; hung; jump; mutilat; overdos; self damag; self harm; self inflict; self injur; shoot; slash; suic"
    - Note: We did indicate that terms identified using these electronic searches because one of these text strings was included in a word that had no relevance to suicidality could be excluded.
- In addition, we asked them to blindly review narratives for any deaths and serious adverse events (SAEs) in order to identify any additional possible instances of "suicide-related events"
  - Note: There were no deaths due to any cause in any of the 24 studies included in these pediatric programs
- We also asked the sponsors to blindly select from among the larger set of "suicide-related events" a subset of events that could be consider "suicide attempts," defined to include all patients who exhibited self-injurious behavior.
- We asked sponsors to provide a narrative for each patient identified as having one or more potential events, and also a table including the same information for each such patient.

The letter also asked for analyses for the cases identified using these approaches similar to those described above for Paxil.

Re-Review of Suicidality Data from Pediatric Supplements for Other Antidepressants

While we were waiting for the various sponsors of the antidepressants other than Paxil to respond with their summary data, we went back to the summary adverse event data in the pediatric supplements for these other drugs to re-examine the question of suicidality. The major question of interest was whether or not there were other antidepressants with possible signals of increased risk for suicidality, as was observed for Paxil. There were several limitations to this re-examination. First, the methods for detecting and coding events were not standard across these programs. Second, since we wanted to have similar numerator categories to those used for the Paxil data, for purposes of comparison across drug programs, we classified any events described in the adverse event listings, etc for these drug programs into the two categories of interest: "possibly suicide-related" and "suicide attempt." One obvious flaw in this approach was that the FDA reviewer was not blinded during this reclassification process. Nevertheless, it was hoped that this somewhat crude re-examination of these summary data might shed some light on the possibility of signals emerging from other antidepressant programs.

While the methodology for this initial exploration was necessarily crude, it did provide some further insight into the treatment-emergent suicidality question across these 9 drug programs. There were several findings of particular interest resulting from this crude look at the pediatric supplements data. First, there were signals of increased risk of suicidality for patients assigned to

drug for more than the paroxetine program, and second, the findings were not consistent across the studies even within individual programs. Finally, the signals were coming predominantly from the MDD studies within these programs.

Wyeth Labeling Change and Dear Health Care Professional Letter for Effexor, and Regulatory Response

During this period while we were re-examining the suicidality data from the pediatric supplements and beginning to receive responses to our requests for summary data from the sponsors for the other antidepressants, Wyeth, the sponsor for Effexor (venlafaxine) and Effexor XR, decided to make labeling changes for its products with regard to suicidality and hostility. This action was based on its re-analyses of the Effexor pediatric trials data. The labeling change was the addition of a statement to the Usage in Children/Pediatric Use section of Precautions to note increased reports of hostility and suicidality. This labeling change was accompanied by a Dear Health Care Professional letter (August 22, 2003) noting the findings and also noting that these products are not recommended for use in pediatric patients. It should be noted that sponsors have the authority to make changes of this nature, i.e., that are perceived to strengthen labeling from the standpoint of safety, without prior approval by FDA.

This action by Wyeth was followed in September, 2003 by a regulatory response by the MHRA in the UK similar to their response to the report on paroxetine suicidality data. They issued a public statement advising that these products should not be used in pediatric MDD, accompanied by a change in labeling to contraindicate these products in pediatric MDD. FDA has not taken any regulatory action based on these findings for venlafaxine, since we view these as preliminary data that require the same level of more detailed review needed for the other antidepressant drug products.

FDA Internal Regulatory Briefing

An important milestone in our consideration of the pediatric suicidality data was an internal briefing for upper level CDER management held on September 16, 2003. This briefing was held at a time when we had available to us only a preliminary review of the summary data for the Paxil program and a crude re-analysis of suicidality data from the pediatric supplements, i.e., we had not yet received even the summary data from the pediatric programs other than Paxil. There were several agreements reached at this meeting, including two that were of particular importance for our further plans for addressing this issue. It was acknowledged that a very broad net had been cast in trying to capture events of potential interest with regard to possible suicidality, and questions were raised about what many of these events actually represented. Thus, there was agreement that it would be useful to try to have all events of potential interest blindly reclassified by outside experts in suicidality in order to have greater confidence in what the signals represented. Second, there was acknowledgement that there was inconsistency in the signals across individual studies for the various programs for which signals of increased risk for suicidality emerged, based on the re-analyses of pediatric supplement data. Thus, there was also agreement that it would be useful to attempt to obtain patient level data sets for all of these trials in order to permit a more refined analyses using adjustment for potentially important covariates.

These agreements strongly influenced the subsequent course of our efforts to better understand these data.

Updated FDA Public Health Advisory and Talk Paper

We issued an updated public health advisory and talk paper on October 27, 2003, based on our assessment of the pediatric suicidality data at that point in time. We indicated that preliminary data suggested an excess of reports of suicidality for several antidepressant drugs, however, we noted that additional data and analysis would be needed. We also noted that we intended to bring this issue to an advisory committee meeting. We advised caution in the use of any of these drugs in MDD, and reminded prescribers of the standard language already in antidepressant labeling alerting clinicians to the need for close supervision of high risk patients, particularly during initial drug therapy.

Responses to FDA's Request for Summary Data for Other Antidepressants

Now I want to return to the summary data for the other antidepressant drugs. The responses including the requested data and analyses for these summary data began arriving in late August, and had all arrived by late September, 2003. Unfortunately, as we began reviewing these responses, it became clear that different sponsors had interpreted the July 22nd request differently, resulting in our lack of confidence that the cases of suicidality had been selected for review, classified, and presented to us using similar approaches for all 8 sponsors. This impression was confirmed when we spoke to individual sponsors about their approach to this request. In retrospect, the algorithm we had provided for searching for potential events and selecting patients with events for the summary data analyses was not sufficiently detailed to result in a common understanding. This discovery presented a major hurdle to overcome in our evaluation of these data, since we needed to have confidence in the thoroughness and uniformity of the methods used for gathering and classifying these cases.

I will provide at this point several examples of the kinds of variations in methods we discovered across the different sponsors. This list of variations is just a sampling of the types of variations, and should serve the purpose of making clear why we needed to spend considerably more time ensuring that all relevant cases had been accumulated, and that they had been appropriately classified. We felt this was critical in order for us to complete our assessment of this potential problem.

- We had hoped to have a complete accounting of potential events identified by the search algorithms and SAE narrative reviews, however, in no case did a sponsor provide such an accounting. At one extreme we were provided narratives only for patients judged by the sponsor to have events that represented suicidality, with no explanation as to why other patients identified by the algorithms might have been excluded. In other cases, more details were provided on patients who had been excluded, but none of the reports was completely satisfactory in this regard.
- Although most sponsors conducted the search and selection of cases according to our instructions, in no case did they provide us with the specific criteria used in excluding

cases at various levels of the process.

- For example, although we invited sponsors to exclude cases that might be considered "false positives" in the sense described above, i.e., where the text string of interest occurred in a longer word that was irrelevant to suicidality, we had expected that excluded cases would have been described. Most sponsors did not provide such a listing.
- We had asked for cases coded as accidental overdose, and for the most part received this information, however, we had failed to inquire about cases coded as accidental injury, and most sponsors did not fully address how they handled these cases. In fact, most sponsors simply excluded all cases coded as accidental injury, without further review. As an example, after we began inquiring about the process of excluding cases, we received from one sponsor a line listing of excluded cases that included a case of a child who was excluded as accidental injury with an event characterized only as "patient stabbed himself in the neck with a pencil while taking a test." While this may have in fact represented an accidental injury, we decided it would be important to know enough details about cases coded as accidental injury in order to be confident that such cases were appropriately classified and excluded.
- At least one sponsor acknowledged that they had conducted some of the searching and selection of cases with knowledge of treatment assignment, in particular, for the review of narrative summaries of SAEs.
- Another sponsor acknowledged that they had excluded cases where the events that occurred were not considered "treatment emergent." These were events suggestive of suicidality but for which there was evidence that the event may have also been occurring before randomization. No other information had been provided about the excluded cases in the sponsor's summary submission.
- Another finding that raised concern about the approach to case exclusion and selection resulted from our comparison of our results of suicidality risk for one drug product based on our re-review of the pediatric supplements with that sponsor's analysis of suicidality based on their reclassification of cases in response to our July 22nd request. In this particular instance, there was a striking difference in the results of the two analysis, i.e., a strong signal emerging from our re-examination of the pediatric supplement for that drug compared to only a weak signal emerging from the sponsor's analysis submitted in response to our July 22nd letter.

- As noted earlier, for many of the events included in the various analyses as representative of suicidality, there were questions about whether or not they were appropriately classified as such. Many of these were described as instances of very minor self injury with no indication of suicidal intent.
- There were also substantial differences across different programs in the selection of cases representing suicide attempts, with some sponsors deciding to include essentially all captured events as suicide attempts, even though there was clearly not enough information in the cases to justify such a classification.

Decision to Seek Outside Review and Reclassification of Cases

During this period when we were re-examining the pediatric supplement data and then beginning to explore the summary data provided to us in response to our July 22nd letter, it was becoming increasingly clear that we could not have confidence in the numerator events for the analyses we were provided by the sponsors, because the methods were not well-articulated, and the limited details available about the methods suggested that they varied substantially for different sponsors. Thus, we essentially confirmed the view already reached tentatively at our internal regulatory briefing that it would be desirable to have potential events blindly reclassified by an independent group. We briefly considered doing this internally, but quickly rejected this idea, since (1) we clearly did not have the expertise in suicidality to conduct such a reclassification, and (2) most of those who might logically be involved in such an effort had already seen many of the cases. Thus, we began to look outside the agency, and we initiated a series of discussions with outside experts. We found several experts interested in such an effort, however, there remained the problem of who would coordinate the overall effort, establish methods and criteria for reclassification, etc. Among the experts we discovered in our search was a group at Columbia University who not only had well-recognized expertise in adolescent suicidality, but also had developed an approach to classifying events possibly representative of suicidality that precisely fit our needs. Thus we have been involved in extensive discussions with this group in order to establish a contract for having this reclassification of cases accomplished and also to work out the details of a standard approach to both finding all relevant cases and setting up categories for the reclassification effort that would meet our needs from a regulatory standpoint. At the present time, the contract is in place and we are in the process of preparing case material to provide to this group. It is important to note that, while the Columbia group will serve as the coordinating center for this effort, experts in adolescent suicidality from several other academic centers will also participate in the process in order to ensure broad representation from the expert community. Once we have provided the case materials to this group, one of the initial goals will be to try to reach agreement on an approach to classifying events into appropriate categories.

Second Request for Identification of Events of Potential Interest with Regard to Suicidality

As a result of our discussions with sponsors about their submissions in response to our July 22nd request for summary data on suicidality from their pediatric studies, and our discussions with the expert group at Columbia University about the reclassification of these cases, we worked out a more detailed standard method for sponsors to use in assembling their data regarding any cases of potential interest detected in the searches of their pediatric data base. This document was provided to sponsors for all 9 antidepressant products on Nov 24, 2003. Following is a summary of key aspects of this new standard:

- We asked sponsors to confirm that they had conducted an electronic search of their preferred terms and verbatim terms using the text strings specified in our July 22nd letter, or if not, to describe in detail what they had done.
- We next asked sponsors to provide a complete accounting of the winnowing down of the complete list of potential events/patients identified by these electronic searches to arrive at the events that would need to be blindly reclassified by outside experts. Sponsors were asked to provide the total number of patients identified as having 1 or more such potential

events suggestive of suicidality, as a starting point. We then requested that they fully describe the exclusions from this list, for the following reasons:

- Prerandomization events: Sponsors were to list all patients excluded because all of their potential events occurred prerandomization.
- Events occurring more than 30 days beyond the last dose of randomized treatment: Sponsors were to list all patients excluded because all of their potential events occurred more than 30 days beyond the last dose of randomized treatment.
- False positive events: Sponsors were to list all patients excluded because all of their potential events could be characterized as "false positives" in the sense that a preferred or verbatim term was selected because one of the text strings occurred within that term and the term has no relevance to suicidality, e.g., "gas" in "gastrointestinal."
- We asked for summary narratives for all remaining patients with potential events, including patients classified as having accidental injury or accidental overdose (i.e., using preferred terms).

- In addition, we asked sponsors to provide narratives for all patients having one or more serious adverse events (SAE, based on regulatory definition) that occurred either in the randomized doubleblind phase of the controlled trials or within the +30 days beyond the last randomized dose period described earlier.

Blinded Reclassification of Potential Suicidality Events

We have now received responses to this Nov 24th request from most of the sponsors, and, as noted, we are in the process of preparing this information to forward to our outside contractors. We expect to be working closely with them over the next month in order to reach agreement on (1) the approach they will use in cleaning and blinding the narratives for information that might bias their assessment (to be done by an independent group who will not be involved in the reclassification of events), (2) the categories into which events will be classified and the criteria for such placements, (3) the process by which disagreements will be resolved, or if not resolved, the process for reaching the best judgement for classifying any particular case. We expect that it will take at least another several months to complete this reclassification effort. A member from the Columbia group will be making a presentation at the Feb 2nd meeting to describe their role in this project in greater detail.

There is one caveat to this effort. It is ultimately limited by 2 significant problems. First, as noted earlier, the approach to eliciting suicidal ideation and behavior was of unknown sensitivity. Second, the approach to identifying potential events may have missed certain events if they were not classified as serious, since detection for the other events depended on matching on certain text strings, and the list of text strings was necessarily limited.

Interim Overview of Results from Sponsors' Analyses of their Original Summary Data (i.e., for drugs other than Paxil)

Given that we are not confident in what the numerator data represent in the summary analyses provided by the sponsors for these pediatric studies, we will not be presenting detailed results from these analyses at this time. However, I have included one summary data table (**Appendix 2**) in order to make two important observations. **Appendix 2** summarizes risk data by individual study for the 15 pediatric major depressive disorder (MDD) studies for which we have data. While we have been provided data both for "on-therapy" and for "on-therapy + 30 days" events, I have focused on the "on-therapy" data, since these are the least problematic from the standpoint of interpretation. While we do sometimes utilize an "on-therapy + 30 days" timeframe for capturing events of interest, this analysis is problematic in this case for two reasons. First, it may be confounded by discontinuation symptoms occurring following withdrawal of medication, and second, different sponsors used different rules in deciding what events to include and exclude from the +30 days period in their analyses. For simplicity, I have provided the data for all ages combined, rather than breaking it out by age group. The table provides risk (percentage of patients having at least 1 event) and risk ratio (when this can be calculated). Risk is provided both for the category "possibly suicide-related" and the subgroup of events classified as "suicide attempts."

I think there are two important observations from this table:

(1) A signal of increased risk on drug is apparent for at least 4 of the 7 programs, i.e., paroxetine, sertraline, venlafaxine, and citalopram, with perhaps a weak signal for nefazodone.

(2) There is inconsistency across the individual studies within the programs for which there is an apparent signal, with the exception of venlafaxine, where both studies reveal a signal. For paroxetine, a signal emerges from 1 study (329), but without even a weak signal for the other 2 studies in the program. This is also the case for sertraline and citalopram, where a signal emerges from 1 of 2 studies in each case, with no signal emerging in the other study. While fluoxetine is generally without a signal, in the "suicide attempts" analysis for study X065 there is actually a signal for drug. There are several instances where the risk ratio favors drug over placebo.

Overall, I think **Appendix 2** reveals that, while there are signals of increased risk of events suggestive of suicidality for several of these drugs, the signals for the most part are coming from a single trial within each of these programs. An important additional point, however, is that we are not yet confident in what the identified events represent.

Planned Analyses of Patient Level Data for Pediatric Suicidality

As noted earlier, the observation of inconsistency of the signal across studies within individual programs based on a crude re-analysis of suicidality from the pediatric supplements resulted in a recommendation from our internal regulatory briefing to request patient level data to permit us to conduct a more refined analysis including adjustment for potentially important covariates. Since the summary data provided by the sponors in response to our July 22, 2003 request have confirmed that finding of inconsistency, we are planning on proceeding with this more detailed analysis of the suicidality data from these programs. A standard letter requesting patient level data sets was issued to all sponsors on October 3, 2003. The variable list was expanded several

times in subsequent weeks, and the final variable list is included as **Appendix 3**. We have now received all of these data sets from sponsors, and we are in the process of developing an analysis plan to explore for excess risk of suicidality using a statistical model that provides for adjustment of covariates. The numerator events for this analysis will be identified based on the reclassification of patient events by our outside experts. A member of our safety group will make a presentation on the current status of our plans for this analysis at the Feb 2nd meeting.

Update on Most Recent Regulatory Action on Antidepressant Treatment of Pediatric MDD by MHRA

The MHRA (UK) made a public announcement on Dec 10, 2003 indicating that, in addition to its earlier contraindications of paroxetine and venlafaxine in pediatric MDD, it was now contraindicating sertraline, citalopram, and escitalopram as well for this condition. This announcement noted that the risk benefit profile is unassessable for fluvoxamine, and that, in its view, the risk benefit profile is favorable in pediatric MDD only for fluoxetine.

[Note: Nefazodone and bupropion are not approved drug products in the UK. Mirtazapine is an approved product in the UK, however, MHRA has offered no comment on the pediatric data for this drug.]

Summary of Issues That Complicate the Anaylsis of the Pediatric Suicidality Data; Questions for the Committee

In this section, I will first recap the major issues that have complicated our attempts to understand the pediatric suicidality data, and then list the specific issues for which we would like committee feedback to assist us as we move forward in trying to address this concern. We are not asking for votes on any particular questions, but rather, discussion by the committees and any feedback you might have to offer on our current plans for further exploring these data.

Ascertainment for Suicidality

One of the concerns about these studies is the fact that they were not conducted in a manner to fully and adequately assess patients for emergent suicidality. This is apparent in reviewing the descriptive information for the events identified as possibly suggestive of suicidality. These descriptions are frequently sparse and lacking the kind of detail that would ordinarily be useful in assessing whether or not the events might legitimately be considered to represent suicidality. There is, of course, no fix for this problem with regard to these studies. However, one of our outside experts will address the issue of how one might develop guidance for more adequate assessment for emergent suicidality in future studies. We would welcome any advice from the committees on the development of such guidance.

One might reasonably ask why this would be a concern for these studies, since, despite the generally inadequate ascertainment, signals for drug associated suicidality did emerge. In fact, however, one can easily construct possible explanations for biases being introduced by inadequate ascertainment that work either for drug or against drug. Rather than having to

speculate about possible bias, it would have been preferable to have included adequate ascertainment in the first place.

Possible Failure to Fully Capture All Events of Potential Interest with Regard to Suicidality

Quite apart from a concern about ascertainment is the issue of the method used to search the database for events of possible interest. GSK had developed an algorithm for searching for potential events representing suicidality in their database, and we proposed a variation of this to other sponsors. However, this is admittedly a compromise. It is still conceivable that certain cases of interest might have been missed by the search methods employed. The only failsafe approach to identifying all possible events of interest would be to have experts blindly evaluate every case report form for the more than 4000 patients who participated in these trials. Since that is not feasible, we welcome advice from the committee on possible modifications to the search strategies used for identifiying cases that might have been missed. Additional searches at this point would further delay the analyses of these data, and so this needs to be taken into consideration. However, if the committees feel there are serious deficiencies in the search methods employed, it would be helpful to hear about alternative approaches that might be suggested.

Approaches to Classifying Events into Meaningful Categories for the Purpose of Further Analysis

As noted, an important next step is to decide on categories into which events of interest might be classified, along with operational definitions for such classifications. The approach used by sponsors thus far has been to classify cases first into a crude category of "possibly suicide-related," and then a further subgrouping of that broader group into a "suicide attempt" class. Since we are just now beginning to address this question with our outside experts, we would welcome any advice the committees might have on how to classify these events for the purpose of further analysis.

Patient Level Data Analysis

There will be a brief presentation by a member of our safety group on our plans for the patient level data analysis. Since we are in the preliminary stages of this analysis, this would again be an opportune time to get feedback on how to approach this analysis. In addition, you have seen our list of potential covariates for inclusion in this analysis, and we would welcome any thoughts you might have on this list. If we have left out important covariates, please let us know, since this would be the time to try to gather any additional information that you feel might be helpful in trying to understand these data.

Future Approaches to Trying to Address the Question of What Benefits These Drugs Might Have in Pediatric MDD

As noted earlier, the attempts to demonstrate efficacy in short-term trials for these drugs have not been successful, for the most part. We would welcome your thoughts on how to interpret and

understand these largely negative results, and also any thoughts you might have on alternative approaches to demonstrating benefits in this population. An approach often used in expanding information on effectiveness in adult MDD populations is the randomized withdrawal design, in which patients who have responded during open treatment with an antidepressant drug are randomized to either continuation of drug or switch to placebo. The endpoint in these trials is typically time to relapse, and the success rate for these trials is far higher than the roughly 50% success rate in acute trials in adult MDD. We would welcome your thoughts on whether or not this design might be useful in evaluating possible benefits of these drugs in pediatric MDD.

Feedback on Other Relevant Topics

You should not feel limited to providing feedback on the above topics. The purpose of this meeting is to give you interim feedback on where we are at present with our attempts to understand these data, and to gain your insights into how we might proceed. Thus, we would welcome your feedback on other issues as well that you feel are relevant to our continuing evaluation of these data.

Appendix 1
Summary of Efficacy Results (Primary Outcomes) for Short-Term Placebo-Controlled Pediatric Studies in Major Depressive Disorder

Drug Program/Study Number	Age Range	Outcome[1] (Drug vs Placebo)
Paroxetine/329	12-18	Negative[2]
Paroxetine/377	13-18	Negative
Paroxetine/701	7-17	Negative
Fluoxetine/HCJE	8-17	Positive
Fluoxetine/X065	8-17	Positive
Sertraline/A050-1001	6-17	Trend
Sertraline/A050-1017	6-17	Negative[3]
Venlafaxine/382	7-17	Negative
Venlafaxine/394	7-17	Negative
Citalopram/CIT-MD-18	7-17	Positive
Citalopram/94404	13-18	Negative
Nefazodone/CN104-141	12-18	Trend
Nefazodone/CN104-187	7-17	Negative
Mirtazapine/003-004/Study 1	7-17	Negative
Mirtazapine/003-004/Study 1	7-17	Negative

1 Positive ($p \leq 0.05$); Negative ($p > 0.10$); Trend ($0.05 < p \leq 0.10$)
2 Keller, et al, 2001; positive on most secondary endpoints
3 Wagner, et al, 2003; positive on pooling of 2 studies

Appendix 2
Risk (%) and Risk Ratio for Events Classified as "Possibly Suicide-Related" and "Suicide Attempts"
in Pediatric Studies of Major Depressive Disorder
[All subjects; On-Therapy Data]

Drug/Study Number	"Possibly Suicide-Related"			"Suicide Attempts"		
	Drug	Placebo	Risk Ratio	Drug	Placebo	Risk Ratio
Paroxetine/329	6.5%	1.1%	5.9	5.4%	0	--
Paroxetine/377	3.9%	4.2%	0.9	3.9%	4.2%	0.9
Paroxetine/701	1.0%	1.0%	1.0	1.0%	1.0%	1.0
Fluoxetine/HCCJ	0	5.3%	--	0	5.3%	--
Fluoxetine/HCJE	3.7%	3.6%	1.0	0.9%	1.8%	0.5
Fluoxetine/X065	4.2%	4.2%	1.0	4.2%	0	--
Sertraline/A050-1001	4.1%	0	--	1.0%	0	--
Sertraline/A050-1017	2.2%	2.2%	1.0	2.2%	2.2%	1.0
Venlafaxine/382	6.25%	1.18%	5.3	2.50%	1.18%	2.1
Venlafaxine/394	7.84%	0	--	1.96%	0	--
Citalopram/CIT-MD-18	1%	2%	0.5	1%	1%	1.0
Citalopram/94404	13%	8%	1.6	13%	8%	1.6
Nefazodone/CN104-141	1.1%	0	--	1.1%	0	--
Nefazodone/CN104-187	0.5%	0	--	0.5%	0	--
Mirtazapine/003-045	0.59%	1.14%	0.5	0	1.14	--

Appendix 3

[Note: This was the final variable list submitted to sponsors (10-28-03) as an update to the original request for patient level data sets send 10-3-03]

We would appreciate your adding these variables to the previously requested dataset.

HXPSHOSP: This is a Y/N variable indicating that the subject had a history of psychiatric hospitalization prior to entering the RCT.

SCALESUI: The score of the suicide item for the primary scale used to rate baseline severity of depression. As part of your response to this data request, please include the range and meaning of the scores for the suicide item.

Clarifications of 10/27/03 updated request:

- Please note that the description of the variable HXSUIATT referred to history of suicide attempts. The description should be corrected to read "attempt" (see table below). In other words, to qualify for a "yes" on that variable, a subject need only have had one suicide attempt (not multiple).
- "." Will be added as a response option for missing data for the psychiatric history variables
- In the variable "HXNONCOM", "erratic" compliance is defined as not taking the study drug as prescribed.

The changes described above are highlighted in the following table.

Variable name	Length	Type	Description	Coding notes
TRIAL	NS	Character	Trial ID	No missing values are allowed in this variable.
CTPID	NS	Character	Patient ID within each trial.	No missing values are allowed in this variable
UNIQUEID	NS	Character	A unique ID for every patient	It should incorporate both the trial ID and the patient ID within each trial. No missing values are allowed in this variable.
DIAG	NS	Character	Condition for which patient was being treated (e.g., dementia-related psychosis or schizophrenia).	Should be one of the diagnoses listed for the corresponding trial in the "Controlled Trial File". No missing values are allowed in this variable.
DIAGCAT	3	Numeric	Diagnosis category	1= major depressive disorder 2= obsessive compulsive disorder 3= social anxiety disorder 4= other anxiety disorder
AGE	3	Numeric	Age of patient in years	. = Missing.

AGECAT	3	Numeric	Categories of age	1= AGE < 12 2= AGE >= 12 . = Missing
GENDER	3	Numeric	Patient gender	1= Female 2= Male . = Missing
RACE	3	Numeric	Race	1= White Caucasian 2= African-American 3= Hispanic 4= Asian 5= Other . = Missing
BMI	3	Numeric	Body mass index	Calculated as weight in kg/(height *in* meters)^2 . = Missing
SET	3	Numeric	Setting at randomization	1= Inpatient 2= Outpatient . = Missing
LOC	3	Numeric	Location of trial center	1= North America 2= Non-north America . = Missing
HXSUIATT	3	Numeric	The subject had a history of suicide attempt prior to entering the RCT	0=No 1=Yes . = Missing
HXSUIID	3	Numeric	The subject had a history of suicidal ideation prior to entering the RCT	0=No 1=Yes . = Missing
HXPSHOSP	3	Numeric	The subject had a history of psychiatric hospitalization prior to entering the RCT	0=No 1=Yes . = Missing
HXSUBAB	3	Numeric	The subject had a history of substance abuse prior to entering the RCT	0=No 1=Yes . = Missing
HXHOST	3	Numeric	The subject had a history of hostility or aggressive behavior prior to entering the RCT	0=No 1=Yes . = Missing
HXIRRAG	3	Numeric	The subject had a history of irritability or agitation prior to entering the RCT	0=No 1=Yes . = Missing
RANTX	NS	Character	Name of post-randomization treatment assignment	"Your drug name", "Placebo", or the name of the active control drug No missing values are allowed in this variable.
RANTXCAT	3	Numeric	Category of the drug	1=SSRI 2=non-SSRI 3=placebo
DOSE	3	Numeric	Dose of the post-randomization investigational treatment; If a flexible dose scheme was used, then report the modal dose. If there were multiple modal doses, select the maximal modal dose	0=Placebo . = Missing

DFRAN	10	Date	Date of first dose of randomized treatment	Use date format: MM /DD/YYYY, e.g. 3/4/2000 . = Missing
DLRAN	10	Date	Date of last dose of randomized treatment	Use date format: MM /DD/YYYY e.g. 6/14/2000 . = Missing
EXPOSURE	3	Numeric	Number of days of exposure to randomized treatment	Should represent the difference between "DFRAN" and "DLRAN". [DLRAN-DFRAN]+1 . = Missing
HXNONCOM	3	Numeric	There is some evidence in the subject's medical record or case report form that the subject had a history of erratic compliance with the study medication during the RCT	0=No 1=Yes
RCTYEARS	12	Numeric	Exposure in years	=Exposure/365.25 . = Missing
SEVSCALE[2]	3	Numeric	Primary scale used to rate baseline severity of depression	1=HAM-D 2=CDRS-R 3=K-SADS-L 4=Kutcher 5=Other 6= NA (if not measured)
BASESEV	3	Numeric	Baseline severity score	. = Missing
HAMD17	3	Numeric	Score on HAM-D 17 if performed (or adapted from HAM-D 21)	. = Missing
SCALESUI	3	Numeric	The score of the suicide item for the primary scale used to rate baseline severity of depression	. = Missing
DURATION [Add DURACAT variable if duration of illness was recorded as a categorical variable]	3	Numeric	Duration of illness prior to randomization in months	. = Missing
SUIEVENT	3	Numeric	A suicide-related event as defined in July 2003 submission occurred during the RCT	0= No 1=Yes
SUIATT	3	Numeric	A suicide attempt as defined in July 2003 submission occurred during the RCT [Suicide attempt is a subset of suicide-related event]	0=No 1=Yes

2 HAM-D – Hamilton Depression Scale; CDRS =Children's Depression Rating Scale-Revised ; K-SADS-L = 9 item depression subscale of the Schedule for Affective Disorders and Schizophrenia for School Age Children- Lifetime version ; Kutcher = Kutcher Adolescent Depression Rating Scale

EVENTDC	3	Numeric	The first suicide-related event occurred following discontinuation	0=No 1=Yes
DAYEVENT	3	Numeric	The number of days to the first suicide-related event counting from the day of the first dose. Counting from the first day of drug should occur even if the event occurred after the patient discontinued the drug.	. = Missing or patient did not have an event
TEAEAG	3	Numeric	A treatment-emergent adverse event coded to the preferred term agitation occurred during the RCT	0=No 1=Yes
TEAEHOST	3	Numeric	A treatment-emergent adverse event coded to the preferred term hostility occurred during the RCT	0=No 1=Yes
SOURCE	4	Character	First 4 letters of your drug name	

NS=not specified.

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cc:
HFD-120/TLaughren/RKatz/JRacoosin/PDavid
HFD-040/RTemple
HFD-020/JJenkins

DOC: PDAC_Memo_Feb2004_TL02.doc

Food and Drug Modernization Act (FDAMA) Section 113: Status Report on Implementation

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Theresa Toigo

The Food and Drug Administration Modernization Act (FDAMA; herein referred to as the "Modernization Act"), enacted November 21, 1997, amended the Federal Food, Drug, and Cosmetic Act. Section 113 of FDAMA directed the Secretary of the Department of Health and Human Services (DHSS), acting through the Director of the National Institutes of Health (NIH), to establish a publicly accessible data bank of information about clinical trials for serious or life threatening diseases and conditions. The National Library of Medicine made the first version of the Clinical Trials Data Bank available to the public on February 29, 2000, on the Internet at http://clinicaltrials.gov. The data bank included mainly NIH-sponsored trials. On March 18, 2002, the Food and Drug Administration (FDA) issued a final guidance entitled *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*. One and one-half years after publication of the final guidance, FDA issued a press release acknowledging the listing of the 1,000th industry-sponsored study in *ClinicalTrials.gov*. Although this milestone is gratifying, more needs to be done by FDA, pharmaceutical companies, and other sponsors. The challenge for FDA is to assess the need for further efforts to facilitate or perhaps to compel the pharmaceutical industry's participation in *ClinicalTrials.gov*.

INTRODUCTION

Congress has demonstrated a longstanding interest in improving public access to information about opportunities to participate in clinical trials of promising new treatments. In November 1988, Congress passed the Health Omnibus Programs Extension (HOPE) Act. Section 2317 of the HOPE Act directed the Secretary of the Department of Health and Human Services (DHHS), to establish services to disseminate information on HIV research, treatment, and prevention.[1] These services included providing information about clinical trials of investigational drugs, including biologic products, for HIV-related diseases. Almost 10 years later, Congress passed the 1997 Food and Drug Administration Modernization Act (Modernization Act). Section 113 of the Modernization Act directed the DHHS Secretary, acting through the Director of the National Institutes of Health (NIH), to establish a publicly accessible data bank of information about clinical trials for serious or life threatening diseases and conditions.[2]

The intent and language of Section 113 of the Modernization Act and Section 2317 of the 1988 HOPE Act are similar. Both directed DHHS to make information about clinical trials publicly available. In 1989, the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and NIH established the AIDS Clinical Trials Information Service (ACTIS) to provide information on clinical trials for HIV-related diseases. In 2000, NIH, through its National Library of Medicine (NLM), and FDA developed the *ClinicalTrials.gov* site, to provide information on clinical trials for serious or life threatening diseases as required by the Modernization Act.[3] Although the provisions of the 1988 HOPE Act which established ACTIS, are similar to those of Section 113 of the Modernization Act, the focus has shifted from technical data for health professionals to information accessible to the public.

AIDS CLINICAL TRIALS INFORMATION SERVICE

In 2002, ACTIS was reviewed after more than a decade providing HIV/AIDS clinical trial information to the public. As ACTIS moved into its second decade, the service merged with its sister service, the HIV/AIDS Treatment Information Service (ATIS), to form AIDSinfo.[5] AIDSinfo includes the services that were available from both ACTIS and ATIS. More recently, the AIDSinfo clinical trials search screen was designed to help users find HIV/AIDS-related

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clinical trials in *ClinicalTrials.gov*. Using the AIDSinfo search screen, each search is automatically limited to trials studying HIV/AIDS.

Although experience gained from developing and maintaining the ACTIS database was helpful, the broad scope of the Modernization Act required a general clinical trials data bank rather than separate data banks for each disease category. Design and development for *ClinicalTrials.gov*, therefore, was more technically and organizationally challenging. Issues pertaining to design and implementation, including lessons learned in developing the database, have been well described.[6] One study concluded that because data in the system are constantly changing, no phase of this project is ever completed.

INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE-THREATENING DISEASES: ESTABLISHMENT OF A DATA BANK

NLM made the first version of the Clinical Trials Data Bank available to the public on February 29, 2000, on the Internet at http://ClinicalTrials.gov. The data bank included mainly NIH-sponsored trials. At about the same time, FDA published the first of three guidance documents.

On March 29, 2000, FDA published in the Federal Register a notice of availability (NOA) for a draft guidance entitled *Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Establishment of a Data Bank*.[7] The draft guidance provided recommendations for industry on filing protocol information to the Clinical Trials Data Bank. It included discussion about the types of clinical trials for which submissions will be needed under Section 113 of the Modernization Act and the types of information to be filed.

Section 113 of the Modernization Act requires that sponsors of investigational new drug applications (IND's) submit to the Clinical Trials Data Bank a description of the purpose of each experimental drug, eligibility criteria for participation in the trial, the location of clinical trial sites, and a point of contact for those wanting to enroll in the trial. The statute requires the information to be provided in a form that can be readily understood by the public. The guidance addressed questions to be considered when submitting protocol information under the Modernization Act. For example, What is a serious or life-threatening disease? What is a trial to test effectiveness? and What does submission to the data bank "not later than 21 days after approval" mean?

A life threatening disease is a disease or condition where the likelihood of death is high unless the course of the disease is interrupted and includes diseases with potentially fatal outcomes where the endpoint of the clinical trial analysis is survival. The seriousness of a disease is a matter of judgment but is based on such factors as survival, day-to-day functioning, and the likelihood the untreated disease will progress to a more serious condition. To respond to the effectiveness requirement in the statute, a trial to test effectiveness is defined as a phase 2, phase 3, or phase 4 trial with efficacy endpoints. Section 113 of the Modernization Act requires that sponsors forward information to the Clinical Trials Data Bank no later than 21 days after approval. Because FDA does not specifically approve an IND protocol, we recognized the need to clarify the date of submission to the data bank. For purposes of responding to Section 113 of the Modernization Act, the guidance recommends that sponsors submit protocol information to the Clinical Trials Data Bank no later than 21 days after the trial is first opened for enrollment; on amending the protocol with respect to one of the required data elements; or when recruitment for the study is interrupted, resumed, or completed.

INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE-THREATENING DISEASES: IMPLEMENTATION PLAN

On July 9, 2001, FDA published in the Federal Register an NOA for the second draft guidance entitled *Information Program on Clinical Trials for Serious or Life-Threatening Diseases: Implementation Plan*.[8] This guidance addressed procedural issues, including how to file mandatory and voluntary protocol information in the Clinical Trials Data Bank. Information is submitted to the data bank through a Web-based protocol registration system (PRS) available at http://prsinfo.clinicaltrials.gov/. The guidance set up a time frame for filing the information. It also discussed exemption from the reporting requirements of Section 113, which are based on submitting certification to the DHHS Secretary that disclosure of information for a particular protocol would substantially interfere with the timely enrollment of subjects in the clinical investigation.

On March 18, 2002, FDA published in the Federal Register an NOA for the final guidance entitled *Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions*.[9] The final guidance combined the two draft guidances into a single guidance, incorporated comments received on the draft guidances, and provided more details on the use of the PRS. For example, the guidance clarified that intermediaries acting for a sponsor can submit data to the PRS and the PRS includes a mechanism for uploading and downloading XML-formatted records. The guidance also clarified how to submit requests for exemption when disclosure of information would substantially interfere with enrollment of subjects in a clinical investigation.

The FDA initiated a program during 2002 to inform pharmaceutical companies and other IND sponsors of the statutory requirement that they list their studies in *ClinicalTrials.gov*. FDA sent letters directing sponsors to the guidance document and describing mandatory and voluntary data submission through the PRS.

Pharmaceutical companies have made important progress in making summary trial information available through the

ClinicalTrials.gov site. As of November 18, 2003, 254 pharmaceutical companies and 29 educational or organizational sponsors had registered. Of the sponsors who have registered, 215 pharmaceutical companies and 22 educational or organizational sponsors have listed 1093 protocols.

FDA's Office of Special Health Issues (OSHI) is completing a review of participation by IND sponsors during 2002. OSHI identified 2060 new commercial protocols filed between January 1, 2002 and September 30, 2002; extracted protocol information and identified protocols that met the criteria for inclusion (phase 2, 3 or 4 protocols testing effectiveness for a serious disease); and compared protocol listings in *ClinicalTrials.gov* with protocol listings in the OSHI database.

INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE-THREATENING DISEASES: BEYOND IMPLEMENTATION

FDA is analyzing data from the review of sponsor participation in *ClinicalTrials.gov*. At present, some pharmaceutical companies are not providing adequate information about the trials. Some companies list their clinical trials but provide limited information about the trial, making it difficult for patients to find the trial and make informed decisions. Some companies do not provide the sponsor name or the name of the drug; 10% of the protocols do not include specific drug names. For these trials, sponsors generally list "investigational drug" as the drug name. Because patients often search *ClinicalTrials.gov* using a specific drug name, they will not find a trial for the drug if it is listed in the database as "investigational drug." Academic institutions and organizations not affiliated with pharmaceutical companies include both drug and sponsor names.

Some companies list no trials in *ClinicalTrials.gov*. Some list only a few trials that meet the criteria specified in the guidance. Other companies voluntarily list trials that go beyond the criteria specified in the guidance, which FDA and NLM welcome them to do. Data compiled by the FDA's Office of Special Health Issues and presented at a recent FDA Science Forum show that 48% of the mandated industry-sponsored and 91% of the mandated NIH cancer-related trials were in *ClinicalTrials.gov*.[10] A preliminary review of non-cancer protocols in the sponsor participation study suggests a single-digit participation rate in some serious disease categories. FDA is working to further quantify the extent of participation in *ClinicalTrials.gov* required under the Modernization Act.

FDA recently acknowledged the listing of the 1,000th industry-sponsored trial in *ClinicalTrials.gov*.[11] Although this milestone is gratifying, more needs to be done by FDA, pharmaceutical companies, and other sponsors. FDA should further clarify guidance on which trials and what information needs to be listed in *ClinicalTrials.gov*. FDA should identify opportunities to remind sponsors of the Modernization Act's Section 113 requirements. Companies should review their systems for identifying and submitting protocols to *ClinicalTrials.gov* and reconsider why mandated protocols are not being submitted in accordance with federal law. Patient advocacy groups should continue to be proactive in encouraging FDA and pharmaceutical companies to make information about ongoing trials more available through *ClinicalTrials.gov*.

SUMMARY

DHHS developed *ClinicalTrials.gov* in response to legislation calling for a publicly accessible registry of clinical trials for patients with serious or life threatening diseases and conditions. The project is an evolving long-term program involving collaboration among federal agencies, patient advocates, and pharmaceutical companies. As Congress recognized in enacting Section 113 of the Modernization Act, programs that enhance patient access to clinical trials may benefit public health. At the same time, expanding the pool of research participants may benefit pharmaceutical company sponsors by speeding enrollment in their clinical trials. Aside from the obvious benefits to various parties from participating in *ClinicalTrials.gov*, Federal law requires that pharmaceutical companies make clinical trials information more publicly available. Many pharmaceutical companies are not participating in *ClinicalTrials.gov*, or are not fully participating. The challenge for the Food and Drug Administration is to assess the need for further efforts to facilitate or, perhaps, to compel participation in *ClinicalTrials.gov*.

ENDNOTES

1. Health Omnibus Programs Extension (HOPE) Act of 1988, Pub. L. No. 100-607, 2317 (ACT, 1988).
2. The Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 113 (1997).
3. National Institutes of Health, http://ClinicalTrials.gov
4. Katz, Deborah G., Dutcher, Gale A., Teigo, Theresa A., Banks, Ruthann, Temple, Freda, Calden, Cynthia C. *The AIDS Clinical Trials Information Service (ACTIS): A Decade of Providing Clinical Trials Information Public Health Reports*, 117(2):123-130, March/April 2002.
5. U.S. Department of Health and Human Services, AIDs info. *See generally*, <http://www.aidsinfo.nih.gov>
6. McCray, Alexa T., Ide, Nicholas C. *Design and Implementation of a National Clinical Trials Registry* Journal of the American Medical Informatics Association Volume 7 Number 3 May/June 2000
7. U.S. Food and Drug Administration, Information Program on Clinical Trials Serious or Life-Threatening Diseases: Establishment of a Data Bank. *See generally*, < http://www.fda.gov/OHRMS/DOCKETS/98fr/001033gl.pdf>
8. U.S. Food and Drug Administration, Information Program on Clinical Trials Serious or Life-Threatening Diseases: Implementation Plan. *See generally*, <http://www.fda.gov/OHRMS/DOCKETS/98fr/001033gd.pdf>
9. U.S. Food and Drug Administration, Information Program on Clinical Trials Serious or Life-Threatening Diseases and Conditions. *See generally*, <http://www.fda.gov/OHRMS/DOCKETS/98fr/00d-1033_gdl0003.pdf>
10. Derba, J. Teigo, T. Woods, J. Evelyn,B. Banks, D FDAMA Section 113: Informat Program on Clinical Trials for Serious or Life Threatening Diseases: Update Implementation. *See generally*, https://www.cfsan.fda.gov/~lrd/forum03/U-04.HTM
11. U.S. Food and Drug Administration, A Milestone for ClinicalTrials.gov Web http://www.fda.gov/bbs/topics/NEWS/2003/NEW00965.html

Pediatric Program Summary Statistics **60**

Since the pediatric exclusivity program began, 283 Written Requests have been issued and 88 drugs have been granted exclusivity. Among these, only fluoxetine has been approved for the treatment of major depressive disorder in pediatric patients; the labeling changes for pediatric major depressive disorder that were made following these studies are summarized as follows:

- Effectiveness established in patients 8-17 years of age for MDD
- Decreased weight gain has been observed in association with the use of fluoxetine, as with other SSRIs. In one 19-week clinical trial pediatric subjects treated with fluoxetine gained an average of 1.1cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than those treated with placebo. Therefore, height and weight should be monitored periodically in pediatric patients treated with fluoxetine.
- Mania/hypomania led to discontinuation of 1.8% of fluoxetine treated patients vs. 0% of placebo controlled patients in the three placebo-controlled trials combined. Regular monitoring for the occurrence of mania/hypomania is recommended
- Higher average steady state fluoxetine and norfluoxetine concentrations were observed in children than in adolescents. These differences were almost entirely explained by differences in weight.
- Separate dosing recommendations in lower weight children

The Division of Neuropharmacologic Drug Products has developed a template for pediatric written requests for the study of antidepressants, which is provided here.

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Sample Written Request for Antidepressants

This is a sample Written Request outlining the pediatric studies the Agency believes will provide a meaningful health benefit to the pediatric population for antidepressants. An actual Written Request may differ from this sample depending upon the nature of the specific drug product and any other indications for which it is used. To receive a formal Written Request for pediatric studies under section 505A of the Federal Food, Drug, and Cosmetic Act for a particular antidepressant agent, please submit a proposed pediatric study request to the Division of Neuropharmacologic Drug Products. The proposed pediatric study request should incorporate the material in this sample and include descriptions of any other studies necessary to provide a meaningful health benefit to pediatric populations. Please refer to the outline in the "Guidance For Industry - Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act," for additional information.

NDA XX-XXX
Sponsor
Attention: Contact
Address

Three Years From the
Date of the Original WR_____

Dear Contact:

Reference is made to your Proposed Pediatric Study Request submitted on [Insert date] to your New Drug Application for [Insert Drug].

To obtain needed pediatric information on [Insert drug], the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the trials in pediatric patients with depression described below.

PEDIATRIC DEPRESSION

Background Comments on Pediatric Depression

Under current regulations [21 CFR 201.57(f)(9)(iv)], a new claim in a pediatric population could be established by extrapolating the effectiveness results of adequate and well controlled studies in adults for the same entity if it were believed that depression was essentially the same disease in adults and children. Under FDAMA (1997), a claim might be based on a single study in pediatric patients along with confirmatory evidence from another source, perhaps adult data for that disorder, an approach considered in the draft guidance document entitled "Guidance for Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products". This approach too requires some degree of belief that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to make data from the adult efficacy studies pertinent to pediatric patients. Unfortunately, in our view there is little reason to assume continuity between adult and pediatric depression and our concern about the extrapolability of adult depression data to pediatric depression is more than theoretical. While we, of course, acknowledge the one published positive report of fluoxetine in pediatric depression (Emslie, et al, 1997), we are concerned about the preponderance of negative studies of antidepressants in pediatric populations. We recognize that all of these negative studies utilized tricyclic antidepressants, and that, in addition, there are other possible explanations for the negative outcomes, e.g., sample size, entry criteria, outcome measures, etc. Nevertheless, these negative trials (at least 12 in number) lead to a substantial concern about the ability to extrapolate positive antidepressant findings from adult to pediatric patients. Consequently, we believe that a pediatric depression claim for any antidepressant already approved in adult depression would need to be supported by two independent, adequate and well controlled clinical trials in pediatric depression. In addition, a pediatric depression program would need to include pharmacokinetic information and safety information in the relevant pediatric age groups. For pediatric depression, we consider the relevant age groups to include children (ages 7 through 11) and adolescents (ages 12 through 17).

Specific Study Requirements for Development Program in Pediatric Depression

Types of Studies:

Pediatric Efficacy and Safety Studies

Pediatric Pharmacokinetic Study

Pediatric Safety Study

Objective/Rationale:

The overall goal of the development program is to establish the safety and efficacy of the study drug in the treatment of pediatric depression, and to develop other information, e.g., pharmacokinetic, pertinent to using the drug in the pediatric population.

Study Design:

Pediatric Efficacy and Safety Studies

For the controlled efficacy studies, conduct two randomized, double-blind, parallel group, placebo-controlled acute treatment trials, with a recommended duration of at least 6 to 8 weeks. We recommend that at least one of the two studies should be a fixed dose study including two or more fixed doses of the study drug. You may consider dosing patients on the basis of patient weight. Randomization must be stratified by the two age groups studied. Ideally, a relapse prevention trial would follow from the acute treatment trials, involving the randomization of responders from the acute treatment trials to continuation on either study drug or placebo, with follow-up observation for relapse for a period of 6 months or more. Please note that a relapse prevention trial is not required under this written request.

Pediatric Pharmacokinetic Study

A pharmacokinetic study to provide information pertinent to dosing of the study drug in the relevant pediatric population. These data could come from traditional pharmacokinetic studies, or alternatively, from population kinetic approaches applied to controlled efficacy trials or to other safety trials. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Pediatric Safety Study

Safety data should be collected in the controlled efficacy trials. Longer-term safety data should be generated in longer-term open extensions from these trials and/or in separate longer-term open safety studies.

Age Group in Which Study(ies) will be Performed - All Studies:

Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these strata.

Number of Patients to be Studied or Power of Study to be Achieved:

Pediatric Efficacy and Safety Studies
While it is difficult to specify the sample size needed to show a difference between drug and placebo in this population, it should be noted that, in the only published positive antidepressant trial in pediatric depression (Emslie, et al, 1997), there were 48 patients in each of the two treatment arms.
Pediatric Pharmacokinetic Study
A sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.
Pediatric Safety Study
A sufficient number of pediatric patients to adequately characterize the safety of [Insert drug] at clinically effective doses for a sufficient duration.

Entry Criteria:
The protocols should include a valid and reliable diagnostic method for recruiting children and adolescents with major depressive disorder.

Study Endpoints:
Pediatric Efficacy and Safety Studies
It is essential to identify a single primary outcome for the controlled efficacy trials, and ordinarily this should be change from baseline to endpoint on whatever symptom rating scale you have chosen for your trials.
Pediatric Pharmacokinetic Study
Pharmacokinetic measurements as appropriate.
Pediatric Safety Study
Appropriately frequent standard measures of safety (clinical - including signs and symptoms and laboratory).

Statistical Information:
Pediatric Efficacy and Safety Studies
These trials should have a detailed statistical plan. Ordinarily these trials should be designed with at least 80% statistical power to detect a treatment effect of conventional ($p=0.05$) statistical significance.
Pediatric Pharmacokinetic Study
Descriptive analysis of the pharmacokinetic parameters.
Pediatric Safety Study
Descriptive analysis of the safety data.

Study Evaluations:
Pediatric Efficacy and Safety Studies
A scale specific to pediatric depression and sensitive to the effects of drug treatment of pediatric depression, e.g., the Children's Depression Rating Scale-Revised, and a global measure, e.g., the Clinical Global Impression (CGI).
Pediatric Pharmacokinetic Study
The pharmacokinetic assessments should be made with respect to the study drug and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the pharmacokinetic parameters including AUC, half-life, C_{max}, t_{max}, and apparent oral clearance in pediatric subjects in the relevant age range. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available under [www.fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].
Pediatric Safety Study
Routine safety assessments should include vital signs, weight, clinical laboratory, ECGs, and monitoring for adverse events. Although not a part of this Written Request, we remind you that it may be important to determine the effect of the study drug on the growth and development of pediatric patients, and we encourage you to consider longer-term studies of a year or more to address this question if the acute studies demonstrate antidepressant activity.

Drug Information:
Use age appropriate formulations in the studies described above. Since the pediatric patient population consists of both children (ages 7 to 11) and adolescents (ages 12 to 17), your marketed dosage formulation should be adequate for these studies.

Drug Concerns:
Specific concerns, if any, related to administration of drug to pediatric patients is to be conveyed in this paragraph.

Labeling that may result from the studies:
The pediatric depression efficacy, safety, and pharmacokinetic studies described in this request could result

in the addition to labeling of information pertinent to these studies.

Format of reports to be submitted:

Full study reports or analyses, not previously submitted to the Agency, addressing the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. Include other information as appropriate

Timeframe for submitting reports of the Study(ies):

Reports of the above studies must be submitted to the Agency within 3 years from the date of this letter to be eligible to qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact [Insert Name], Regulatory Project Manager, at [Insert telephone number].

Sincerely yours,

[Office Directors Name]
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Question 11: A listing of all the pediatric/adolescent clinical trials involving antidepressants that the FDA received data for which there was an obligation for the company to submit the data to the FDA.

Firm	Drug	NDA	Supp #	Pediatric Study	Study #	Trial Completion Date	Date submitted to FDA	FDA Action & Letter Date:
Lilly	Prozac (fluoxetine) Capsules	18-936	S-064	Fluoxetine versus Placebo in Adolescent Depressed Patients	HCCJ	1-Mar-88	14-Sep-00	Approved Prozac for MDD and OCD in pediatric patients, January 3, 2003
Lilly	Prozac (fluoxetine) Capsules	18-936	S-064	Fluoxetine versus Placebo in the Acute Treatment of Major Depressive Disorder in Children and Adolescents	X065	28-Feb-95	14-Sep-00	Approved Prozac for MDD and OCD in pediatric patients, January 3, 2003
Lilly	Prozac (fluoxetine) Capsules	18-936	S-064	Fluoxetine versus Placebo in Childhood/Adolescent Depression	HCJE	21-Jul-00	14-Sep-00	Approved Prozac for MDD and OCD in pediatric patients, January 3, 2003
Lilly	Prozac (fluoxetine) Capsules	18-936	S-064	Fluoxetine vs. Placebo in the Treatment of Children and Adolescents with Obsessive Compulsive Disorder	HCJW	1-Feb-00	14-Sep-00	Approved Prozac for MDD and OCD in pediatric patients, January 3, 2003
Lilly	Prozac (fluoxetine) Capsules	18-936	S-064	Fluoxetine pharmacokinetics in pediatris patients	HCIU	6-Oct-98	14-Sep-00	Approved Prozac for MDD and OCD in pediatric patients, January 3, 2003
Pfizer	Zoloft (sertraline) Tablets	19-839	S-017	Double-Blind Comparison of Sertraline and Placebo in Children and Adolescents With Obsessive Compulsive Disorder	90CE21-0498	4/4/1994	12/19/1996	Approval (10/10/97)
Pfizer	Zoloft (sertraline) Tablets & OC	19-839 & 20-990	S-044 & S-010	A Multicenter 10-Week Randomized Double-blind Placebo-controlled Flexible Dose Outpatient Study of Sertraline in Children and Adolescents With Major Depressive Disorder	A0501001	5/17/2001	12/14/2001	Non-approval (9/30/02). Approval (9/16/03) for safety labeling
Pfizer	Zoloft (sertraline) Tablets & OC	19-839 & 20-990	S-044 & S-010	A Multicenter 10-Week Randomized Double-blind Placebo-controlled Flexible Dose Outpatient Study of Sertraline in Children and Adolescents With Major Depressive Disorder	A0501017	3/26/2001	12/14/2001	Non-approval (9/30/02). Approval (9/16/03) for safety labeling
Pfizer	Zoloft (sertraline) Tablets & OC	19-839 & 20-990	S-044 & S-010	A multicenter 24-week, open-label, extension study of sertraline in children and adolescent outpatients previously diagnosed with major depressive disorder	A0501015	10/26/2001	12/19/2002	Approval (9/16/03) for safety labeling
Pfizer	Zoloft (sertraline) Tablets	19-839	S-017	Tolerance and pharmacokinetics of sertraline after single and multiple dosing in children and adolescents with obsessive compulsive disorder or depression	90CK21-0525	10/18/1993	12/19/1996	Approval (10/10/97)
Pfizer	Zoloft (sertraline) Tablets & OC	19-839 & 20-990	S-033 & S-001	Open Follow-Up Study of Sertraline in Children and Adolescents with Obsessive Compulsive Disorder	91CE21-0536	2/21/1995	3/31/2000	Approval (10/12/01)

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Firm	Drug	NDA	Supp #	Pediatric Study	Study #	Trial Completion Date	Date submitted to FDA	FDA Action & Letter Date:
Pfizer	Zoloft (sertraline) Tablets & OC	19-839 & 20-990	S-033 & S-001	An Open-Label, Long-Term Evaluation of Sertraline in Children and Adolescents With Obsessive Compulsive Disorder or Depression	91CK21-0550	4/7/1994	3/31/2000	Approval (10/12/01)
Pfizer	Zoloft (sertraline) Tablets & OC	19-839 & 20-990	S-044 & S-010	Sertraline treatment of adolescent outpatients with Major Depression	R-0246	9/26/1996	12/14/2001	Non-approval (9/30/02). Approval (9/16/03) for safety labeling
Pfizer	Zoloft (sertraline) Tablets & OC	19-839 & 20-990	S-044 & S-010	Sertraline in the Treatment of Adolescent Depressive and Dysthymic Disorders: An Open Trial	STL-CDN-94-002	Apr-97	12/14/2001	Non-approval (9/30/02). Approval (9/16/03) for safety labeling
GlaxoSmithKline	Paxil (paroxetine) Tablets	20-031	S-037	A Multicenter, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression.	329	Feb-98	11-Apr-02	Approvable 10/10/2002
GlaxoSmithKline	Paxil (paroxetine) Tablets	20-031	S-037	A Double-blind, Multicenter Placebo Controlled Study of Paroxetine in Adolescents with Unipolar Major Depression	377	May-98	11-Apr-02	Approvable 10/10/2002
GlaxoSmithKline	Paxil (paroxetine) Tablets	20-031	S-037	A Randomized, Multicenter, 8-Week, Double-blind, Placebo-Controlled Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Major Depressive Disorder	701	Jan-01	11-Apr-02	Approvable 10/10/2002
GlaxoSmithKline	Paxil (paroxetine) Tablets	20-031	S-037	A Randomized, Multicenter, 10-Week, Double-Blind, Placebo-Controlled, Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Obsessive Compulsive Disorder (OCD)	704	Jul-01	11-Apr-02	Approvable 10/10/2002
GlaxoSmithKline	Paxil (paroxetine) Tablets	20-031	S-037	A 32 Week, Two Phase, Multicenter Study to Investigate the Safety and Effectiveness of Paroxetine (10-60 mg/day) in the Treatment of Children and Adolescent Outpatients with Obsessive Compulsive Disorder	453	Dec-98	11-Apr-02	Approvable 10/10/2002
GlaxoSmithKline	Paxil (paroxetine) Tablets	20-031		A 16 Week Double-Blind, Placebo Controlled Study to Investigate the Efficacy and Tolerability of Paroxetine in the Treatment of Children and Adolescents with Social Anxiety Disorder/Social Phobia (29060/676)	676	Oct-01	Final study report submitted to IND 5 Dec 2002 (Serial #440)	NA

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GlaxoSmithKline	Paxil (paroxetine) Tablets	20-031	S-037	A Multicenter Study to Assess the Pharmacokinetics of Paroxetine Following Repeat Dose Administration in Children and Adolescents with Obsessive Compulsive Disorder (OCD) and/or Depression	715	Sep-01	11-Apr-02	Approvable 10/10/2002
GlaxoSmithKline	Paxil (paroxetine) Tablets	20-031	S-037	A Multicenter, Open-Label, 6-Month Extension Study to Assess the Long-Term Safety of Paroxetine in Children and Adolescents with Major Depressive Disorder (MDD) or Obsessive Compulsive Disorder (OCD)	716	Jan-02	Interim report 11-Apr-02; Final report to IND 25-Jun-03 Serial #447)	Approvable 10/10/2002
GlaxoSmithKline	Wellbutrin (bupropion) Tablets	18-644	NA	A Double-Blind Comparison of Efficacy and Safety of Bupropion versus Placebo in Children with Attention Deficit Disorder and/or Conduct Disorder	75	1986	Summary - Oct-90 IND 13,845 Serial No. 037	NA
GlaxoSmithKline	Wellbutrin (bupropion) Tablets	18-644	NA	A Single-Blind Pilot Study of the Safety and Efficacy of Wellbutrin in Children with Attention Deficit and/or Conduct Disorders (Open Label)	41	Jun-83	Summary Dec-83. Initial Medical Report Sept-84 - IND 13,845	NA
Solvay	Luvox (Fluvoxamine maleate) Tablets	20-243	006	Fluvoxamine in the Treatment of OCD: A Multicenter Double-Blind Placebo-Controlled Study in Outpatient Children and Adolescents	RH114.02.01/ Report CR200.0116	17-Aug-94	21-Dec-95	Supplement approved on 25 Mar 1997 for treatment of OCD in the pediatric population
Solvay	Luvox (Fluvoxamine maleate) Tablets	20-243	021	Fluvoxamine in the Treatment of Obsessive Compulsive Disorder: An Open-Label One-Year and Humanitarian Extension Following a Multicenter Double-Blind Placebo-Controlled Study in Outpatient Children and Adolescents	RH114.02.01E/ Report CR200.0144	26-Jul-95	2-Dec-99	Supplement approved on 28 Sept 2000 for revised labeling to add information on long-term safety and pharmacokinetic data in pediatric patients
Solvay	Luvox (Fluvoxamine maleate) Tablets	20-243	021	The Multiple-Dose Pharmacokinetics Study of Fluvoxamine in Children and Adolescents	S114.1102/ Report CR200.0067	14-May-99	2-Dec-99	Supplement approved on 28 Sept 2000 for revised labeling to add information on long-term safety and pharmacokinetic data in pediatric patients
Forest	Celexa (citalopram) Tablets	20-822	S-016	A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of citalopram in children and adolescents with depression (MDD).	CIT-MD-18	April 10, 2001	April 18, 2002	Non-Approvable - FDA Letter Dated 9/23/02. Pediatric Exclusivity was granted.

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Firm	Drug	NDA	Supp #	Pediatric Study	Study #	Trial Completion Date	Date submitted to FDA	FDA Action & Letter Date:
Forest	Celexa (citalopram) Tablets	20-822	S-016	A double-blind study comparing citalopram tablets (Lu 10-171, 10-40 mg per day) and placebo in the treatment of major depression in Adolescents (MDD).	94404	April 23, 2001	April 18, 2002	Non-Approvable - FDA Letter Dated 9/23/02. Pediatric Exclusivity was granted.
Forest	Celexa (citalopram) Tablets	20-822	S-016	An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression	CIT-PK-07	November 11, 2000	April 18, 2002	Non-Approvable - FDA Letter Dated 9/23/02. Pediatric Exclusivity was granted.
Forest	Celexa (citalopram) Tablets	20-822	S-016	An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Subjects	CIT-PK-13	August 26, 2000	April 18, 2002	Non-Approvable - FDA Letter Dated 9/23/02. Pediatric Exclusivity was granted.
Forest	Celexa (citalopram) Tablets	20-822	N/A	An Open-label Extension Study of Citalopram Treatment in Depressed Children and Adolescents (Extension to CIT-PK-07)	CIT-PK-19	February 6, 2001	April 25, 2003	None
Forest	Celexa (citalopram) Tablets	20-822	N/A	An Open-label Extension Study of the Safety and Efficacy of Citalopram in Children and Adolescents with Depression (Extension to CIT-MD-18)	CIT-PK-20	November 20, 2001	April 25, 2003	None
Forest	Lexapro (escitalopram) Tablets	21-323	N/A	A Single Dose Pharmacokinetic Study of Escitalopram in Healthy Adolescent and Adult Subjects	SCT-PK-10	June 30, 2002	Reported in IND Annual Report dated 8/28/03 (IND 58,380 - SN 310)	None
Wyeth	Effexor (venlafaxine) Tablets	20-151	S-024	A Preliminary Safety, Tolerance, Pharmacokinetic, and Efficacy Study of Venlafaxine in Children and Adolescents With Conduct Disorder	0600A-126-US	Report Date: June 24, 2002 Current version (amended) date: August 5, 2002	9/25/2002	Not Approved = March 20, 2003; Approved on March 23, 2004 for safety labeling
Wyeth	Effexor XR (venlafaxine) Extended-Release Capsules	20-699	S-030	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Venlafaxine ER in Pediatric Patients	0600B1-169-US	Report Date: June 16, 2002; Current version (amended) date: July 31, 2002	9/25/2002	Not Approved = March 20, 2003; Approved on March 23, 2004 for safety labeling
Wyeth	Effexor XR (venlafaxine) Extended-Release Capsules	20-699	S-030	Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents With Major Depression	0600B1-382-US	Report Date: July 23, 2002	9/25/2002	Not Approved = March 20, 2003; Approved on March 23, 2004 for safety labeling

Question 11. A listing of all the pediatric/adolescent clinical trials involving antidepressants that the FDA received data for which there was an obligation for the company to submit the data to the FDA.

Firm	Drug	NDA	Supp #	Pediatric Study	Study #	Trial Completion Date	Date submitted to FDA	FDA Action & Letter Date:
Wyeth	Effexor XR (venlafaxine) Extended-Release Capsules	20-699	S-030	Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents With Major Depressive Disorder	0600B1-394-US	Report Date: July 1, 2002	9/25/2002	Not Approved = March 20, 2003; Approved on March 23, 2004 for safety labeling
Wyeth	Effexor XR (venlafaxine) Extended-Release Capsules	20-699	S-030	Open-Label Long-Term Safety Study of Venlafaxine ER in Children and Adolescents With Major Depressive Disorder	0600B1-395-US	Report Date: August 8, 2002	9/25/2002	Not Approved = March 20, 2003; Approved on March 23, 2004 for safety labeling
Wyeth	Effexor XR (venlafaxine) Extended-Release Capsules	20-699	S-030	Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents With Generalized Anxiety Disorder	0600B2-396-US	Report Date: August 6, 2002	9/25/2002	Not Approved = March 20, 2003; Approved on March 23, 2004 for safety labeling
Wyeth	Effexor XR (venlafaxine) Extended-Release Capsules	20-699	S-030	Double-Blind, Placebo-Controlled Study of Venlafaxine ER in Children and Adolescents With Generalized Anxiety Disorder	0600B2-397-US	Report Date: July 19, 2002	9/25/2002	Not Approved = March 20, 2003; Approved on March 23, 2004 for safety labeling
Bristol Myers Squibb	Serzone (nefazodone) Tablets	20-152	S-032	A Multicenter, Double-Blind, Placebo-Controlled Trial of Nefazodone in Depressed Adolescents	CN104-141	9/19/01(DB) 3/25/02(LT)	4/16/02 (DB) Pending (LT)	Not Approvable 9/18/02
Bristol Myers Squibb	Serzone (nefazodone) Tablets	20-152	S-032	A Multicenter, Double-Blind, Placebo-Controlled Trial of Two Dose Ranges of Nefazodone in the Treatment of Children and Adolescents With a Major Depressive Episode	CN104-187	11/15/01 (DB) 5/15/02 (LT)	4/16/02 (DB) Pending (LT)	Not Approvable 9/18/02
Bristol Myers Squibb	Serzone (nefazodone) Tablets	20-152	S-032	An Open Label Pharmacokinetic Trial of Nefazodone in Depressed Children and Adolescents	CN104-136	9/26/96 (ST) 12/30/96 (LT)	4/16/02 (ST) 4/16/02 (LT)	Not Approvable 9/18/02
Organon	Remeron (mirtazapine) Tablets	20-415	S-011	A multi-center, randomized, double-blind, placebo-controlled, efficacy and safety study of Remeron in outpatient children and adolescents with major depressive disorder.	003-045	Nov-00	May-01	Not Approvable on 2/27/02.
Organon	Remeron (mirtazapine) Tablets	20-415	S-011	A single dose, pharmacokinetic trial of Remeron (mirtazapine) in children and adolescents with major depression	003-047	Dec-00	May-01	Not Approvable on 2/27/02.

Summaries of Medical and Clinical Pharmacology Reviews Pediatric Studies

as of August 20, 2004

Summaries of Medical and Clinical Pharmacology Reviews

Drug	Sponsor	Review Summary	
Alendronate - Fosamax	Merck	Medical	Clinical Pharmacolo
Atovaquone and Proguanil - Malarone	GlaxoSmithKline	Medical	Clinical Pharmacolo
Benazepril - Lotensin	Novartis	Medical	Clinical Pharmacolo
Budesonide - Pulmicort	AstraZeneca	Medical	None*
Ciprofloxacin - Ciloxan	Alcon	Medical	Clinical Pharmacolo
Ciprofloxacin - Cipro	Bayer	Medical	Clinical Pharmacolo
Citalopram - Celexa New!!	Forest Labs	Medical	Clinical Pharmacolo
Dorzolamide - Trusopt	Merck	Medical	None*
Esmolol - Brevibloc	Baxter	Medical	Clinical Pharmacolo
Fenoldopam - Corlopam	Abbott	Medical	Clinical Pharmacolo
Fentanyl - Duragesic	ALZA	Medical	Clinical Pharmacolo
Fexofenadine - Allegra	Aventis	Medical	Clinical Pharmacolo
Fluconazole - Diflucan	Pfizer	Medical	Clinical Pharmacolo
Fludarabine - Fludara	Berlex	Medical	Clinical Pharmacolo
Fluticasone - Flonase	GlaxoSmithKline	Medical	Clinical Pharmacolo
Fluticasone - Flovent	GlaxoSmithKline	Medical	Clinical Pharmacolo
Fosinopril - Monopril	Bristol-Myers Squibb	Medical	Clinical Pharmacolo

Glyburide and Metformin - Glucovance	Bristol-Myers Squibb	Medical	Clinical Pharmacolo
Irinotecan - CAMPTOSAR	Pfizer	Medical	Clinical Pharmacolo
Lansoprazole - Prevacid	TAP	Medical	Clinical Pharmacolo
Leflunomide - Arava	Aventis	Medical	Clinical Pharmacolo
Methylphenidate - Concerta	McNeil	Medical	Clinical Pharmacolo
Mirtazapine - Remeron New!!	Organon	Medical	Clinical Pharmacolo
Nefazodone - Serzone New!!	Bristol-Myers Squibb	Medical	Clinical Pharmacolo
Nelfinavir - Viracept	Agouron	Medical	Clinical Pharmacolo
Norgestimate and Ethinyl Estradiol - ORTHO TRI-CYCLEN	Johnson & Johnson	Medical	Clinical Pharmacolo
Ofloxacin - Ocuflox	Allergan	Medical	Clinical Pharmacolo
Orlistat - Xenical	Hoffmann-La Roche	Medical	Clinical Pharmacolo
Oseltamivir - Tamiflu	Roche	Medical	Clinical Pharmacolo
Oxybutynin - Ditropan	Johnson & Johnson	Medical	Clinical Pharmacolo
Paricalcitol - Zemplar	Abbott	Medical	None*
Paroxetine - Paxil New!!	GlaxoSmithKline	Medical	Clinical Pharmacolo
Rofecoxib - Vioxx	Merck	Medical	Clinical Pharmacolo
Sertraline - Zoloft New!!	Pfizer	Medical	None*
Sodium Ferric Gluconate - Ferrlecit New!!	Watson	Medical	Clinical Pharmacolo
Sumatriptan - Imitrex	GlaxoSmithKline	Medical	Clinical Pharmacolo
Temozolomide - Temodar	Schering	Medical	Clinical Pharmacolo
Tolterodine - Detrol and Detrol LA	Pfizer	Medical	Clinical Pharmacolo
Topotecan - Hycamtin	GlaxoSmithKline	Medical	Clinical Pharmacolo
Venlafaxine - Effexor	Wyeth Ayerst	Medical	Clinical Pharmacolo
Zolmitriptan - Zomig	AstraZeneca	Medical	Clinical Pharmacolo

* No clinical pharmacology review was conducted for this drug. back to top of table

Some files may require Adobe Acrobat Reader.

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FDA/Center for Drug Evaluation and Research
Last Updated: August 20, 2004
Originator: OCTAP
HTML by MAU

REVIEW AND EVALUATION OF CLINCIAL DATA

NDA 20-822 SE5-016 63

Sponsor: Forest Labs

Drug: Celexa. (citalopram hydrocloride)

Material Submitted: Pediatric Supplement SE5-016

Date Submitted: 4/18/02

Date Received: 4/19/02

Medical Reviewer: Earl D. Hearst, MD

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Only one of two clinical studies is positive and this supplement is not approvable.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

In our 7/12/02 memo we asked to the sponsor to submit open-label 24 week safety data from these studies at a later date.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Two pharmacokinetic (CIT-PK-07 and CIT-PK-13) and two clinical studies (94 404 and CIT-MD-18) were submitted.

. CIT -PK-07 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. CIT -PK-13 "An Evaluation of the Pharmacokinetics, Safety, and Tolerability of Citalopram in Pediatric and Adult Patients with Depression."

. 94 404 "A Double-blind Study Comparing Citalopram Tablets and Placebo in the Treatment of Major Depression in Adolescents."

. CIT-MD-18 "A Randomized Double-Blind, Placebo-controlled Evaluation of the Safety and Efficacy of Citalopram in Children and Adolescents."

B. Efficacy

Only one of the two clinical studies can be considered positive.

. CIT-MD-18

On the primary efficacy parameter, the change from baseline in CDRS-R at Week 8, citalopram produced significantly greater improvement than placebo.

Change from Baseline to Week 8 in CDRS-R [Mean ± SEM]			
	Placebo (N=85)	*Citalopram (N=89)*	*p-value*
Mean ± SEM	-16.5 ± 1.6	-21.7 ± 1.6	0.038

The citalopram group exhibited significantly greater improvement than the placebo group beginning at Week 1 and at all subsequent clinic visits. Analysis of the response rate on the CDRS-R also revealed a significantly higher percentage of responders (CDRS-R ≤ 28 at study endpoint) in the citalopram group (36.0%) as compared to the placebo group (23.5%) (p=0.041).

. 94 404

In this 12-week study, a therapeutic effect of citalopram in the treatment of adolescent depression as compared to placebo could not be found. The patients showed improvement on the efficacy scales as a function of time, but the placebo response was high and not different from that of citalopram.

C. Safety

There are no significant safety issues in this population. See studies below.

CIT-MD-18

No deaths occurred during the conduct of the study. The rate of discontinuation for adverse events was 5.6% in the citalopram group and 5.9% in the placebo group. There was one serious adverse event, in a placebo treated patient, and one clinically significant ECG abnormality, also in a placebo treated patient.

94 404

No deaths occurred during the study.

Withdrawals due to AEs occurred for 9% of the patients and were similarly distributed among treatment groups.

SAEs were reported by 16 patients in the placebo group and by 18 patients in the citalopram group. The majority of the patients with SAEs reported hospitalizations due to psychiatric disorders (9 patients in the placebo group and 14 patients in the citalopram group). In the placebo group, the other SAEs were surgical interventions (3 patients), epileptic fit, head trauma, medication error, and hospitalization for social reasons. In the citalopram group, the other SAEs were dyspnea, non-suicidal overdose, hospitalization for social reasons, and abortion.

CIT -PK-07

There were no deaths or serious adverse events reported. No patients discontinued from the study due to an adverse event.

There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients.

CIT -PK-13

There were no deaths or serious adverse events reported.
No patients discontinued from the study due to an adverse event.
There were no apparent clinically relevant differences in adverse event type or frequency between the adult and pediatric patients.

D. Dosing

CIT-MD-18

The clinical trial was conducted as a randomized, double-blind, placebo-controlled, multicenter, parallel-group, 2-arm, flexible dose study comparing citalopram (20-40 mg/day) with placebo in pediatric outpatients diagnosed with MDD. The concentration of citalopram was approximately 13% higher in the children as compared to the adolescents.

94404

This was a multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled, flexible-dose study. At screening, patients were randomly assigned to 12 weeks of double-blind treatment with either citalopram 10mg daily or placebo. Based on the investigator's clinical evaluation, there was a possibility of a 10mg dose increase for patients in the citalopram group at the end of Week 1 (to a maximum of 20mg), Week 2 (to a maximum of 30mg), Week 5 (to a maximum of 40mg), or Week 9 (to a maximum of 40mg). The mean citalopram serum concentrations at Week 12 were 130, 217, and 288nmol / L after treatment with 20, 30, or 40mg, respectively.

E. Special Populations

94404

No consistent pattern in serum levels in males as compared to females was observed.

CIT-MD-18

The concentration of citalopram was approximately 13% higher in the children as compared to the adolescents. However, the correlation analyses revealed no significant correlation between age and citalopram concentration (r=-0.059; p=0.650) or escitalopram concentration (r=0.048; p=0.714). Body weight also appeared to be uncorrelated with either citalopram concentration (r=-0.218; p=0.089) or escitalopram concentration (r=-0.119; p=0.357). Improvement on the CDRS-R also showed no significant relationship to plasma levels of either citalopram (r=0.123; p=0.341) or its active enantiomer escitalopram (r=0.104; p=0.422).

F. Exclusivity

Exclusivity has been granted based on the completion of these studies.

NDA 20-415 SE5-011
Sponsor: Organon
Drug: Mirtazapine (Remeron)
Material Submitted: Pediatric Supplement SE5-011
Date Submitted: 5/1/01
Date Received: 5/7/01
User Fee Due Date: 3/7/02 **64**
Medical Reviewer: Ann-Kathryn Maust, MD

Executive Summary

The data presented in this supplement do not support the efficacy of Remeron in the treatment of pediatric MDD. Some of the safety findings may be different from what occurred in adult studies and might need to be noted in the labeling. (For details, see safety results for Studies 003045 and 003047 and the Conclusions and Recommendations section at the end of this review.) Also, the safety data is limited to short term exposure. Additional safety and PK information may need to be submitted.

If labeling revisions will be made as a result of this submission, changes might need to be made to the sponsor's proposed labeling.

The sponsor requested pediatric exclusivity but cannot receive it because a long term study was not done.

Clinical Review

I. Introduction and Background

Organon submitted this NDA supplement after receiving a written request to conduct pediatric studies for Remeron (mirtazapine). The proposed indication is pediatric MDD and the proposed dose is 15-45 mg q day.

Andrew Mosholder, MD, provided mentoring during the writing of this review.

II. Clinical Data Sources

The two pediatric studies that were submitted and reviewed are #003-045 and #003-047. Study 003-045 consists of Studies 1 and 2 and is an efficacy and safety study that also includes some PK information. Study 003-047 is a PK study. The sponsor presented safety findings from Studies 003-045 and 003-047 separately.

III. Clinical Review Methods

A. Materials Consulted in Review

The study reports and raw data were reviewed.

B. Evaluation of Financial Disclosure

Mitchell J. Weinberger, Executive Director of Clinical Development at Organon, certified on Form 3454 that he did not enter into any financial arrangements with the investigators that might have influenced the outcome of the study. He also certified that he acted with due diligence to obtain from the listed investigators or from the sponsor the information required under 54.4 and that it was not possible to do so. The reasons given for not obtaining the information from some of the investigators were the following: (1) no longer employed by site and site unable to locate, (2) unable to obtain required certification. A list of investigators was provided.

IV. Review of Efficacy

A. Design of Protocol # 003-045 (Protocol for Studies 1 and 2)

This was a multicenter, randomized, double-blind, placebo-controlled, flexible/fixed dose efficacy and safety study of Remeron in outpatient children and adolescents with MDD. The primary objective was to compare the efficacy (separately for Study 1 and Study 2) and safety of Remeron to placebo. The planned sample consisted of 123 patients in each of the two studies. The patients in Study 1 were to be enrolled at 17 sites, and Study 2 patients were to be enrolled at 15 sites. A maximum of 18 sites could have been used in each study. In each study, 82 patients were to receive Remeron, and 41 patients were to receive placebo for 56 days. Visits occurred weekly, except Visits 5 and 7 (Days 35 and 49, respectively) were optional. Patients aged 7 to less than 18 years must have met DSM-IV criteria for MDD (non-psychotic, chronic or recurrent) on Kiddie-SADS P-L. In addition, patients had to meet the following criteria at baseline: score of $\geq$ 15 on first 17 items of the HAM-D 21; score of < 70 on C-GAS; raw score of $\geq$ 40 on CDRS-R; must have never taken Remeron. Patients were to be excluded if they had (1) a history of drug or alcohol abuse within 90 days before the first screening; (2)Bipolar I or II or a parent with Bipolar I; (3) ever been diagnosed with an eating disorder; (4) a concurrent diagnosis of OCD or schizophrenia; (5) made a serious suicide attempt during the current MDD episode or had ever made a suicide attempt that resulted in hospitalization; (6) failed > 2 adequate trials of antidepressants; and for other reasons noted on p. 9 of the protocol. Plasma samples were obtained on Days 28 and 56 (or the subject's final day of treatment) for the purpose of analyzing mirtazapine levels.

The active group received a starting dose of Remeron 15 mg qhs, with the option to increase the dose to 30-45 mg in 15 mg increments during the subsequent weeks (up to Day 28). On and after Day 28, patients were to remain on a fixed Remeron dose. The placebo group received placebo qhs. Concomitant use of any other psychotropic drug was not permitted.

The primary efficacy measure was the total CDRS-R (Children's Depression Rating Scale-Revised) raw score. Other assessments that were done are noted in the tables on pages 41-42 of volume 6.

Safety evaluations included the following. At screening: VS, weight, height, PE, ECG, hematology, chemistry, UA, urine drug test, pregnancy test. Throughout the study: AE monitoring, VS, weight. At study end or on final treatment day: VS, weight, height, PE, ECG, hematology, chemistry, UA. The last three tests mentioned were also done on Day 28. Approximately 1 month after the end of treatment, a follow-up interview occurred to evaluate any after effects of treatment.

B. Results of Studies 1 and 2

1. Study 1

Sample characteristics of all subjects treated or AST (which means all subjects who were randomized and received at least one dose of study medication): 44 patients were randomized to placebo and 82 to Remeron. The mean age was 12.3 years for the Remeron group and 12.4 years for the placebo group. In the Remeron group, the male to female distribution was 52.4 % to 47.6%. In the placebo group, the distribution was 43.2% to 56.8%. The percentages of Caucasian and African American patients in the study were 83.3% and 11.9%, respectively. The table below shows the distribution of patients by treatment group.

	Remeron	Placebo
Randomized	82	44
All-Subjects-Treated	82	44
Intent-to-Treat*	82	44
Total Discontinued	13	9
Completed Treatment	69	35

* All patients from the AST group who had at least one post-baseline assessment of the primary efficacy variable

In the Remeron group, 5 patients discontinued due to an AE, 2 discontinued due to lack of efficacy, and 6 discontinued due to other reasons. In the placebo group, 1 patient discontinued due to an AE, 3 discontinued due to lack of efficacy, and 5 discontinued due to other reasons.

The table below shows the mean and median doses for the Remeron AST group.

Mean daily dose range	N	Mean	SD	Median
15-30 mg	26	24.2	5.1	25.6
30-45 mg	56	36.6	2.8	37.5

Analyses of efficacy parameters were based on the ITT group using the LOCF approach. See table below for results for the primary efficacy measure. A statistically significant difference was not observed.

Mean Total Raw CDRS-R Scores in Study 1 (p-value = 0.421)

Remeron (N=82)	35.08
Placebo (N=44)	37.24

Analyses of secondary efficacy parameters revealed no statistically significant differences between the Remeron and placebo treatment groups. (CGAS scores were not compared statistically.)

Conclusion: This trial provides no evidence that Remeron is effective for the treatment child and adolescent MDD.

2. Study 2

Sample characteristics of AST: 44 patients were randomized to placebo and 88 to Remeron. The mean age was 11.9 years for the Remeron group and 12.3 years for the placebo group. In the Remeron group, the male to female distribution was approximately 48% to 52%. The distribution in the placebo group was ~ 46% to 55%. The percentages of Caucasian and African American patients in the study were ~ 78% and 13%, respectively. The table below shows the distribution of patients by treatment group.

	Remeron	Placebo
Randomized	88	45
All-Subjects-Treated	88	44
Intent-to-Treat	83	41
Total Discontinued	19	8
Completed Treatment	69	36

In the Remeron group, 4 patients discontinued due to an AE, 6 discontinued due to lack of efficacy, and 9 discontinued due to other reasons. In the placebo group, 2 patient discontinued due to an AE, 3 discontinued due to lack of efficacy, and 3 discontinued due to other reasons.

The table below shows the mean and median doses for the Remeron AST group.

Mean daily dose range	n	Mean	SD	Median
15-30 mg	44	22.2	5.2	24.4
30-45 mg	44	36.4	3.2	37.3

Analyses of efficacy parameters were based on the ITT group using the LOCF approach. See table below for results for the primary efficacy measure. A statistically significant difference was not observed.

Mean Total Raw CDRS-R Scores in Study 2 (p-value = 0.19)

Remeron (N=82)	35.39
Placebo (N=41)	38.76

Analyses of secondary efficacy parameters revealed no statistically significant differences between the Remeron and placebo treatment groups. (CGAS scores were not compared statistically.)

Conclusion: This trial provides no evidence that Remeron is effective for the treatment child and adolescent MDD.

REVIEW AND EVALUATION OF CLINICAL DATA

65

NDA: 20-152
SUPPLEMENT: S-032
SPONSOR: BRISTOL-MYERS SQUIBB
DRUG: NEFAZODONE HYDROCHLORIDE (SERZONE)
MATERIAL SUBMITTED: Pediatric Exclusivity Supplement
DATE SUBMITTED: 4-16-02
PDUFA DUE DATE: 10-17-02
REVIEWER: Andrew D. Mosholder, M.D., M.P.H.

Executive Summary

I. Recommendations

I recommend a "not approvable" action for this supplement.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program: The following table describes the three clinical trials in this submission.

Study	Description
CN104136	Open label, 8 week pharmacokinetic study; nefazodone 50-300 mg/day (children) and 100-600 mg/day (adolescents); n=28; included long term open label followup treatment ≥ 18 weeks.
CN104141	Randomized, double blind, placebo controlled, multicenter, 8 week trial. Nefazodone 100-600 mg/day versus placebo; n=201 depressed adolescents. Double blind extension treatment of up to 26 weeks.
CN104187	Randomized, double blind, placebo controlled, multicenter, 8 week trial. Nefazodone 100-300 mg/day, nefazodone 200-600 mg/day and placebo; n= 278 children and adolescents with depression. Open label follow up treatment of up to 26 weeks.

This supplement includes safety information on a total of 371 pediatric patients exposed to nefazodone (133 children and 238 adolescents). The total exposure to nefazodone in these trials was 115 person-years. A total of 97 subjects received nefazodone for over 180 days.

B. Efficacy

The results for the two efficacy trials are shown below. Please refer to the table above for information on the study design.

Study 187: The primary outcome measure was the change from baseline in the CDRS-R total score. The results are shown below. Separation between nefazodone and placebo was not demonstrated, and in fact the mean improvement for the placebo group was numerically superior to that of the high dose group.

Treatment	N	Baseline	Mean change from baseline	p-value vs. placebo
Placebo	93	58.3	-21.6	-
Low dose	90	61.2	-23.2	0.43
High dose	90	61.0	-20.6	0.65

Study 141: The primary outcome measure was the change from baseline in CDRS-R (the first 17 items). The mean change from baseline on the CDRS-R total score at endpoint was –25.8 for nefazodone patients and –22.1 for placebo patients (p-value = 0.077).

Secondary outcome measures included the CGI improvement response rate, with response defined as a score of 1 or 2, and the HAMD total score. The percent of patients meeting the aforementioned criteria for response on the CGI was 63% for nefazodone and 44% for placebo (p-value = 0.004). On the HAMD total score, the mean change from baseline to final visit was –9.9 for nefazodone and –8.0 for placebo (p-value = 0.025).

This study provides some evidence that nefazodone is active in the treatment of adolescent major depressive disorder. However, the difference between placebo and nefazodone was only marginally statistically significant on the CDRS-R, the primary outcome measure. Therefor, although there is some evidence of a drug effect, this study does not meet the usual statistical criteria for a positive efficacy trial.

C. Safety: Based upon these trials, the safety profile for nefazodone in the pediatric population does not appear to be significantly different from that in adults. Two nefazodone-treated subjects in these studies developed clinically significant rashes, but causality is difficult to assess.

D. Dosing: No dosing recommendations can be made based upon these data, since efficacy in the pediatric population was not established.

E. Special Populations: This supplement is limited to data in the pediatric population.

CLINICAL REVIEW

NDA: 20-031 **66**
SUPPLEMENT: S-037
SPONSOR: GlaxoSmithKline
DRUG: Paroxetine HCl (Paxil)
MATERIAL SUBMITTED: Pediatric Exclusivity Supplement
DATE SUBMITTED: 4-11-02
PDUFA DUE DATE: 10-11-02
REVIEW COMPLETION DATE: 10-7-02
REVIEWER: Andrew D. Mosholder, M.D., M.P.H.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: In my opinion, the supplement is approvable.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps: In my opinion, no particular Phase IV commitments are necessary.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

This supplement included data from three acute treatment randomized controlled trials in pediatric major depressive disorder (MDD), one acute treatment trial in pediatric obsessive compulsive disorder (OCD), one relapse prevention trial in OCD, and open label treatment. Preliminary safety findings from a recent study in pediatric social phobia were also included. The table below lists the trials.

Study	Description
	Social Phobia
676	Randomized, double blind, placebo controlled, parallel group, 16-week trial; paroxetine 10-50 mg/day versus placebo; n=328 children and adolescents with social phobia. Study completed but only data on serious adverse events available for this submission.
	MDD
329	Randomized, double blind, placebo controlled, parallel group, 8 week trial; paroxetine 20-40 mg/day versus placebo; n=275 adolescents aged 12-18 years with MDD. Continuation phase allowed for up to 6 months of additional double blind medication.
377	Randomized, double blind, placebo controlled, parallel group, 12 week international trial; paroxetine 20-40 mg/day versus placebo; n= 275 adolescents aged 13-18 years with MDD
701	Randomized, double blind, placebo controlled, parallel group, 8 week trial; paroxetine 10-50 mg/day versus placebo; n=203 children and adolescents with MDI

Obsessive Compulsive Disorder	
453	Randomized, double blind, placebo controlled, 16 week relapse prevention trial; 16 week open label treatment with paroxetine followed by randomization of responders to placebo or paroxetine 10-60 mg/day; n= 335 children and adolescents with OCD (in double blind phase)
704	Randomized, double blind, placebo controlled, parallel group, 10 week trial; paroxetine 10-50 mg/day versus placebo; n=203 children and adolescents with OCD
Open label safety	
716	Open label, 6 month extension for subjects in studies 701, 704 or 715; paroxetine 10-15 mg/day; n= 261 children and adolescents with MDD or OCD. Study ongoing as of 10-1-01 cutoff date.
Pharmacokinetic	
715	Open lablel, multiple rising dose pharmacokinetic study; paroxetine 10-30 mg for up to 10 weeks; n=62 children and adolescents with either MDD or OCD

The integrated safety database for this supplement included data on 932 pediatric patients treated with paroxetine, for a total exposure of 283 patient-years.

B. Efficacy

The three randomized, controlled trials in MDD, listed above, all failed to show a separation of paroxetine treatment from placebo on their primary efficacy measures.

Study 377: There were a total of 33 sites in 10 different countries (Belgium, Italy, Spain, U.K., Holland, Canada, South Africa, United Arab Emirates, Argentina, and Mexico). The objective of this study was to evaluate the safety and efficacy of paroxetine in the treatment of adolescent unipolar major depression. The initial phase of the study was a 2-week placebo washout. Following this, subjects were to be randomized to 12 weeks of treatment with either paroxetine or placebo; dosing of paroxetine was flexible (20, 30 or 40 mg daily). Subjects were then tapered off study medication over a 2 week period. The sample was to be 264 outpatients with unipolar major depression, aged 13-18 years. The two primary outcome measures were (1) the proportion of subjects with at least a 50% reduction from baseline in their Montgomery Asberg Depression Rating Scale (MADRS) score, and (2) change from baseline in the K-SADS-L depression subscale. A total of 182 subjects received paroxetine and 93 received placebo. The sample was predominantly female (gender ratio approximatley 2:1) and Caucasian, with a mean age of approximately 15 years. There were no obvious imbalances between treatment groups with respect to demographic characteristics. The results for the primary outcome measures failed to distinguish between paroxetine and placebo. The proportion of patients meeting the response criterion was 60% for paroxetine and 58% for placebo (p-value = 0.62). The mean change from baseline in K-SADS-L depression subscale was –9.3 for paroxetine and –8.9 for placebo (p-value = 0.70). Conclusions: This trial did not provide any evidence that paroxetine is active in the treatment of adolescent MDD.

Study 701: There were 40 U.S. sites and one Canadian site for this trial. The objective of this trial was to compare the safety and efficacy of paroxetine and placebo in the treatment of children and adolescents with MDD. This was a randomized, double blind, placebo controlled, parallel group, flexible dose study. Subjects were to have a screening evaluation followed by a baseline evaluation approximately one week later, and if eligible were then randomized to receive either paroxetine 10-50 mg/day or placebo, for a duration of 8 weeks. Randomization was to be stratified by age group (7-11 years, and 12-17 years). The initial dose was to be 10 mg

daily for all subjects, with dose increases permitted weekly in increments of 10 mg, up to the maximum of 50 mg. At the end of the study the dosage was down-titrated by10 mg/day every 7 days, with discontinuation after subjects received 10 mg for one week. The protocol specified the following as the primary outcome measure: "Change from baseline in Children's Depression Rating Scale – Revised (CDRS-R) total score at the Week 8 LOCF endpoint." The intended sample size was 192. Subjects were to have MDD, with a CDRS-R socre of at least 45 at both baseline and screening. Three hundred five subjects were screened, and 206 were randomized (104 to paroxetine and 102 to placebo). There were slightly more premature discontinuations in the paroxetine group (31) than in the placebo group (23). On the mean change from baseline at endpoint in CDRS-R total score, which was the primary outcome measure, the result for the placebo group was numerically superior to that for the paroxetine group (-23.4 versus –22.6 for placebo and paroxetine, respectively). With respect to secondary outcome measures, there were no results showing statistical superiority of paroxetine over placebo. Conclusions: This trial did not provide any evidence that paroxetine is effective in the treatment of pediatric MDD.

Study 329

There were 13 U.S. sites for this trial. The purpose of this trial, as stated in the protocol, was to "compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression." This was a multicenter, randomized, double-blind, placebo controlled, three-arm, parallel group study. The duration of acute treatment was to be 8 weeks, with the option of a 6-month extension of double blind treatment for subjects who had responded. After a 7-10 day screening period eligible subjects were to be randomized to imipramine, paroxetine, or placebo. The randomization ratio was 1:1:1, with randomization in blocks of 6 subjects. The titration scheduled specified an initial daily dose of imipramine of 50 mg, with titration to 200 mg by the beginning of the fourth week. The dosage of paroxetine was 20 mg which was to be initiated without titration. In the event of inadequate response by the end of 4 weeks, the medication could be titrated up to 300 mg of imipramine or 40 mg of paroxetine. Medication was administered in divided doses on a BID schedule. Concomitant psychotropic medications were prohibited. There were two primary outcome measures specified: the change in HAMD 17 item total score at endpoint, and the proportion of responders at endpoint. A subject was to be considered a responder at week 8 if he or she had a HAMD-17 score $\leq$ 8, or a decrease from baseline in the HAMD-17 of at least 50%. The subjects were to be 300 adolescents, aged 12-18 years, with MDD according to DSM-III-R criteria, and a minimum HAMD-17 score of 12. The current episode of major depression was to be at least 8 weeks in duration. Ninety patients were randomized to paroxetine, 94 to imipramine, and 87 to placebo. Adverse events were the most frequent reason for discontinuation from the imipramine arm; otherwise there were not major differences in the disposition of subjects between treatment groups. Over 70% of paroxetine and placebo patients completed the trial. The result on the HAMD for the paroxetine arm was numerically superior to the other treatment groups, but the difference was not statistically significant. For the second primary outcome measure, the proportion of patients who met the aforementioned criteria for response (HAMD-17 score $\leq$ 8, or a decrease from baseline in the HAMD-17 $\geq$50%), the proportion of responders at endpoint was greater for paroxetine than placebo, but this difference was not statistically significant. The difference in the proportion of responders was, however, marginally statistically significant using an observed cases analysis. On the secondary outcome measure of remission, the percentage of patients with a HAMD score $\leq$ 8 at endpoint, the result was 63.3% for paroxetine, 50.0% for imipramine, and

46.0% for placebo. On this outcome the difference from placebo was statistically significant for paroxetine (p-value = 0.019) but not for imipramine. On the CGI-Improvement scale, the results showed superiority of paroxetine over placebo by a statistically significant margin for the observed cases analysis, but not for the LOCF analysis. Conclusions: Although there was some evidence of activity of paroxetine on the secondary outcome measures, the paroxetine treatment group did not separate statistically from placebo on the a priori primary efficacy measures in this trial. There was no evidence that impramine was more effective than placebo in this trial. On balance, this trial should be considered as a failed trial, in that neither active treatment group showed superiority over placebo by a statistically significant margin.

OCD Study 704:
Please refer to the study report for a complete list of investigators. The purpose of this study was to detemine the safety and efficacy of paroxetine for the treatment of pediatric OCD. This was a randomized, double blind, multicenter, parallel group, flexible dose study. Subjects were to have a screening assessment, followed in approximately one week by a baseline assessment. If subjects met the entry criteria at the baseline evaluation, they were randomized to either paroxetine or placebo. Randomization was to be stratified by 2 age subgroups (7-11 years of age versus 12-17 years of age). The initial dosage of paroxetine was to be 10 mg daily, which could be increased by 10 mg/day at weekly intervals as needed, up to a maximum of 50 mg/day. Placebo patients could receive one to five tablets of matching placebo per day. The duration of the acute treatment phase was to be 10 weeks. There was to be no concomitant psychotropic medication, or concomitant psychotherapy. When discontinuing treatment, subjects were to be down-titrated by increments of 10 mg per week until they had remained on 10 mg/day for 7 days; at that point the medication was stopped. Optional open label treatment, up to 6 months in duration, was to be made available to subjects following the trial (under Protocol 716). Subjects were to be assessed every 1-2 weeks during the acute treatment phase of the trial; efficacy assessments included CY-BOCS and CGI (Severity and Improvement). Subjects were to be between 7 and 17 years old, with OCD for at least 2 month's duration. The goal was to randomize roughly equal numbers of children (aged 7-11 years) and adolescents (aged 12-17 years), with a total of 204 subjects. OCD was to be the primary psychiatric diagnosis, and the CY-BOCS score was to be at least 16 at both the screening and baseline visits. The change from baseline in the CY-BOCS (LOCF at week 10) was designated the primary outcome variable. The study was conducted from January 2000 through July 2001. Of the 265 subjects who were screened, a substantial majority (207) were randomized, 98 to paroxetine and 105 to placebo. Overall, the sample was predominantly male (117 males and 86 females). The mean age of the children was approximately 9 years for both paroxetine and placebo groups, and the mean age of the adolescents was approximately 14 years. The sample was predominantly Caucasian (88%); 6% of subjects were African-American, and the remainder "other." There were no Asian subjects in the trial. The median duration of OCD was 3 years. Psychiatric comorbidity of some type was present in 31% of paroxetine patients and 40% of placebo subjects. The mean daily dose of paroxetine at endpoint was 30.1 mg/day for the entire sample, and was slightly higher for adolescents (36.5 mg/day) than for children (25.4 mg/day). On the primary outcome variable, the week 10 LOCF mean change from baseline in CYBOCS for the intent-to-treat sample, the results were as follows.

	Paroxetine	Placebo
N (ITT sample)	91	98

Baseline LS mean	24.2	25.1
Mean change, LOCF, wk 10	-9.3	-5.5
p-value (ANCOVA)	<0.001*	

* adjusted for baseline score, age group, gender, and psychiatric comorbidity

Conclusions: This trial provides evidence that paroxetine is active in the treatment of pediatric OCD.

OCD Study 453: There were a total of 26 investigators for this trial. All sites were in the U.S. The purpose was to assess the effect of paroxetine treatment on relapse in pediatric OCD patients. This was a multicenter, randomized, double blind, placebo controlled trial. The first phase of the study was to be an open label, 16 week period of treatment with paroxetine. Subjects were administered a starting dose of 10 mg/day, and the dose could be increased to a maximum of 60 mg/day. At the end of the 16 weeks of treatment, subjects were to be randomized to either placebo or paroxetine if they met the following criteria: at least a 25% improvement from baseline on the CYBOCS total score, and a CGI-improvement score of 1 or 2. The dosage during the double blind portion of the trial was not to be adjusted. Subjects who were randomized to placebo were to be down-titrated blindly in increments of 10 mg per week. At the end of double blind treatment, subjects were down-titrated in a similar fashion. The duration of double blind treatment was to be 16 weeks. During the double blind portion of the trial, a subject was to be withdrawn from the trial and referred for treatment if they met any of these criteria: worsening of CGI-improvement score by 1 point for 2 consecutive visits, worsening of CGI-improvement score by >2 points at any visit, or CGI-improvement score >5. The subjects were to be aged 8-17 years, with OCD by DSM-IV criteria as their primary diagnosis, confirmed by the K-SADS-L. The goal was to enroll 375 subjects in open label treatment, with the expectation that 180 of these subjects could subsequently be randomized. Subjects were to have a score of at least 16 on the CYBOCS at both screening and baseline. The primary outcome measure was the proportion of patients who relapsed (according to the criteria above) during double blind treatment. Time to relapse was specified as a secondary analysis. A total of 339 subjects entered the open label treatment phase, and 194 of these subjects were subsequently randomized, 95 to paroxetine and 98 to placebo. The median age was 10 for the paroxetine subjects and 9 for placebo subjects. The sample was over 90% Caucasian. There was a slight gender imbalance between treatment groups; 51% of the paroxetine subjects were female, while only 41% of the placebo patients were female. The intent-to-treat sample included 193 subjects. The percentage of patients who relapsed was 35% for paroxetine and 45% for placebo; this difference was not statistically significant, however (p-value = 0.14). The results varied by age subgroup: subjects under 12 years of age showed a lower percentage of relapsers for paroxetine compared to placebo, while the percentage of relapsers was essentially equal between treatment groups for the adolescents. For time to relapse, the hazard ratio of 1.5 favored paroxetine over placebo, but this was not statistically significant (p-value = 0.10). Conclusions: This trial failed to show that paroxetine is effective in the prevention of OCD relapse in pediatric patients.

C. Safety

The most prominent adverse reactions not seen in corresponding adult trials appear to involve behavioral effects; these events were coded with terms such as hostility and emotional lability. As previously noted, the sponsor's method of coding these events was potentially confusing, and thus additional information will be helpful for the purpose of definitively assessing the potential behavioral toxicity of paroxetine treatment in pediatric patients.

There was one postmarketing spontaneous report that described a fatal allergic reaction in an 11 year old boy following a single dose of paroxetine.

Further assessment of the safety profile will have to await the sponsor's reply to requests for additional information, such as the request regarding ECG data.

D. Dosing

The sponsor's proposed labeling recommends an initial dose of 10 mg daily with titration up to 50 mg/day as needed and tolerated. It also advises that physicians should be mindful of children's lower body weights when titrating the dosage, and that the daily dose should be advanced at a rate of 10 mg/week. This was the regimen employed in the pivotal OCD trial. However, based upon the similarities in pharmacokinetics between adolescents and adults, OCPB has recommended that the 10 mg starting dose be for children only; please refer to Dr. Jackson's review for details.

E. Special Populations: This supplement is limited to pediatric data.

REVIEW AND EVALUATION OF CLINICAL DATA

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NDA: 19-839 SE5-044 and 20-990 SE5-010
SPONSOR: Pfizer
DRUG: Sertraline
MATERIAL SUBMITTED: Pediatric Exclusivity Supplement
DATE SUBMITTED: 12-14-01
DATE RECEIVED: 12-17-01
PDUFA DUE DATE: 10-17-02
REVIEWER: Andrew D. Mosholder, M.D., M.P.H.
REVIEW COMPLETION DATE: 8-13-02

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The sponsor's proposed claim for the treatment of pediatric major depressive disorder is not supported by the data in this submission. Both pivotal studies failed to distinguish sertraline from placebo on the primary outcome measures. The sponsor has proposed pooling the data from the two trials to yield a statistically significant result, on the basis that the trials were conducted under identical protocols. This, however, would be a major departure from our usual policies discouraging pooling of efficacy data.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps If Approvable: This is not applicable.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program: The sponsor conducted two randomized, double blind, placebo controlled, parallel group trials, designated 1001 and 1017. Each trial involved approximately 200 children and was 10 weeks in duration. The protocols for both trials were identical. In addition to these double blind studies, there were 3 open label safety studies, one of which was ongoing at the time of submission.

B. Efficacy: If the data from the two trials are pooled then the results show statistical superiority for sertraline over placebo. However, neither trial by itself showed superiority of sertraline to placebo on the a priori primary outcome measures.

C. Safety: The most important safety finding is the degree of weight loss observed with sertraline in comparison to placebo. Weight loss was particularly prominent among children, with 7.1% of the children on sertraline losing at least 7% of their baseline weight, compared to no children on placebo having such weight loss.

D. Dosing: The dosages studied were identical to those for adults; i.e., 50-200 mg daily.

E. Special Populations: This supplement is limited to pediatric data.

CLINICAL REVIEW

Executive Summary Section

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Clinical Review for NDA 20-151 Supplement SE5-024

Non-Approval Action for Pediatric Supplement for Effexor XR; negative results for Effexor XR in the treatment of Major Depressive Disorder (MDD and negative trial in Effexor XR in the treatment of Generalized Anxiety Disorder) in pediatric patients

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The original supplement for the expanded indications of the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in children and adolescents was submitted September 25, 2002 as Supplement SE5-024 to NDA 20-151. Two of two studies of MDD failed to provide evidence of efficacy over placebo. Only one of two studies provided convincing evidence of efficacy over placebo in the treatment of GAD. It is my view that none of the efficacy results of this negative program for venlafaxine in pediatric MDD and GAD should be noted in labeling. However, there are safety findings of decreased weight gain and growth with venlafaxine use in this pediatric sample and I recommend that they should be added to labeling.

I recommend that the sponsor pool the four, 8-week, placebo controlled studies of MDD and GAD combined and look at the mean changes in weight and height in the venlafaxine treated patients versus the placebo treated patients.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Effexor and Effexor XR are combination serotonin and norepinephrine reuptake inhibitors that are approved for the treatment of Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD) in adults. This supplement was submitted in support of pediatric labeling for Effexor XR in the treatment of MDD and GAD. This supplement presents the results of four studies: two studies in support of a claim for GAD and two in support of a claim for MDD. The MDD studies individually fail to provide evidence that Effexor XR is effective in the treatment of MDD in pediatric patients. Although one of two clinical trials did not individually support the efficacy of Effexor XR in the treatment of GAD, the sponsor proposed that the indication might be approved on the basis of one study.

It should also be noted that the sponsor had sought pediatric exclusivity for this program under FDAMA, and they are given 6 months of additional exclusivity based on the fact that they conducted the studies required under the Written Request. The Written Request stipulated that two positive studies were required to support a claim for MDD and GAD.

Since the proposal was to use the currently approved Effexor XR formulations for this expanded population, there was no need for chemistry or pharmacology reviews. Glenn Mannheim, MD did the primary review of the clinical efficacy and safety data from the clinical group. Fanhui Kong, PhD, from biometrics, also reviewed the efficacy data. Ron Kavanagh, PhD, reviewed the pediatric pharmacokinetic data.

There are two pharmacokinetic studies of venlafaxine in the pediatric population; one is done with the IR formulation (126-US) and one is done with the ER formulation (169-US). 126-US was a multiple dose study and 169-US was a single dose PK study. Dr Kavanagh pointed out that dose normalized AUCs are lower in adolescents than in adults and even lower in preadolescents and younger children. Therefore, Dr. Kavanagh concluded that children, depending on age, might need a 2-4 fold higher dose on a mg/kg/basis as compared to adults. Adolescents needed only a slightly higher mg/kg/dose as compared to adults to achieve equivalent exposures (with the caveat that the exposures to the active metabolites, NDV and NODV, were not considered). However, because effectiveness has not been demonstrated, we will not add pharmacokinetic data for pediatric patients to labeling.

B. Efficacy

Summary of Studies of MDD

Two, 8-week, multi-center parallel group randomized, double blind, placebo controlled flexible dose studies did not provide any evidence of venlafaxine's efficacy in the treatment of MDD in children. These studies employed doses ranging from 37.5 to 225-mg/day. They were adequately powered studies with 161 (103 completing) patients in study 382 and 193 patients (143 completing) in study 394. There were no differences between placebo and drug treatment groups at week eight (8) via the last-observation-carried-forward (LOCF) on-therapy evaluation (382: P=0.338; 394: P=0.386).

Summary of Studies of GAD

The sponsor submitted the results of two 8-week, double blind, placebo controlled, parallel group, flexible dose studies of children aged 6-17 years. Effexor XR demonstrated efficacy in only one of two studies (397-US).

Study 396-US did not separate Effexor XR treatment from placebo at any time point. The following table (Table 9.4.1A) from the sponsor's report shows that there was no time point at which the two treatment groups were significantly different. This difference from study 397-US is difficult to explain. Potential explanations for study failure such as differences in mean ages, placebo responses, drop-out rates, and mean daily doses, were nearly identical across the studies. In the end, drug effect was markedly different between the two studies with a mean adjusted venlafaxine change from baseline in 396-US of -15.5 and in 397-US of -18.7. Treatment separation from placebo was statistically significant starting at week 2 in study 397-US and generally speaking became stronger over the duration of the study. This was not the case in Study 396-US.

Study 396-US Primary Efficacy Variable Analysis Summary

TABLE 9.4.1A. COMPARISON BETWEEN TREATMENT GROUPS FOR C-KIDDIE-SADS GAD 9 DELINEATED ITEMS (INTENT-TO-TREAT PATIENTS) - LOCF ANALYSIS

Week on-therapy	Therapy Group	Number of Patients	Mean Score	Change From Baseline	Adj Change From Baseline	Standard Error	Adj Means (95% CI)	Placebo Minus Ven ER Adj Means (95% CI)	p-Values F-test
Baseline	Placebo	82	39.7				39.5 (39.5,39.5)		
	Venlafaxine ER	78	39.3				39.5 (39.5,39.5)		
Week 1	Placebo	81	35.2	-4.4	-4	0.8	35.5 (34.0,37.0)		0.276
	Venlafaxine ER	74	34.6	-4.7	-5	0.8	34.5 (33.0,36.0)	1.0 (-0.8,2.9)	
Week 2	Placebo	82	31.2	-8.4	-7.9	1.01	31.6 (29.6,33.6)		0.486
	Venlafaxine ER	77	30.8	-8.9	-8.8	1	30.7 (28.8,32.7)	0.9 (-1.6,3.3)	
Week 3	Placebo	82	29.9	-9.8	-9.1	1.06	30.3 (28.1,32.5)		0.257
	Venlafaxine ER	78	28.1	-11.2	-10.7	1.04	28.8 (26.7,30.9)	1.5 (-1.1,4.2)	
Week 4	Placebo	82	29.6	-10.1	-9.6	1.03	29.9 (27.7,32.1)		0.088
	Venlafaxine ER	78	27.2	-12.1	-11.9	1.04	27.6 (25.5,29.7)	2.3 (-0.3,5.0)	
Week 6	Placebo	82	28.6	-11.1	-11.8	1.11	27.7 (25.3,30.1)		0.180
	Venlafaxine ER	78	25.6	-13.6	-13.8	1.18	25.7 (23.4,28.0)	2.0 (-0.9,4.9)	
Week 7	Placebo	82	26	-13.7	-13.9	1.2	25.6 (23.1,28.1)		0.342
	Venlafaxine ER	78	23.7	-15.6	-15.3	1.16	24.2 (21.8,26.6)	1.5 (-1.5,4.5)	
Week 8	Placebo	82	26.7	-13	-12.6	1.17	26.9 (24.4,29.4)		0.060
	Venlafaxine ER	78	23.5	-15.8	-15.5	1.12	24.0 (21.6,26.4)	2.9 (-0.1,5.9)	
Final	Placebo	82	26.8	-12.9	-12.7	1.17	26.8 (24.3,29.3)		0.075
	Venlafaxine ER	78	23.6	-15.7	-15.5	1.12	24.0 (21.6,26.4)	2.8 (-0.2,5.8)	

Study 397-US Primary Efficacy Variable Analysis Summary

TABLE 9.4.1A. COMPARISON BETWEEN TREATMENT GROUPS FOR C-KIDDIE-SADS GAD TOTAL (9 DELINEATED ITEMS) LOCF ANALYSIS

Time on Therapy	Therapy Group	Number of Patients	Mean Score	Adj. Change From Baseline	Standard Error	Adj Means (95% CI)	Placebo Minus Ven ER Adj. Means	p-Value F-test
Baseline	Placebo	77	40.3			40.4 (40.4 - 40.4)		
	Ven-ER	76	40.4			40.4 (40.4 - 40.4)		
Week 1	Placebo	74	36.1	-6.8	0.86	33.5 (31.8 - 35.1)		.683
	Ven-ER	76	35.7	-7.2	0.87	33.1 (31.6 - 34.6)	0.4 (-1.4 - 2.1)	
Week 2	Placebo	77	34.9	-7.1	0.91	33.3 (31.5 - 35.3)		.021
	Ven-ER	76	32.7	-9.8	1.02	30.6 (28.6 - 32.5)	2.7 (0.4 - 5.0)	
Week 3	Placebo	77	32.8	-10.3	1.02	30.1 (27.8 - 32.3)		.005
	Ven-ER	76	29.9	-13.9	1.08	26.4 (24.2 - 28.6)	3.7 (1.1 - 6.2)	
Week 4	Placebo	77	31.7	-12.0	0.93	28.4 (25.9 - 30.8)		.009
	Ven-ER	76	28.2	-15.7	1.19	24.7 (22.3 - 27.0)	3.7 (1.0 - 6.4)	
Week 6	Placebo	77	30.3	-13.0	1.12	27.3 (24.8 - 29.8)		.007
	Ven-ER	76	27.1	-17.0	1.15	23.4 (20.9 - 25.8)	4.0 (1.1 - 6.8)	
Week 7	Placebo	77	30.0	-12.7	1.08	27.7 (25.0 - 30.4)		.002
	Ven-ER	76	25.7	-17.5	1.12	22.8 (20.2 - 25.4)	4.8 (1.8 - 7.9)	
Week 8	Placebo	77	30.2	-12.4	1.18	28.0 (25.1 - 30.8)		< .001
	Ven-ER	76	24.8	-18.6	1.16	21.7 (19.0 - 24.5)	6.2 (3.0 - 9.5)	
Final	Placebo	77	30.2	-12.5	1.19	27.9 (25.1 - 30.7)		< .001
	Ven-ER	76	24.8	-18.7	1.16	21.7 (18.9 - 24.4)	6.2 (3.0 - 9.4)	

Abbreviations: C-KIDDIE-SADS GAD = Columbia-Kiddie Schedule for Affective Disorders and Schizophrenia; LOCF = last observation carried forward; Ven ER = venlafaxine extended release
EFF397.tbl 26 Mar 2002

Conclusions Regarding Efficacy Data

Given the pediatric PK data, under dosing is a tempting hypothesis to entertain for the reason of the failure of study 396-US in GAD; however, the mean age and mean mg/kg dose across studies 396-US and 397-US are nearly identical. This therefore argues against under dosing alone as an explanation for this inconsistency.

Under dosing likewise is probably not the most likely explanation for the failure of the MDD pediatric studies with Effexor XR. Development programs for MDD in children with the exception of fluoxetine are failing even with adequate dosing. This is not the case with OCD. This is even more mysterious given that in adults only about half the doses of SSRIs that are required to treat Panic, OCD and Social Phobia are necessary to treat MDD.

There are no drugs approved for the treatment of GAD in children. Therefore, it is difficult to say whether or not the treatment response of pediatric patients with GAD will behave more like OCD or MDD. In the tricyclic antidepressant (TCA) era, off-label use of TCAs in the treatment of panic disorder was common but there did not seem to be much utility in using these drugs for GAD. OCD did not respond to TCAs in general with the one exception being clomipramine.

Most people would not have predicted the lack of efficacy of SSRI (and now venlafaxine) antidepressant treatments in children given the experience in adults. This lack of predictability and the historical lack of uniformity in treatment response across the anxiety disorders as a group leads me not to endorse the approval of a pediatric indication for GAD based on one positive study and positive results in adults. Though ultimately with experience it may prove to be sufficient evidence for efficacy, there is not enough experience at this point with GAD for me to come to that conclusion.

C. Safety

The pediatric safety of venlafaxine was explored in four placebo controlled 8-week studies (two in MDD and Two in GAD) and one open label extension study of MDD. One other 6-week phase I-II study of Conduct disorder (Study 126) was included in the sponsor's review of the safety. Thus 339 patients were exposed to Effexor XR in the four 8-week placebo controlled studies and 86 MDD patients received Effexor XR for up to 6-months. This represents 52.2 patient-years of exposure in patients with MDD and GAD.

The safety profile of venlafaxine ER in children and adolescents appears to be generally comparable to the safety profile in adults with some differences. The mean increase from baseline in the total serum cholesterol was higher than adults in the pooled GAD, but, not in the pooled MDD trials. A slightly higher mean pulse rate and ECG heart rate in children and adolescents than in adults was seen. Increases in blood pressure in children were of similar magnitude with adults.

In the pediatric population, a smaller increase in height in children in the pooled GAD studies versus placebo was noted. This was not noted in the MDD group; however, it is surprising that this was noted at all in an 8-week study period. Though height was significantly increased from baseline after 8 weeks of treatment for both venlafaxine ER- treated and placebo- treated patients, the adjusted mean increase at month 2 in the placebo group (1.3 cm) was significantly greater than the venlafaxine ER group (0.4 cm). Mean height in the long term open label treated patients only increased 1.2-cm over 6-months.

Both MDD and GAD patients treated with venlafaxine had mean decreases in weight. The mean weight losses were 0.5 kg (MDD) and 0.6 kg (GAD) over an 8-week period while there was a mean weight gain in the placebo treated MDD and GAD patients. Weight changes in both MDD and GAD patients were statistically significant.

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Drug Utilization for Selected Antidepressants Among Children & Adolescents in the U.S.

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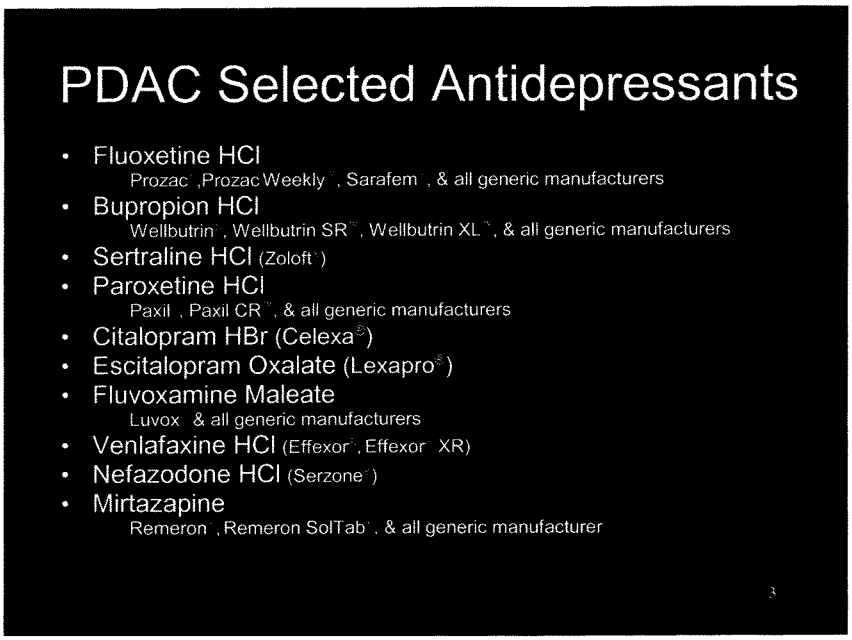
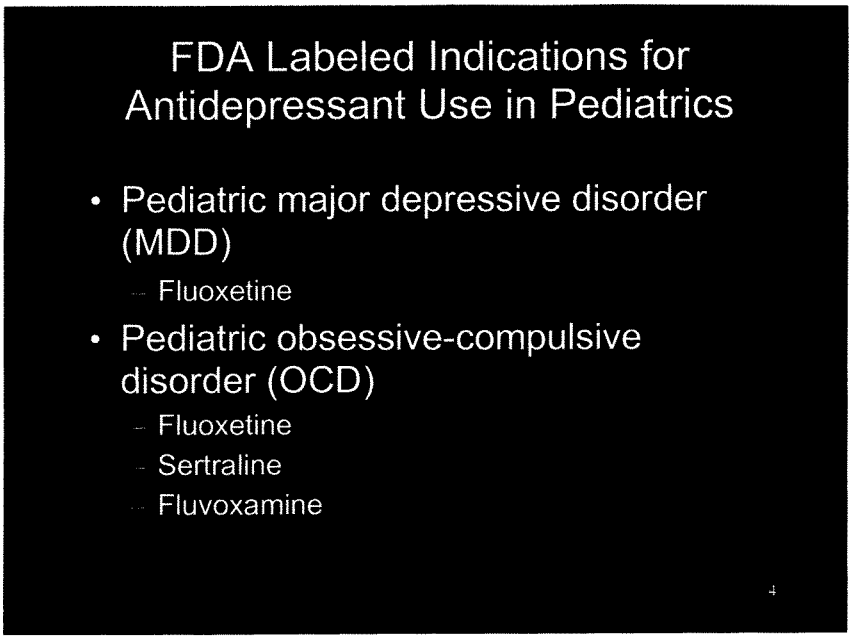
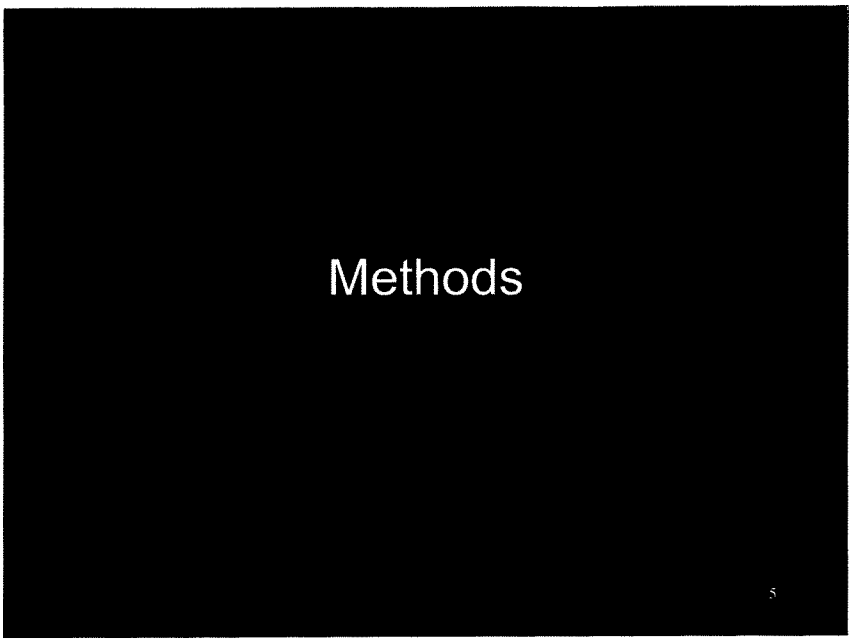
February 2, 2004

Objectives

- To describe the use of selected antidepressant products in 1-17 year olds in the U.S.
- To examine the physician specialties responsible for the prescribing of these products to 1-17 year olds
- To identify the primary diagnoses for which these products are used in 1-17 year olds

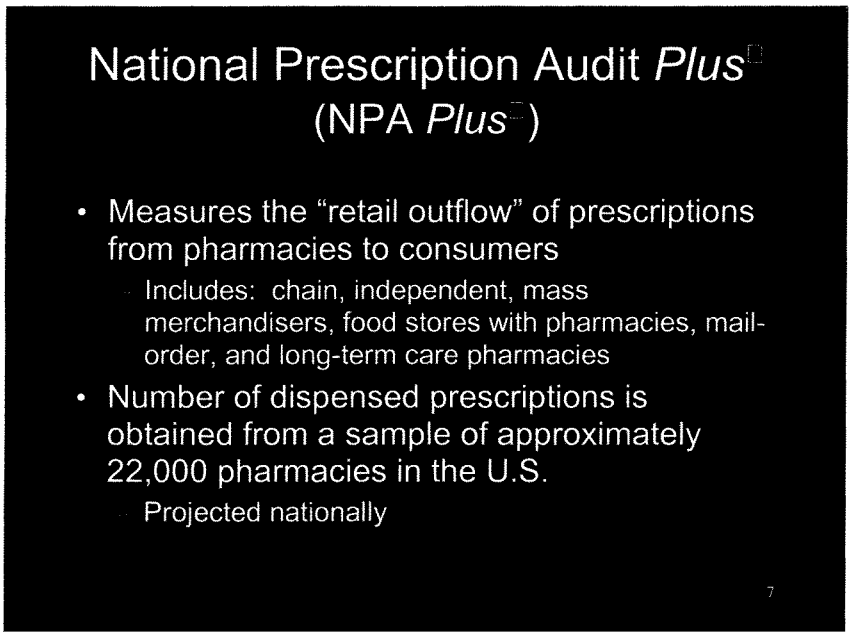

PDAC Selected Antidepressants
• Fluoxetine HCl
Prozac®, Prozac Weekly®, Sarafem®, & all generic manufacturers
• Bupropion HCl
Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®, & all generic manufacturers
• Sertraline HCl (Zoloft®)
• Paroxetine HCl
Paxil®, Paxil CR®, & all generic manufacturers
• Citalopram HBr (Celexa®)
• Escitalopram Oxalate (Lexapro®)
• Fluvoxamine Maleate
Luvox® & all generic manufacturers
• Venlafaxine HCl (Effexor®, Effexor® XR)
• Nefazodone HCl (Serzone®)
• Mirtazapine
Remeron®, Remeron SolTab®, & all generic manufacturer


FDA Labeled Indications for Antidepressant Use in Pediatrics
• Pediatric major depressive disorder (MDD)
– Fluoxetine
• Pediatric obsessive-compulsive disorder (OCD)
– Fluoxetine
– Sertraline
– Fluvoxamine
4


Methods

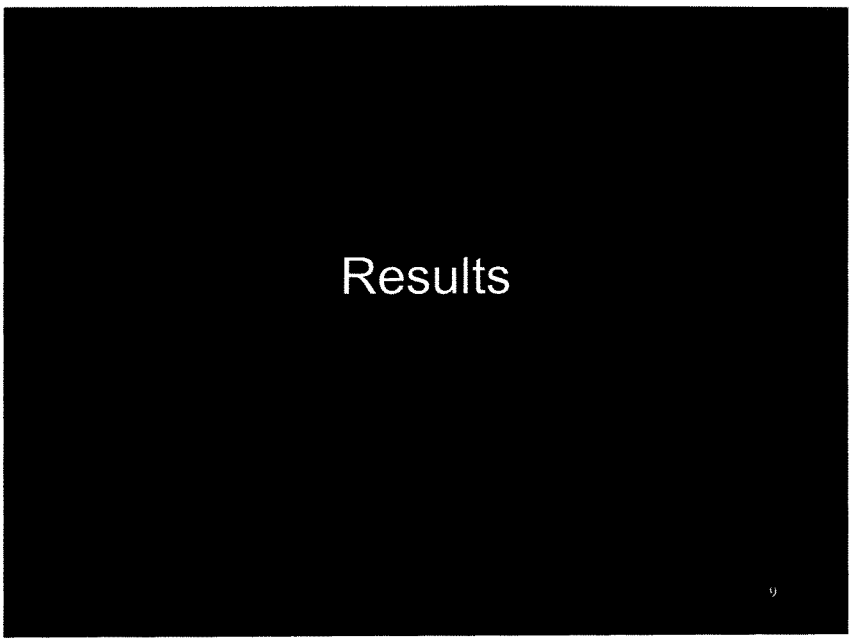
Methods

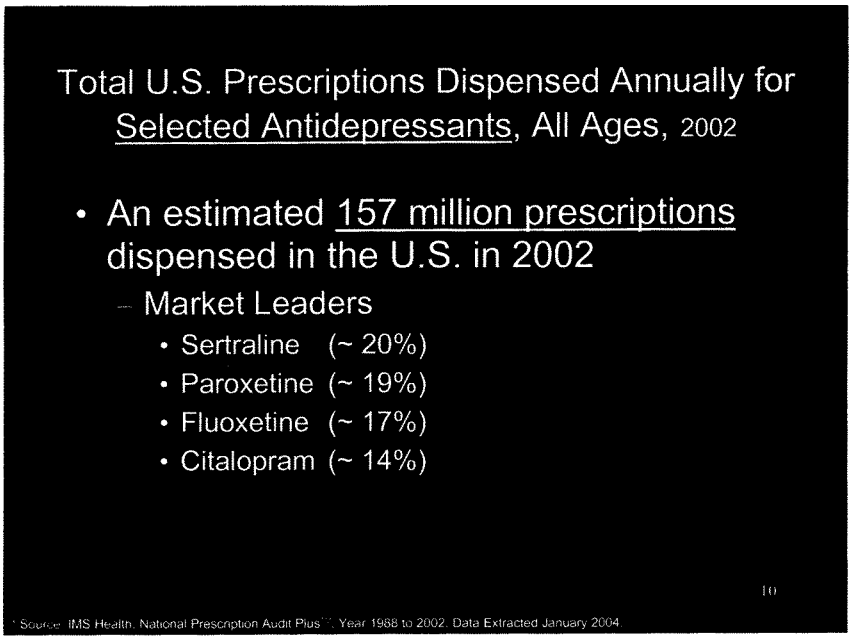
- Data analyzed from January 1988 – December 2002
- Outpatient Drug Utilization Data Sources
  - IMS Health, National Prescription Audit *Plus* (NPA *Plus*)
  - IMS Health, National Disease and Therapeutic Index (NDTI)


National Prescription Audit Plus
(NPA Plus)
• Measures the "retail outflow" of prescriptions from pharmacies to consumers
– Includes: chain, independent, mass merchandisers, food stores with pharmacies, mail-order, and long-term care pharmacies
• Number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies in the U.S.
– Projected nationally
7

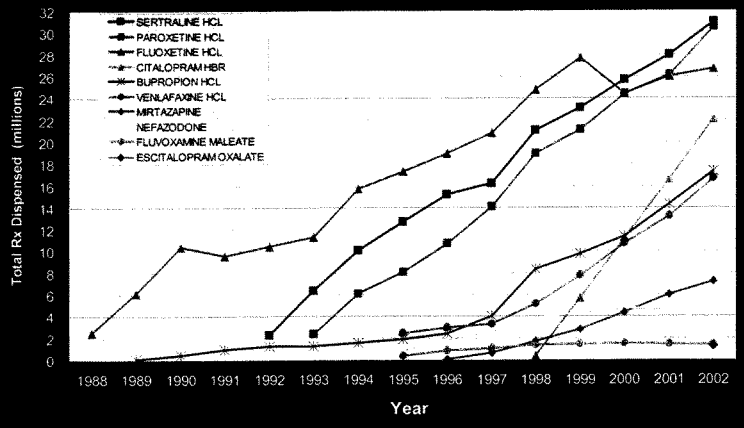
National Disease and Therapeutic Index (NDTI)

- Collects data on drug products and diagnoses mentioned during office-based physician visits
- Provides descriptive information on profiles and trends of diagnoses, patients, and treatment patterns occurring in office-based practice
- Data are gathered from a sample of 2,000-3,000 office-based physicians in the U.S.
  - Projected nationally

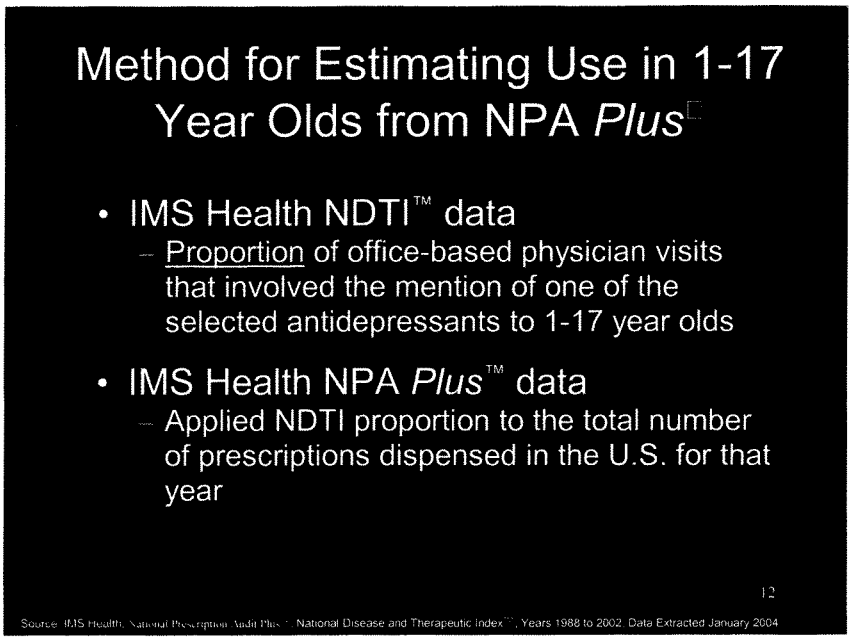

Results

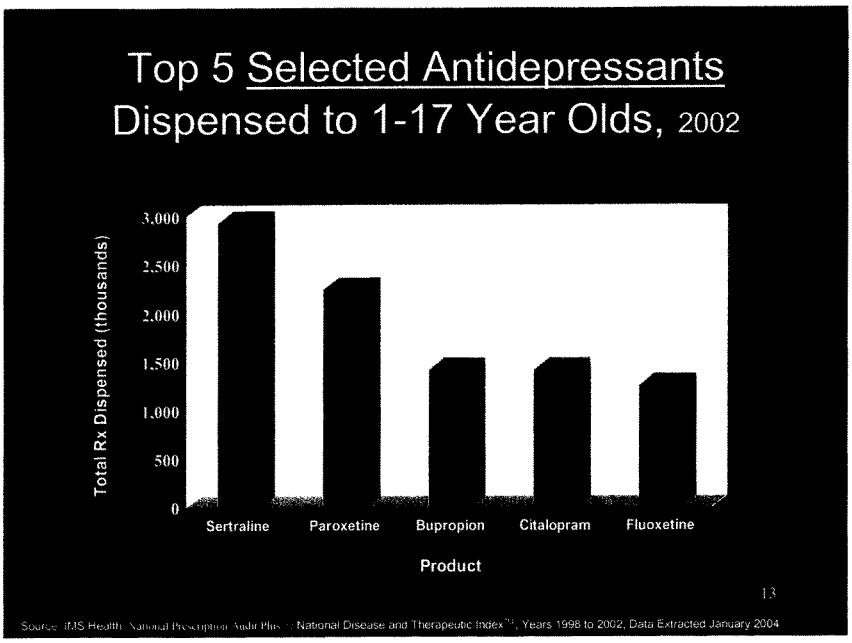

Total U.S. Prescriptions Dispensed Annually for Selected Antidepressants, All Ages, 2002
• An estimated 157 million prescriptions dispensed in the U.S. in 2002
– Market Leaders
• Sertraline (~ 20%)
• Paroxetine (~ 19%)
• Fluoxetine (~ 17%)
• Citalopram (~ 14%)
10
Source: IMS Health, National Prescription Audit Plus™, Year 1988 to 2002, Data Extracted January 2004.

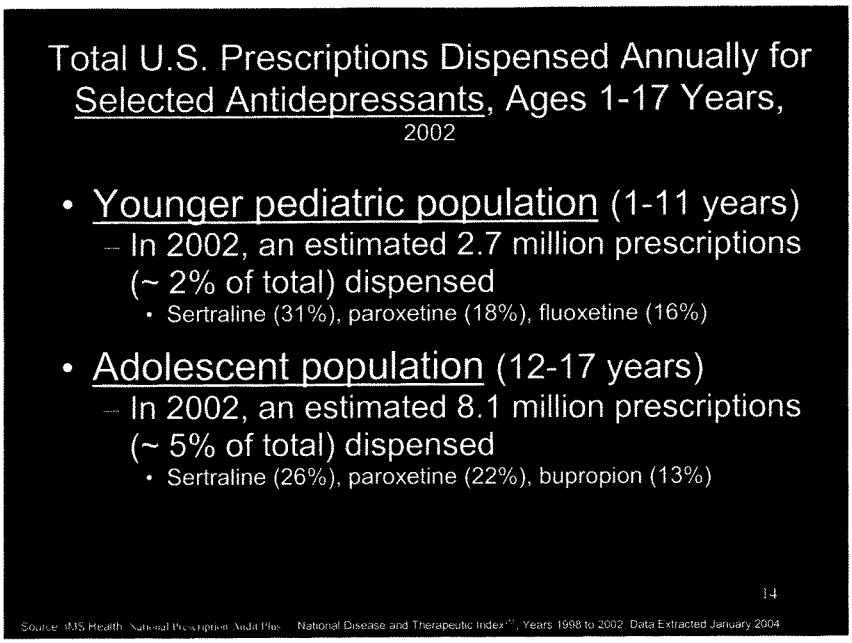
Total U.S. Prescriptions Dispensed Annually for Selected Antidepressants, All Ages, 1988-2002

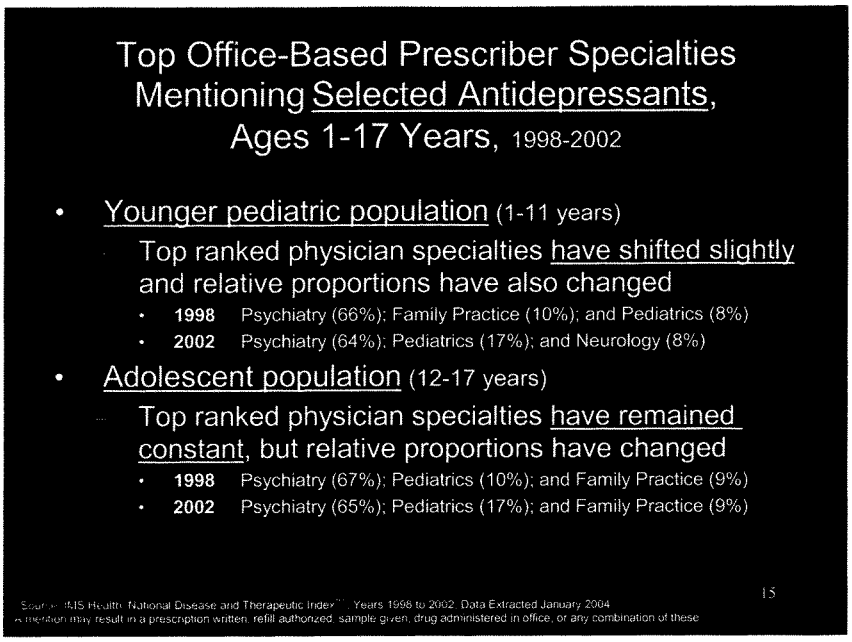


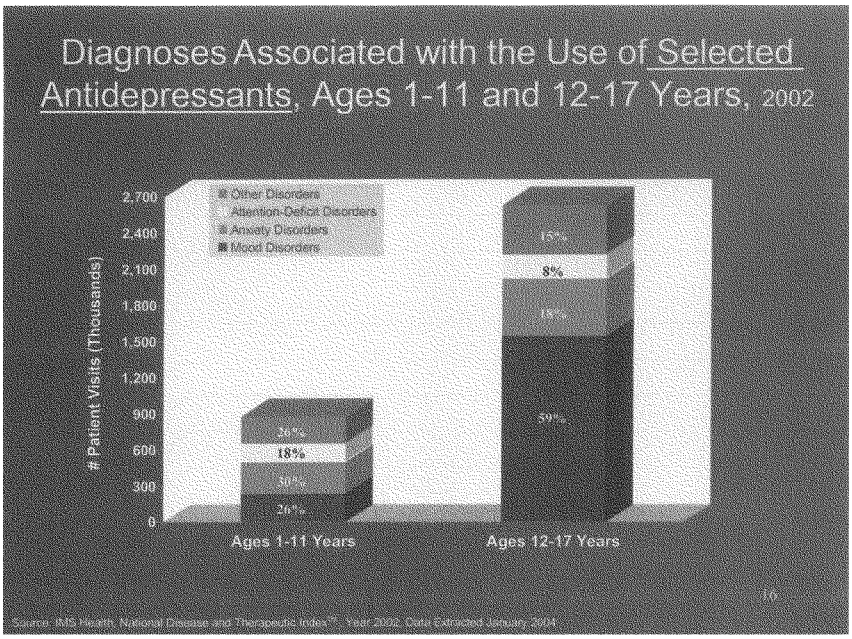
* Source: IMS Health, National Prescription Audit Plus™, Year 1988 to 2002. Data Extracted January 2004.

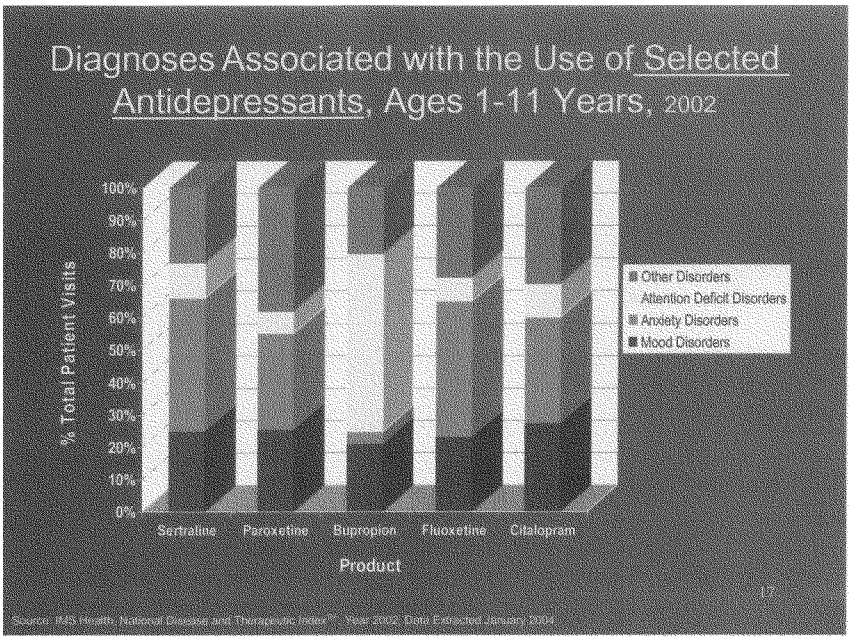

Method for Estimating Use in 1-17 Year Olds from NPA Plus
• IMS Health NDTI™ data
– Proportion of office-based physician visits that involved the mention of one of the selected antidepressants to 1-17 year olds
• IMS Health NPA Plus™ data
– Applied NDTI proportion to the total number of prescriptions dispensed in the U.S. for that year
12
Source: IMS Health, National Prescription Audit Plus™, National Disease and Therapeutic Index™, Years 1988 to 2002. Data Extracted January 2004

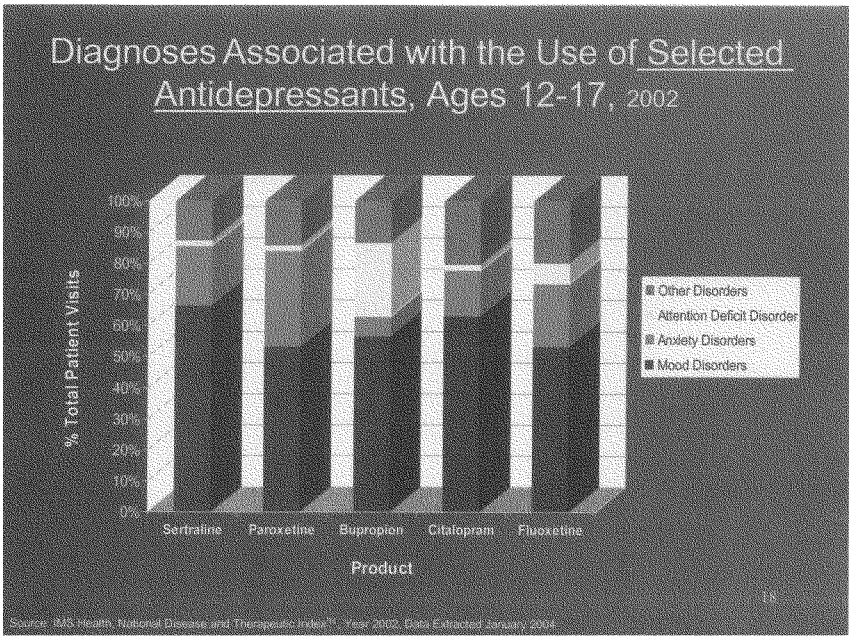

Top 5 Selected Antidepressants Dispensed to 1-17 Year Olds, 2002
Total Rx Dispensed (thousands)
3,000
2,500
2,000
1,500
1,000
500
0
Sertraline
Paroxetine
Bupropion
Citalopram
Fluoxetine
Product
13
Source: IMS Health, National Prescription Audit Plus™, National Disease and Therapeutic Index™, Years 1998 to 2002, Data Extracted January 2004

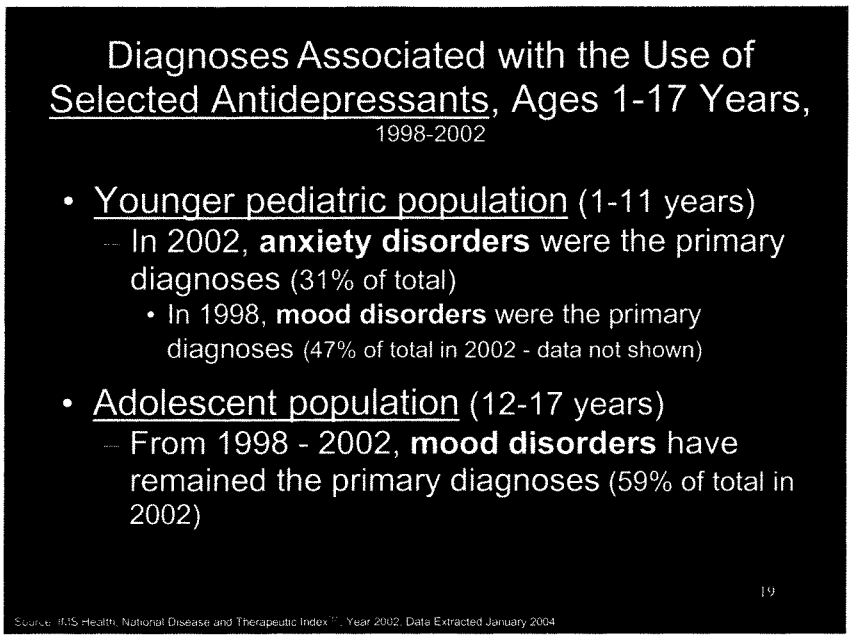

Total U.S. Prescriptions Dispensed Annually for Selected Antidepressants, Ages 1-17 Years, 2002
• Younger pediatric population (1-11 years)
– In 2002, an estimated 2.7 million prescriptions (~ 2% of total) dispensed
• Sertraline (31%), paroxetine (18%), fluoxetine (16%)
• Adolescent population (12-17 years)
– In 2002, an estimated 8.1 million prescriptions (~ 5% of total) dispensed
• Sertraline (26%), paroxetine (22%), bupropion (13%)
14
Source: IMS Health, National Prescription Audit Plus, National Disease and Therapeutic Index, Years 1998 to 2002. Data Extracted January 2004


Top Office-Based Prescriber Specialties Mentioning Selected Antidepressants, Ages 1-17 Years, 1998-2002
• Younger pediatric population (1-11 years)
Top ranked physician specialties have shifted slightly and relative proportions have also changed
• 1998 Psychiatry (66%); Family Practice (10%); and Pediatrics (8%)
• 2002 Psychiatry (64%); Pediatrics (17%); and Neurology (8%)
• Adolescent population (12-17 years)
Top ranked physician specialties have remained constant, but relative proportions have changed
• 1998 Psychiatry (67%); Pediatrics (10%); and Family Practice (9%)
• 2002 Psychiatry (65%); Pediatrics (17%); and Family Practice (9%)
15
IMS Health, National Disease and Therapeutic Index™, Years 1998 to 2002. Data Extracted January 2004
A mention may result in a prescription written, refill authorized, sample given, drug administered in office, or any combination of these


Diagnoses Associated with the Use of Selected Antidepressants, Ages 1-11 and 12-17 Years, 2002
Other Disorders
Attention-Deficit Disorders
Anxiety Disorders
Mood Disorders
Patient Visits (Thousands)
2,700
2,400
2,100
1,800
1,500
1,200
900
600
300
0
36%
18%
20%
26%
15%
8%
18%
59%
Ages 1-11 Years
Ages 12-17 Years
16
Source: IMS Health, National Disease and Therapeutic Index®, Year 2002, Data Extracted January 2004


Diagnoses Associated with the Use of Selected Antidepressants, Ages 1-11 Years, 2002
% Total Patient Visits
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Sertraline
Paroxetine
Bupropion
Fluoxetine
Citalopram
Product
Other Disorders
Attention Deficit Disorders
Anxiety Disorders
Mood Disorders
17
Source: IMS Health, National Disease and Therapeutic Index®, Year 2002 Data Extracted January 2004


Diagnoses Associated with the Use of Selected Antidepressants, Ages 12-17, 2002
% Total Patient Visits
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Sertraline
Paroxetine
Bupropion
Citalopram
Fluoxetine
Product
Other Disorders
Attention Deficit Disorder
Anxiety Disorders
Mood Disorders
Source: IMS Health, National Disease and Therapeutic Index™, Year 2002, Data Extracted January 2004


Diagnoses Associated with the Use of Selected Antidepressants, Ages 1-17 Years, 1998-2002
• Younger pediatric population (1-11 years)
– In 2002, anxiety disorders were the primary diagnoses (31% of total)
• In 1998, mood disorders were the primary diagnoses (47% of total in 2002 - data not shown)
• Adolescent population (12-17 years)
– From 1998 - 2002, mood disorders have remained the primary diagnoses (59% of total in 2002)
19
Source: IMS Health, National Disease and Therapeutic Index™, Year 2002, Data Extracted January 2004

Limitations

- Outpatient Drug Use Data
  - Data on dispensed prescriptions include prescriptions filled in the outpatient pharmacy setting only
  - Prescriptions dispensed for ages 1-17 years extrapolated from physician office visit data
  - Data on prescriber specialties and indications
    - Taken from a sample of 2,000-3,000 office-based physicians
    - A mention of a product during a office visit may not result in a patient actually filling the prescription in a pharmacy

Conclusions

- Antidepressant use among children & adolescents appears to be widespread
  - Increasing annually since 1988
- Psychiatrists, pediatricians, and primary care providers continue to be the primary prescribers
- Diagnoses for the outpatient use of selected antidepressants
  - Ages 1-11 Years
    - Anxiety disorders (31%), mood disorders (27%), attention-deficit disorder (17%)
  - Ages 12-17 Years
    - Mood disorders (59%), anxiety disorders (18%), attention-deficit disorder (8%)

21

PhRMA Clinical Study Results Database Proposal

Background

The PhRMA *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results*[1] (the *Principles*) express the commitment of PhRMA member companies to communicate the results of clinical studies (clinical trials), both positive and negative:

> "We commit to timely communication of meaningful results of controlled clinical trials of marketed products or investigational products that are approved for marketing, regardless of outcome."

While publication of study results in a peer-reviewed medical journal is the preferred method of communication, the *Principles* recognize that not all studies will merit publication in such a journal and thus provide for alternate methods of communication, such as "abstract submission with a poster or oral presentation at a scientific meeting or making results public by some other means."

PhRMA believes an appropriately designed electronic database will also fulfill our members' commitment to communicate meaningful clinical study results. By providing a central, widely accessible repository for clinical trials results and a standardized format for the reporting of such results, a clinical study results database will serve the valuable function of making clinical study results on marketed products more transparent. PhRMA thus supports the establishment of a focused database as described below.

Proposal

A. Elements of the Database

The database should consist of three major elements:

(1) a link to the electronic version of the drug label, where available;

(2) a bibliography of articles on the drug in question that have been published in peer-reviewed medical journals together with a link to the actual article wherever possible; and

(3) a complete summary of each hypothesis-testing trial (as defined below), regardless of outcome, that has not been published in a peer-reviewed medical journal.

The summary should be presented in a standardized, industry-accepted format (see Section B for details). It should provide scientific information in a non-promotional manner consistent with applicable regulatory requirements. This will both facilitate posting to the database and present the data clearly and concisely to those who might use the database. Additionally, given the importance of Food and Drug Administration (FDA) approval and the FDA-approved drug labeling, the database should contain a conspicuous notice referring users to the most current

[1] The PhRMA *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results* can be downloaded from www.phrma.org.

FDA-approved prescribing information on the drug in question, as well as the link to the drug label itself, where available.

Results of Hypothesis-Testing Trials

PhRMA believes that, consistent with the PhRMA *Principles*, the database should consist of the results of all hypothesis-testing clinical trials for products that are approved by the FDA for marketing in the U.S., regardless of the outcome of the trial or where the trial is conducted. Additionally, the database should include only studies sponsored by the drug manufacturer, who is responsible for the quality and accuracy of the study data.

Hypothesis-testing trials are defined in the PhRMA *Principles* as follows:

> "Hypothesis-testing (also known as "confirmatory") clinical trials are always well controlled and are intended to provide meaningful results by examining pre-stated questions (i.e., hypotheses) using predefined statistically valid plans for data analysis, thereby allowing firm conclusions to be drawn to support product claims." (Question and Answer to PhRMA *Principles*, p. 30)

The PhRMA *Principles* further explain that "[h]ypothesis-testing trials may occur at any stage of drug development, and include all phase III trials, some earlier phase trials and many trials of marketed products." Specific examples of hypothesis-testing trials are provided in the PhRMA *Principles (see* Question and Answer to PhRMA *Principles*, p. 31).

Thus, PhRMA member companies are committed to submitting the results of all hypothesis-testing clinical trials on marketed drugs in the U.S. to a database regardless of whether the results are positive or negative. Furthermore, PhRMA commits to assessing this model for future expansion to a global database to include products marketed outside the U.S.

The principal focus of this database is to improve the transparency regarding clinical studies on marketed pharmaceuticals. It is the information on these products and studies that are of most use to physicians, patients, and other users and should be the primary focus of this database.

The Current Approved Labeling

The package insert provides the FDA-approved prescribing information and thus should be the physician's initial focus of attention. Consequently, the database should contain a conspicuous notice referring database users to the most current FDA-approved prescribing information and a link to the electronic version of the prescribing information on the drug in question, where available (if the database later is expanded to apply internationally, the notice can be revised to refer people to the most current, locally approved prescribing information). In addition, the notice should state that the database is being made available for informational purposes only and that prescribing decisions should be made based on the aj proved package insert.

B. Overview of Reporting Format for Clinical Study Results

PhRMA supports the posting of a summary that provides clear and accurate scientific information in a standard, non-promotional presentation format to those who use the database. PhRMA believes that the synopsis described in the E3 Guideline issued by the International

Conference on Harmonization (ICH) addresses this.[2] ICH represents the pharmaceutical regulatory authorities and industry from the United States, European Union, and Japan. Its guidelines are developed via a consensus process and are incorporated into the regulatory requirements of those regions. The E3 synopsis is concise and should contain numerical data illustrating results, not just text or p-values.

C. Timing of Submission

The FDA annual report regulations call for a "summary of completed unpublished clinical trials"[3] to be submitted to the agency one year after completion of the trial(s).[4] PhRMA believes that this is a reasonable target for submitting study summaries to the database. References to scientific papers should be posted when they are published. It must be noted that the posting of any results of a clinical study may be delayed for those studies that have been, or will be, submitted to a journal for publication. Premature disclosure of results may compromise peer-reviewed publication, and pharmaceutical companies have no control over journal publication schedules, which can involve lengthy review processes. The database will indicate those studies that have been submitted for publication following their conclusion. However, if a paper on the study in question has not been published within one year of the announced intent to publish (as indicated in the database), a summary will be posted to the database.

D. Location and Operation of Database

PhRMA supports the creation and administration of an electronic clinical study results database by an independent, non-governmental third party. The database should provide free access to posted clinical trials results by interested health care professionals, patients, and others. The database should accept and post information about clinical study results sponsored by the company that holds the New Drug Application (NDA)/ Biologics License Application (BLA) for the drug when presented in the template described above. In this way, the database administrator and company can assure users that the information is current and accurate.

However, the initial establishment of the database will be undertaken by PhRMA to bring this information forward in a timely manner as a service to the medical community.

E. Proposal Effective Date

PhRMA member companies are encouraged to submit the above information on marketed products to the database as soon as possible following the October 1, 2004, implementation date. The goal of this industry effort is to have substantial information on all trials completed after October 1, 2002 (the effective date of the PhRMA *Principles*), by the one-year anniversary of the establishment of the database. Companies would have the option to post information on studies of marketed products generated prior to the effective date of the *Principles*.

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[2] Structure and Content of Clinical Study Reports; Guideline approved by the International Conference on Harmonization; July 1996; This Guideline is available electronically on the FDA Internet Site at: http://www.fda.gov/cder/guidance/iche3.pdf.

[3] A trial is considered completed upon the last visit of the last patient enrolled in the trial.

[4] 21 C.F.R. §314.81(b)(2).

Appendix – Illustrative Data Fields for the Summary (based on ICH E3 template)

<table>
<tr><td colspan="3">These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert</td></tr>
<tr><td colspan="3">REFERENCE DIRECTING USERS TO APPROVED DRUG LABEL FOR PRESCRIBING INFORMATION
Link to drug label, where available</td></tr>
<tr><td>Proprietary Drug Name</td><td>Generic Drug Name</td><td>Therapeutic area and FDA approved indications</td></tr>
<tr><td colspan="3">Name of Sponsor/Company:</td></tr>
<tr><td colspan="3">Title of Study:</td></tr>
<tr><td colspan="3">Principal Study Investigators:</td></tr>
<tr><td colspan="3">Study centre(s):</td></tr>
<tr><td colspan="3">Publication (reference, if applicable)</td></tr>
<tr><td>Studied period (years): (date of first enrollment) (date of last completed)</td><td colspan="2">Phase of development:</td></tr>
<tr><td colspan="3">Objectives:</td></tr>
<tr><td colspan="3">Methodology:</td></tr>
<tr><td colspan="3">Number of patients (planned and analyzed):</td></tr>
<tr><td colspan="3">Diagnosis and main criteria for inclusion:</td></tr>
</table>

Test product, dose and mode of administration, batch number:
Duration of treatment:
Reference therapy, dose and mode of administration, batch number:
Criteria for evaluation: Efficacy: Safety:
Statistical methods:
SUMMARY – CONCLUSIONS EFFICACY RESULTS: SAFETY RESULTS: CONCLUSION: Date of the report:

DRUG	MANUFACTURER	TOP SALES YEAR	SALES ($ BILLION)	DRUG COMPANY BENEFITS FROM PEDIATRIC EXCLUSIVITY PROVISION ($ BILLION)
71				
PROZAC	Eli Lilly	2000	$2.57	$0.90
ZOLOFT	Pfizer	2003	$2.58	$0.90
PAXIL	GlaxoSmithKline	2002	$2.31	$0.81
LUVOX	Solvay	2000	$0.20	$0.07
CELEXA	Forest Laboratories	2002	$1.52	$0.53
EFFEXOR	Wyeth	2003	$2.05	$0.72
TOTAL				$3.93

○