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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# PSYCHOPHARMACOLOGIC DRUGS

# ADVISORY COMMITTEE

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C O N T E N T S

P R O C E E D I N G S

**Call to Order, Introductions**

DR. TAMMINGA: I would like to call this meeting o order. This is a meeting of the Psychopharmacologic rugs Advisory Committee. We are here today to discuss the ndication of sertraline in PTSD.

I am the chair of the committee and my name is arole Tamminga. I come from the University of Maryland. I as hoping that we could just go around the table and have verybody introduce themselves.

Dr. Brewerton, might you like to start?

DR. BREWERTON: Yes. My name is Tim Brewerton. I .m Professor of Psychiatry at the Medical University of outh Carolina in Charleston.

DR. GELLER: I am Barbara Geller. I am Professor of Psychiatry at Washington University in St. Louis, and I a child psychiatrist.

DR. NORTH: I am Carol North, Associate Professor of Psychiatry also at Washington University in St. Louis.

DR. COOK: Edwin Cook, Associate Professor of Psychiatry and Pediatrics at the University of Chicago.

DR. LACEY: I am Ella Lacey, consumer representative. I am Professor Emeritus, Southern Illinois Jniversity at Carbondale.

DR. WINOKUR: Andy Winokur, Professor of

Psychiatry and Pharmacology at the University of Connecticut Health Center.

DR. HAMER: I am Bob Hamer. I am Associate Professor of Psychiatry at UMDNJ, Robert Wood Johnson Medical School.

DR. TITUS: I am Sandy Titus. I am the Executive Secretary for this committee. I am on the staff of the advisory committee.

DR. SOUTHWICK: I am Steven Southwick, Professor of Psychiatry at Yale University.

DR. DOMINGUEZ: I am Roberto Dominguez, Professor of Psychiatry at the University of Miami.

DR. HEARST: I am Earl Hearst. I am clinical reviewer with the FDA.

DR. SMITH: I am Dave Smith, FDA statistician.

DR. LAUGHREN: I am Tom Laughren, Team Leader for Psychopharm at FDA.

DR. KATZ: Russ Katz, Acting Director, Division of Neuropharm, FDA.

DR. TAMMINGA: Thank you very much.

Now, we will have Sandra Titus read us the conflict of interest statement.

**Conflict of Interest Statement**

DR. TITUS: The following announcement addresses the issues of conflict of interest with regard to this

eeting and is made a part of the record to preclude even he appearance of such at this meeting.

Based on the submitted agenda and the information provided by the participants, the Agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exception: a waiver has been granted to Dr. Robert Hamer.

A copy of this waiver statement may be obtained by submitting a written request to FDA's Freedom of Information Office, located in Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

DR. TAMMINGA: Thank you very much.

Now, Dr. Katz will give us a welcome.

Welcome

DR. KATZ: Thank you. My remarks will be briefer

than any walk I would take to the podium, so I will just do it from here if it's okay.

I just want to extend my personal thanks to the committee members and welcome. I would like to welcome back the old members of the committee and in particular Drs. Brewerton, North, and Southwick; who have graciously agreed to serve as consultants to the committee, and Drs. Winokur and Cook, who are not technically new members, but I believe it is their first meeting with this committee, as it basically is mine, so I hope we will learn together and have an interesting time.

You know we are going to be breaking new ground here today, so we will have some generic questions about PTSD, about the nature of it and the best way to study it. We will also have some, of course, since we are discussing a particular application, we will have specific questions about this application.

There are some interesting facets of the data that raise questions, not about this drug in particular, but also overlap with questions about the fundamental nature of the condition: So, hopefully, it will be an interesting discussion, I think it will be.

Again, I want to welcome you all back. Thank you very much for the work you have done so far and for the work you are about to do today.

With that, I will turn it over to Tom, who will ive us an overview of the issues.

**NDA 19-839 (S), Zoloft (sertraline hydrochloride)**

**Pfizer Proposed Indication: Treatment of PTSD**

**FDA Overview of Issues**

DR. LAUGHREN: I would also like to welcome the ommittee back.

Whenever we are bringing a new indication to the iommittee, we like to broaden the discussion. The focus ;ere clearly today is on this application, but basically, rhat I am saying- is that we would welcome any comments from .he committee about the generic issues having to do with :his indication.

[Slide.]

These are the three areas that I would like to address this morning. As I say, we welcome the committee to r-,.&e comments on PTSD as a new indication, and also comment about some of the general issues having to do with the development of drugs for PTSD.

As I say, the focus of today's meeting is on this application, and there are some very interesting issues that deal specifically with this application. Finally, at the and of the day, as always, we will ask you to vote on the questions of safety and effectiveness for this drug.

[Slide.]

Now, what about PTSD as a new indication? Of course, this is recognized in the sense that it is in DSM-IV, it was in DSM-III, it has been around for a long time. Even so, there may be some questions about this entity that need to be discussed, for example, are the diagnostic criteria that have been proposed reasonable and acceptable.

Some have questioned whether or not this might be too broad an indication in the sense that there are many different kinds of traumatic experiences that may lead to this, and one question would be is that all one thing.

At the other end, one may question whether or not this truly is an independent entity. Obviously, there is overlap in the clinical features of this entity with other psychiatric disorders, in particular with depression. If you look at the diagnostic criteria or the assessment instruments, there is a lot of overlap in the signs and symptoms that are included, and, in particular, major depressive disorder is often a comorbid diagnosis.

So, in that sense, one may ask the question is this a pseudospecific entity in the sense that maybe this is just a subtype of some of other psychiatric disorder.

[Slide. 1

Now, in addition to those generic issues, as I say, we would welcome any comments the committee may have on general issues in the development of drugs for this

disorder. In doing studies, how should one go about recruiting patients and are these DSM-IV criteria the right criteria to use, are there other inclusion criteria that may be appropriate in adding patients to these studies, and what kinds of conditions should be excluded in these trials of patients having major depression as the primary diagnosis were excluded.

Now, of course, secondary comorbid depression was permitted and was quite common. There are pros and cons to excluding other psychiatric disorders. If the entity in clinical practice exists in association with many other disorders, one would like to know how those patients respond in addition to those patients who may have a relatively pure disorder, so there are pros and cons.

[Slide.]

Now, what about the design of these studies? Ordinarily, for chronic disorders, we ordinarily use parallel group studies although one may ask whether or not a crossover study might be appropriate even for a chronic condition, if that condition is very stable over time and there is return to baseline if treatment is stopped.

Now, what about the duration of these trials? In this program, the trials were 12 weeks in duration. Is that the right length of time to study this disorder?

Another issue is the issue of dose/response. The

trials in this program were titration studies. How important is it to explore this issue of dose/response for this disorder?

[Slide.]

Then again, the issue of how you measure it. In this program, the CAPS-2 and the IES were the primary instruments for assessment. Are those valid and reliable instruments? Are there other instruments that may be appropriate for studying this disorder? With those instruments, what would be the appropriate primary outcomes in those trials?-

[Slide.]

Again, as I mentioned, this is a chronic disorder and one may ask the question whether or not there is a need for long-term data and at what point in development should that information become available should that become an issue for approvability.

Now, as an aside, I should say that we have never, up until now, made that a requirement for approving a new indication in psychiatric disorders.

[Slide.]

As you are well aware, in recent years, FDA has been very interested in trying to get companies to do studies of psychiatric disorders in pediatric populations because obviously, these disorders exist in these

opulations, so that is another question for this disorder - .oes this entity exist in children and should we be ncouraging sponsors to develop drugs in this population.

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Now, I want to switch to focus more specifically n this application. One of the questions again is whether r not these clinical trials for Zoloft in PTSD demonstrated n effect that is specific to PTSD, and the corollary of hat is was this effect independent of Zoloft's recognized ntidepressant effect, is this an important question, and ould this be necessary from a regulatory standpoint to have emonstrated some level of independence from its ntidepressant effect.

[Slide.]

Now, there are a number of ways one might explore his question. One approach, of course, is to look at patients at baseline, look at their baseline characteristics, and one could look at PTSD responsiveness with or without comorbid depression, and that has been done here. So, that is one approach.

Another approach would be to look at the response itself and try and assess whether or not a response on what might be considered PTSD measures is independent of an antidepressant response.

Now, one way of doing that is to look to see if

here are measures of PTSD that are in some sense unique to hat disorder and whether or not you can show a response on hose measures.

Another approach would be again to look at the orrelation of the response on PTSD and on depression, and hat has been done in two ways here. The sponsor of this pplication has looked at that correlation directly. Our wn reviewers' used a slightly different approach in which hey categorized the patients on the basis of whether or not hey were showing a response on depression and then looked t the PTSD response in those two subgroups.

[Slide.]

Another important question here that comes up is he fact that there is a very obvious gender interaction. f you look at the two studies that succeeded in showing an verall effect of Zoloft on the identified primary outcomes, nd then you go back and look at the subgroups, males and females, it is clear that the effect is derived, it appears o be exclusively from the women, and so a question for the committee is, is there some explanation for that finding, is his finding consistent with what is being seen in other trials with this disorder, and again, how should this finding be factored into a regulatory decision about the approvability of this application.

[Slide.]

Another issue is the preponderance of evidence. There were four trials submitted in this application. As I mentioned, two of those four studies were successful in showing an overall effect. Again, a question would be is there an explanation for that finding and how should this be factored into a regulatory decision.

Again as an aside, I should mention that in psychopharmacology, of course, it is not at all uncommon for some studies not to make it. That is more the rule than the exception.

[Slide.]

Finally, the issue of safety. This program overall was relatively small, and so in making a judgment about the safety of Zoloft, we are very heavily relying on the safety experience in other populations. So, a question is, is that a reasonable extrapolation.

[Slide.]

Finally, at the end of the day, of course, we will ask you to vote on these two questions - has the sponsor provided evidence for more than one adequate and well-controlled clinical investigation that supports the conclusion that Zoloft is effective for the treatment of posttraumatic stress disorder and has the sponsor provided evidence that Zoloft is safe when used in the treatment of PTSD.

I will stop there.

DR. TAMMINGA: Thank you very much, Dr. Laughren, or your introduction. It seems the committee has a rather xtensive task before itself today, and significant in that his is a drug that is presented for an indication in which drug has not been previously approved.

Now, we are going to hear from the drug company, rom Pfizer about their submission. I would like to point ut to the committee that we have the overheads in the fizer book that is sitting in front of you in case you ould like to follow along.

I would also like to tell the committee that eople are invited to ask questions during the Pfizer resentation, but if you would limit your questions to clarifying questions, not questions of discussion, since we ill hold the discussion at a later time around the estions which Dr. Laughren just put before us, but clarifying questions to the Pfizer presentations are certainly invited.

Dr. Gary Ryan will take over the presentation for Pfizer.

Dr. Ryan.

**Pfizer Presentations**

**Introduction**

DR. RYAN: Dr. Tamminga, Dr. Katz, Dr. Temple,

members of the Advisory Committee, ladies and gentlemen: I am Gary Ryan, Group Director of Clinical Research with Pfizer.

As you know, sertraline is a selective serotonin reuptake inhibitor which is currently approved for worldwide use in patients diagnosed with major depression, obsessive compulsive disorder, and panic disorder.

Today, we will present the results of our clinical development program in patients diagnosed with posttraumatic stress disorder or PTSD. When we began our clinical trial program in 1993, only a few small placebo-controlled trials for PTSD had been published.

The data to be reviewed today from our sertraline clinical program represents the largest controlled PTSD database presented to date. Our data will not only help elucidate the response characteristics of this debilitating disorder, but also demonstrate that sertraline is a safe and effective treatment for PTSD.

Our PTSD clinical trial program consisted of four placebo-controlled trials enrolling a total of 757 patients. One study was conducted in veterans at VA centers, and three were conducted at non-VA sites in a general population of patients with PTSD.

The results across all primary efficacy measures revealed a statistically significant treatment effect in

avor of sertraline versus placebo in two of the three eneral population trials. No significant treatment effect as observed in the fourth trial conducted in the VA etting.

We believe that our presentation today will rovide information relevant to the overall interpretation f the sertraline PTSD program outcome.

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The objectives of our presentation today are wofold - first, to provide a brief overview of osttraumatic stress disorder including its symptoms, revalence, chronicity, and severity of this disorder.

This will be reviewed by Dr. Charles Marmar, rofessor and Vice Chairman, Department of Psychiatry, at he University of California, San Francisco. Dr. Marmar has onducted clinical research in the PTSD field for over 20 ears.

Our second objective today is to review the esults of the sertraline PTSD clinical program. This will e presented by Dr. Gail Farfel, Senior Associate Director rith Pfizer.

Following Dr. Farfel's presentation, I will present a brief overall conclusion highlighting the issues that both we and the Division believe merit discussion here today.

In addition to Drs. Farfel and Marmar, we also ave Dr. Michael Gaffney, Pfizer biometrician, and Dr. atthew Friedman, Professor of Psychiatry and Pharmacology, artmouth Medical School, and Executive Director for the 'ational Center of PTSD, Dartmouth VA Medical Center, who ill all be available to answer your questions.

Thank you. Dr. Marmar will now present an verview of PTSD.

Overview of PTSD

DR. MARMAR: Thank you very much, Dr. Ryan, and ood morning. I am very pleased to have anpportunity to resent to you an overview, however, brief overview of some f the most salient aspects of posttraumatic stress lisorder, and what I am going to be emphasizing are the diagnostic criteria, the magnitude of the public health roblem, and the preliminary understanding of measurement of come and what we know about psychopharmacological reatment to date prior to this current family of studies.

[Slide.]

With respect to the diagnosis of posttraumatic stress disorder, since 1980, there have been a number of refinements, but basically PTSD is. now understood to consist of five criteria.

The first is this is psychiatric disorder which is precipitated by exposure to a markedly traumatic or

stastrophic, often life-threatening, event, and not only ust the event occur, but the individual's reaction at the ime the event occurs must be characterized by intense fear, anic, helplessness or. horror, so there must be an event and rofound emotion emphasizing fear and terror at the time.

Second, should the event occur and the emotional eaction occur at the time, there are three sets of symptom l-asses, which must persist over time in order for an ndividual to qualify for a diagnosis of posttraumatic tress disorder.

These are the reexperiencing or reliving symptoms, fforts to avoid reminders of the trauma, emotional numbing, .nd physiological hyperarousal, and we will say a little ıore in detail about each of these in a moment.

These three classes of symptoms must persist for ıt least one month, often they persist for months, years, or .en decades. In addition to having the event, having the emotional response to it, and reexperiencing it in this way, the symptoms must cause significant impairment in work and relationship function.

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Now, to be a little bit more specific with regard to the DSM-IV criteria emphasizing the three broad classes of symptom response, which are reliving, numbing, and avoidance, and hyperarousal reaction, each of these is

haracterized by a number of typical features.

With regard to the reliving of the traumatic vent, this is most often seen in the form of painful, nbidden, unwelcome thoughts or images that pop into the ind during the daytime, disturbing dreams of the event, hich may be very literal and almost a movielike sequence of eplaying the event, or sometimes a variation of that, and ncluding intense psychological distress when the person is reminded of the event, of course, motivating efforts to avoid reminders.

The second class actually consists of two subclasses - effortful avoidance and numbing of avoidance. Effortful avoidance really represents a very strong wish on the part of the individual with the disorder to not be exposed to cues in the environment which would bring back unbidden painful memories of the event.

That could be individuals, places where the event occurred, or their symbolic equivalence, people who are associated with the events of that kind, so there tends to be a network of cues which can evoke painful reminders of the event, and they are avoided.

Numbing of avoidance consists of feelings of detachment, often a kind of a fairly broad loss of interest in significant activities, and I would also emphasize difficulties in experiencing loving and tender emotions and

lose relationships.

The third class of criterion for the hyperarousal ymptoms includes sleep difficulties which are very ervasive and perhaps often clinically represent the most ifficult complaints of PTSD patients, irritability and nger management, anger, this controls a major public health roblem of chronic severe PTSD, concentration difficulties, ypervigilance, which means being on guard when it is not ecessary to do so, and increased startle reaction and xaggerated startle reflex to unexpected stimuli, typically ounds.

In order for a person to qualify for a DSM-IV liagnosis of posttraumatic stress disorder, they must xperience a catastrophic event, have disturbing emotions, xperience a pattern of symptoms in these three classes, at least one in the reexperiencing, three from the numbing of voidance, and two from the hyperarousal symptom category, and, in addition, these symptoms must persist over time.

I would like to address briefly the magnitude of the public health problem of posttraumatic stress disorder, and I think that posttraumatic stress disorder is not necessarily broadly understood in the scientific or public community to be the substantial public health problem that it is now being demonstrated to be.

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The first thing to note is based on a recent study published by Kessler and colleagues from a national comorbidity study of over 5,000 subjects, a representative sample of American adults, men and women, the lifetime prevalence of posttraumatic stress disorder in the American adult population is 7.8 percent. That is substantially higher than the lifetime prevalence of other well-recognized disorders, such as panic disorder and OCD.

In addition, posttraumatic stress disorder is a very substantial public health problem disproportionately affecting women. Ten percent of women and 5 percent of men will experience a diagnosable posttraumatic stress disorder at sometime during their lifetime. The point prevalences are lower in the 1 to 3 percent range.

The other thing which is of great interest in terms of public health issues is the answer to the question how many people in their lifetime will be exposed to one of these catastrophic events - rape, severe motor vehicle accident, severe exposure to a natural disaster, combat, and other kinds of traumatic events, how many of us in this room will be exposed to this event at sometime during their lifetime.

The data now strongly suggest that 1 out of 2 American adults will experience such a catastrophic event at sometime in their life, and, of those, 10 to 20 percent of

nose exposed will develop posttraumatic stress disorder. hat leaves then, if we take that proportion of the overall, t leads to the 7.8 percent lifetime rate.

Of interest also is the fact that not all raumatic events carry an equal risk of resulting in osttraumatic stress disorder, and among the different kinds f traumatic events, those that are particularly raumatogenic with regard to the risk for PTSD, sexual ssault is perhaps the most substantially important one, ombat and severe accidental injuries.

Natural disasters, by contrast, probably because hey affect very large numbers of people with relative ıoderate levels of exposure for many, but not all, certainly ıot for those who lose their homes and have family and iriends even killed, but for the majority of people in a .arge-scale earthquake or a large-scale hurricane, levels of posure tend to be more moderate. So, the rates of PTSD ıfter large-scale disasters are substantially lower than after sexual assault.

I suppose another question, to cast this in a broad framework, there was originally a kind of bias in this field 20 or 30 years ago, that stress reactions following catastrophic events would be fairly time-limited and would be more analogous to an adjustment reaction or a normal grief reaction, and we now have data to suggest that once

osttraumatic stress disorder becomes established, it tends o be chronic rather than spontaneously remitting, and that, n addition, specifically, the median time to remission is t least three years, and one out of three patients who evelop posttraumatic stress disorder will continue to xperience it for more than a decade.

Just as an example of this, among Vietnam combat eterans who served in the Vietnam theater, who developed osttraumatic stress disorder after the war, one out of two en and one of three women still have full-blown PTSD today ased on the national prevalence study.

[Slide.]

As I mentioned, the traumatic events most likely o precipitate posttraumatic stress disorder in the general opulation are rape and physical assault. I think it is important to note that these are disasters which occur at the hands of other human beings as opposed to being natural disasters. The prevalence is twice as high in women, and not only are twice as many women affected lifetime with PTSD, according to the women's health issues in posttraumatic stress disorder, but once PTSD occurs, women have a much longer duration of illness until average spontaneous remission.

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Posttraumatic stress disorder, like other anxiety

isorders, of course, rarely occurs in its pure form. The ure, noncomordid forms of posttraumatic stress disorder hat are seen clinically tend to occur early on after the rauma, in single event traumas, in well-functioning people ho are hit unexpectedly by a single event, but where ndividuals have been repeatedly traumatized, as in hildhood abuse or in combat or in sexual assault and omestic violence, it stands to be a repeated trauma, and here symptoms occur over time, months, years to decades, he pattern typically is one of high levels of comorbidity.

[Slide.]

What are the primary comorbidities of osttraumatic stress disorder? First, major depression. ndex cases with posttraumatic stress disorder, nearly one and two will have a diagnosable major depression either efore or as a consequence or complication of posttraumatic ress disorder.

Second, substance abuse disorders. These are high rates of comorbidity in PTSD ranging from 27 percent for drug abuse in women with PTSD to 52 percent in men having alcoholism as a comorbidity in a man with posttraumatic stress disorder.

I think if you were to ask the question in America or internationally, what is the treatment of choice for chronic posttraumatic stress disorder, it is not

sychopharmacology, it is not cognitive behavioral therapy, t is self-medication with alcohol and drugs compounding the .ong-term negative consequences of posttraumatic stress lisorder.

There is also a high comorbidity for diagnosable .nxiety disorders including 7 percent for panic disorder and ıp to 31 percent for simple phobias and spreading phobic avoidances.

[Slide.]

Well, if posttraumatic stress disorder has now )een defined clearly with specific diagnostic criteria, so :hat we can arrive at a sense of the magnitude of the public iealth problem, and it tends to be a prevalent and chronic :ondition, the next question then becomes how disabling is :his condition, and I think there was a bias early on in :his literature that not only were stress reactions :ransient, but they wouldn't greatly disrupt working relationship functioning. This has now been shown :onvincingly in a number of studies not to be the case and chronic PTSD, particularly in its comorbid form, is highly disruptive of both somatic and psychological interpersonal functioning.

[Slide.]

There are a number of studies which indicate higher medical and psychiatric comorbidity, a study by

Jonathan Davidson, who note the increased risk of attempted suicide.

I might just diverge for a moment for a personal anecdote. This week, three clinicians from our PTSD group in San Francisco are preparing to leave for Taiwan to provide training for mental health clinicians following the Taiwan earthquake.

The reason we were invited to go to Taiwan is because there has been a dramatic increase in the suicide rates following the Taiwan earthquakes because of destruction of property or injury of family members.

So, suicide rates are an important issue both in the acute and chronic form of PTSD and also, of course, work and social impairment. Most studies that have looked at medical comorbidities have found higher rates of medical comorbidities in PTSD cases compared to individuals who have experienced a catastrophic event and never develop PTSD.

In a study of our own group of male and female Vietnam combat veterans, we show poorer physical health, a number of physical health indices and well-being indices showing poorer functioning and poorer employment.

Of interest in this particular study from our group, a very careful effort was made to control for the effects of the major comorbidities of PTSD. So, in regression modeling, even after one controls for depression,

panic disorder, alcohol, and drug abuse for its effect on functioning, there is still a major independent effect of being diagnosed with PTSD in the combat arena on poor functioning.

The other studies,, I think are basically very supportive of this general picture in poorer vitality, social functioning, and a recent study by North and colleagues from the Oklahoma bombing cohort indicate also the very substantial impact on work and relationship function.

So, the posttraumatic stress disorder is a prevalent, and where chronic especially, a disabling disorder.

[Slide.]

What do we know about the psychopharmacological treatment of posttraumatic stress disorder? There is a lot of data on this slide, and I am going to try to simplify and say what are the major themes which emerge from this review of the published literature of double-blind controlled studies of medication treatment for PTSD.

The first thing to notice is for a condition which affects 7.8 percent of the American adult population at some time in their life, and can be very chronic and disabling, there are a tiny handful of psychopharmacological studies. This a very badly under-researched area in a major public

ealth arena.

The second thing is none of the medications shown ere are approved for the treatment of posttraumatic stress isorder. I think the other things to say is that if one ooks--and this is kind of an informal way of reflecting the ffect sizes for these studies--you can see for the most art the effects, while meaningful, have been modest. In articular, with one notable exception of a study of a onoamine oxidase inhibitor, the effects in veteran opulations, for reasons that are not completely understood, end to be poorer than the effects in the general opulation.

As one example of that, a study by van der Kolk, hich examined both veterans and general population with SSRI fluoxetine, showed good effects primarily in women urvivors of childhood sexual abuse and poor effects in predominantly male veterans.

The other thing to note is if one looks at the total N of all patients enrolled in randomized controlled trials in the world published literature for posttraumatic stress disorder to date, including those assigned to the placebo condition, it is only slightly over 400 in the entire world literature.

[Slide.]

I would like to conclude by saying just a few

brief remarks concerning measurement of PTSD in a clinical trial outcome setting and comment on a few measures.

I would like to say with regard to the Impact of Event Scale, which was a measure developed in our own group at the University of California at San Francisco in the late 1970s, this is a broadly used measure. It has been used in over 250 publications worldwide on the psychopathology and treatment of PTSD.

It was the first major patient self-report measure to be widely validated for posttraumatic stress disorder. The measure does, however, have a significant limitation, and that is, it measures only the reliving and numbing and avoidance symptoms of PTSD, and entirely does not assess very important hyperarousal symptoms of PTSD, and for that reason, in our group, we have revised the Impact of Event Scale in 1997 for the form which we now call the IESR, which does include all 17 of the symptoms of DSM-IV PTSD, and we no longer recommend the use of the Impact of Event Scale, because it neglects a major domain of PTSD symptom response.

With regard to other important measures, in terms of clinician assessment of posttraumatic stress disorder, there is now a structured diagnostic interview protocol, referred to as the CAPS, Clinician-Administered PTSD Scales. There are several variations of this.

This measure has been developed by the Boston

Division of the National Center for Posttraumatic Stress Disorder, and is broadly considered to be the gold standard of assessment for posttraumatic stress disorder from a clinician evaluator perspective.

Finally, Jonathan Davidson and his colleagues at Duke have developed the Davidson Trauma Scale, which unlike the IES and more like the IESR, is comprehensive for assessing from patient self-report perspectives all 17 of the reexperiencing, numbing/avoidance and hyperarousal symptoms as defined by the DSM.

I would like to conclude at that point and before introducing Dr. Farfel, who will continue with the next presentation, I would be pleased to answer briefly any of your questions, and Dr. Matthew Friedman, who is also here, is the Executive Director of the National Center for PTSD, and I will be working closely to answer questions you have today of a general nature about PTSD.

Are there any questions at this point?

DR. TAMMINGA: Do any of the committee have questions for Dr. Marmar?

[No response.]

DR. MARMAR: If not, I am pleased to introduce Dr. Farfel, who will give the next presentation.

**PTSD Clinical Program/Efficacy and Safety**

DR. FARFEL: Thank you, Dr. Marmar.

[Slide.]

Good morning. I will be presenting to you now Pfizer's clinical development program for sertraline in the treatment of posttraumatic stress disorder or PTSD.

I will review with you the design and conduct of the four clinical trials, as well as the efficacy results, and then provide a brief review of the safety results.

[Slide.]

There were four double-blind placebo-controlled trials in Pfizer's clinical development program. Two initial trials, Studies 640 and 641, were run from 1994 through 1996, and two confirmatory trials, Studies 671 and 682, were run from 1996 through 1998.

The design of the four trials was essentially the same, and the major difference among them was that Studies 640, 671, and 682 were conducted in civilian medical centers, recruiting primarily from the general population, while Study 641 was conducted at VA medical centers, recruiting primarily from the veteran population.

All four trials were of 12 weeks in duration, and the mean number of subjects in each treatment group in each trial was approximately 95, for a total of 376 subjects treated with sertraline and 381 subjects treated with placebo in the program.

[Slide.]

The subject selection criteria for the four trials re listed here. Subjects were to be outpatients of at east 18 years of age, who met DSM-III-R criteria for osttraumatic stress disorder with a duration of symptoms of .t least six months.

Subjects were to have a CAPS-2 rating of at least 0 at baseline, and were not to have a concurrent primary ood or anxiety disorder, although they were allowed to have mood or anxiety disorder considered secondary to PTSD.

Subjects were not to have a current or lifetime istory of a psychotic disorder or bipolar disorder, nor ere they to have met criteria for substance abuse disorder within six months of trial entry.

Last, no behavioral therapy was to be initiated or ngoing at study entry.

[Slide.]

In all four of the clinical trials, subjects began aith a one- to two-week single-blind placebo run-in followed by 12 weeks of randomized treatment with either sertraline or placebo, and there was a one-to-one randomization to sertraline and placebo.

Subjects were dosed once daily beginning with 25 mg/day in the first week and then continuing flexibly titrated between 50 and 200 mg/day thereafter.

Study visits to assess the efficacy and safety

ere conducted weekly from weeks 1, 2, 3, and 4 followed by. iweekly visits at weeks 6, 8, 10, and 12.

[Slide. 1

This slide here lists the primary efficacy easures that were used in Pfizer's clinical trial program. 'he Clinician-Administered PTSD Scale has two parts, Part 1 nd 1. Part 1 is used for diagnosis of PTSD as it was used .n these trials, and Part 2 assesses all 17 of the liagnostic symptoms of PTSD covering all three of the symptom clusters - reexperiencing/intrusion, avoidance/numbing, and hyperarousal. The CAPS-2 is rated by he investigator.

The Davidson Trauma Scale mirrors the same 17 questions as the CAPS-2, covering all three symptom clusters of PTSD, and is rated by the patient.

The Impact of Event Scale, as Dr. Marmar just spoke about, assesses mainly symptoms of intrusion and avoidance, and is rated also by the patient.

The CGI, the Clinical Global Impressions, ratings of severity of illness and improvement are rated by the investigator.

At the time Pfizer began its clinical development program, the Davidson Trauma Scale, or DTS, was being proposed as a replacement for the IES because it assessed all 17 diagnostic symptoms of PTSD, however, at that time in

993, the DTS had not been validated, so it was denoted as a secondary efficacy measure.

Since completion of our clinical trial program, the validation of the DTS has been completed, and it has been shown to be a sensitive and specific and reliable measure of change in PTSD symptoms. For this reason, we will be presenting the Davidson results along with the other primary measures in this presentation.

[Slide. 1

Additional specifics about the PTSD specific symptom measures-are listed here. The CAPS is a structured interview of 30 items which assess the core diagnostic and associated symptoms of PTSD, associated symptoms being symptoms, such as homicidality or survivor guilt.

The primary efficacy measure concerns the CAPS total severity score, which is the sum of the first 17 items, the 17 diagnostic symptoms, assessing both the frequency and the intensity of the symptom on a scale from zero to 4, so the maximum possible total score on the CAPS total severity score is 136 points.

The Davidson Trauma Scale is a patient self-report instrument which also assesses the.17 diagnostic symptoms of PTSD, also in terms of frequency and intensity of the symptom on a scale of zero to 4. So, the maximum score on the Davidson Scale is also 136 points.

The Impact of Event Scale is a patient self-report nstrument which assesses mainly the intrusion and avoidance ymptoms of PTSD, and not numbing or hyperarousal. There re 15 items on the Impact of Event Scale, rated from zero eaning not at all, 1 meaning mild, 3 moderate, or 5 severe, or a maximum total score of 75 points.

[Slide. 1

The next three slides present the subject haracteristics and demographics of the subjects in the PTSD rogram. The three studies run in the general population. tudies 640, 671, and 682 are to the left, and the study run n the VA medical centers, Study 641, is to the right.

Overall, in terms of demographics, there were no ifferences between treatment groups or among the three eneral population studies, whereas, the subjects in the VA study, Study 641, were different, and I will note that an sterisk does denote statistical significance at the 0.05 **Level,** red underlines, red underscores denote that the proportion of subjects in that study differed from the other three studies.

In terms of gender, there were significantly fewer females in the VA study, approximately 20 percent versus 75 percent in the general population studies. There were fewer whites in the VA study compared to the general population studies, and the mean age in the VA study was approximately

5 years compared to 39 years in the general population studies.

The mean weight in the VA studies was slightly higher than that of the general population studies, which would be expected in a study populated primarily by males, and the mean duration of illness in the VA study, at 18 years, was longer than the mean duration of illness in the general population studies.

[Slide. 1

Many subjects who suffer from posttraumatic stress disorder have been exposed to more than one traumatic event, so the index traumatic event was defined at study entry as the trauma that was most troubling to the patient at the time of study entry.

In the three general population studies, primarily, subjects were the victims of sexual or physical assault, and the majority of them suffered from childhood abuse. That category included childhood sexual abuse, childhood physical abuse, or childhood emotional abuse.

In contrast, in study 641, the VA study, significantly fewer subjects were the victims of childhood abuse, and the majority of the subjects had suffered traumatic events connected to being in war or combat.

[Slide.]

As stated by Dr. Marmar in the introduction,

omorbidity with-PTSD is common. In these four double-blind rials, approximately 40 percent of subjects had a comorbid epressive disorder diagnosed by the investigator, and pproximately 22 percent had a comorbid anxiety disorder.

In terms of comorbid drug abuse or alcohol abuse istory, a significantly greater proportion of subjects in he VA Study 641, had a prior history of drug abuse, and ignificantly greater proportion of subjects in Study 641 ad a prior history of alcohol abuse.

These proportions of comorbidity are consistent rith what was seen in the National Comorbidity Survey ncluding the proportion of history of alcohol abuse or drug buse in which it has been shown in several studies that nales tend to have a higher comorbidity of alcohol and drug buse than females.

In terms of history of prior treatment, there were #differences between treatment groups or among the four studies in a proportion of subjects who reported a history of prior treatment.

[Slide.]

The mean dose of sertraline among the four studies by visit week is shown on this table. In all four studies, subjects began at 25 mg once daily for one week, and then were flexibly titrated between 50 and 200 mg based on efficacy and tolerability.

There was no difference among the four studies in the rate of increase of the titration, and completers at week 12 in all four studies were at approximately 150 mg per day, and at endpoint were at approximately 135 mg per day.

[Slide.]

The baseline scores of subjects in the four trials are shown on this table. As a reminder, the Clinical Global Impression rating of improvement is not assessed at baseline.

On the CADS and the DTS, both of which have a maximum possible score of 136, and which have identical question structures and scoring, there was consistency between the treatment groups and among all four studies in the baseline scores, indicating patients of moderate to marked severity of illness.

On the Impact of Event Scale, with a maximum total of 75 points, there was a mean at baseline in all four studies with no difference between treatment groups of approximately 39 points, and on the CGI severity rating, the mean across all four studies was approximately 4.5, again indicating subjects with a moderate to market severity of illness at baseline.

The next series of slides will present the efficacy results from the four trials. I would like to take a moment to orient you to this slide first.

[Slide.]

This slide shows the main efficacy results from study 640, the adjusted mean change from baseline to endpoint on the primary efficacy measures.

Sertraline-treated subjects are represented by the. red bars and placebo-treated subjects are represented by the blue bars.

In the first panel, the results of the CAPS and the Davidson are shown. The second panel contains the results of the Impact of Event Scale, and the third panel contains the results of the CGI ratings of severity and improvement.

In Study 640, on all five of these measures, sertraline-treated subject were significantly improved compared to placebo-treated subjects on all five of these measures.

The next three slides will show you, first, the adjusted mean change by visit week for the observed case analysis for Study 640 for the CAPS and the DTS. Following that, we will show you the mean change in the CAPS by subjects, by discontinuation, by visit week, and then we will show you the LOCF analysis.

[Slide. 1

On the CAPS-2 for Study 640, subjects began to separate, sertraline-treated subjects began to separate from

placebo at week 6 and continued separated through week 12, but reaching statistical significance only at endpoint.

On the subject-rated Davidson Scale, separation began at week 1 and continued reaching significance at week 12 and at endpoint.

[Slide. 1

This graph shows the mean change on the CAPS-2 for study 640 subjects at time of discontinuation. The visit week is on the bottom, and the numbers up here are the N's, the number of subjects that discontinued at any given visit week. The week 12 numbers represent subjects who completed the trial, and then the LOCF analysis is here over to the right.

Sertraline-treated subjects had improved to a greater extent compared to placebo-treated subjects at time of discontinuation at each visit week except for visit week 8 pin which two sertraline subjects had worsened as opposed to improving.

[Slide.]

In the LOCF analysis of the mean changes by visit week for the CAPS-2 and the DTS for Study 640, sertraline-treated subjects were improved compared to placebo at week 6, but reached statistical significance only at week 12, whereas, with the patient-rated Davidson Scale, sertraline-treated subjects were improved compared to placebo-treated

ubjects at each visit week except for weeks 3 and 4.

[Slide.]

The primary efficacy results for Study 671, the econd general population study, are shown here. On four of he measures, the CAPS, the DTS, and the CGI ratings of everity and improvement, sertraline-treated subjects were ignificantly improved compared to placebo subjects.

In the Impact of Event Scale, sertraline-treated ubjects numerically were improved compared to placebo with significance level of p equals 0.07.

[Slide.]

In the observed case analysis on the CAPS and the TS in Study 671, referring to the CAPS panel to the left, ertraline-treated subjects were significantly improved ompared to placebo beginning at week 2 and continuing hrough the remainder of the study.

On the patient-rated DTS, sertraline-treated subjects were improved at multiple time points during the ourse of the study.

[Slide.]

Turning to the graph looking at the mean change in APS score for subjects who discontinued Study 671, reminding you that the completers are over here at week 12 and the LOCF analysis is here to the right, sertraline-treated subjects who discontinued prior to endpoint had

improved compared to placebo-treated subjects at each of the other visit weeks.

[Slide.]

On the LOCF analysis of the CAPS-2 and the DTS for Study 671, sertraline-treated subjects were significantly improved compared to placebo-treated subjects beginning at week 4 and continuing through the remainder of the study on both of these measures.

[Slide.]

The primary efficacy results for Study 682, a third of the general population studies are shown here. In this study, sertraline-treated subjects, signified by the red bars, were not improved compared to placebo-treated subjects on any of the measures, and on the Impact of Event Scale, placebo-treated subjects were significantly improved compared to the sertraline-treated subjects.

The by week analysis of the CAPS or the Davidson for Study 682 did not show the emergence of a treatment effect in favor of sertraline at any of the visit weeks.

[Slide.]

In the fourth study, Study 641, the study conducted in VA medical centers, the sertraline-treated group was not improved compared to the placebo-treated group on any of these five efficacy measures.

What is notable here is that the magnitude of the

change for the sertraline-treated patients compared to the placebo-treated patients is less in this study than was seen in the three general population trials.

Again, the by week analysis of the CAPS and the DRS data did not show an appreciable sertraline treatment effect at any of the visit weeks.

[Slide.]

A post hoc responder analysis was conducted where the definition of a responder was a 30 percent decrease in the CAPS-2 total severity score and a CGI improvement rating of 1 or 2 at endpoint corresponding to much improved or very much improved.

The responder criteria were determined as a consensus of clinician experts who were not familiar with the results of the trials at the time that they were determined. Again, the sertraline-treated subjects here are represented by red bars and the placebo-treated subjects by the blue bars.

In the two positive trials, Study 640 and 671, a significantly higher proportion of sertraline-treated subjects achieved responder status compared to placebo subjects.

In the other two trials, 682 and 641, there was not a significant difference in the proportion of sertraline-treated responders and placebo-treated

esponders.

[Slide.]

To summarize, two of three studies of subjects rom the general population demonstrated the efficacy of ertraline in the treatment of posttraumatic stress isorder.

In a fourth study, conducted primarily in veterans n a VA setting, the fourth study did not provide evidence hat sertraline was efficacious in treating PTSD in this opulation.

[Slide.]

In order to further characterize the effects of ertraline in the PTSD population, we conducted additional nalyses to examine the effect of sertraline-treatment on he symptom clusters of PTSD to also examine whether there ras a treatment by gender effect, and last, to investigate :' issue of comorbidity and the overlap of symptoms between ?TSD and comorbid disorders.

I will note that none of the studies was prospectively powered for conducting these additional analyses.

The next three slides show the results of the analyses of the symptom clusters of PTSD, the reexperiencing/intrusion, avoidance/numbing, and hyperarousal clusters.

[Slide.]

The adjusted mean changes at endpoint are epresented by these boxes, the red boxes being sertraline reatment, the blue being placebo treatment.

The two positive studies, 640 and 671, are shown o the left, the third population study, 682, next towards he right, and then the VA study, 641, to the far right.

In the two positive trials, sertraline-treated ubjects were improved compared to placebo-treated subjects n symptoms or reexperiencing and intrusion. On the CAPS, he Impact of Event Scale, and the DTS, they are improved umerically on all three ratings, reaching statistical ignificance on the IES and the DTS in Study 640.

[Slide.]

For the avoidance/numbing cluster, sertraline-reated subjects were significantly improved compared to lacebo on measures on the CAPS, IES, and the Davidson Scale in Study 640, and also on the CAPS and the DTS, the Davidson Scale, in Study 671.

In Study 682 and 641, there was no treatment effect in favor of sertraline, and in Study 641, as I failed to mention on the previous slide, but it is similar here, the magnitude of the treatment response is much less than was seen in the general population, studies.

[Slide. 1

On symptoms Of the hyperarousal cluster--and the Impact of Event Scale is not here as it does not assess hyperarousal--sertraline-treated subjects were improved in the two positive study compared to placebo subjects on all four measures, reaching statistical significance on both the CAPS and the DTS in Study 671, and on the DTS in Study 640.

As was seen with the other clusters, there was no significant treatment effect in favor of sertraline in Study 682 or 641, and the magnitude of the response in 641 was Less than what was seen in the other general population studies.

[Slide.]

To summarize, two of three studies in the general population have demonstrated the efficacy of sertraline in the treatment of posttraumatic stress disorder. In these two positive studies, sertraline-treated subjects were improved compared to placebo on symptoms of all three clusters - reexperiencing/intrusion, avoidance/numbing, and hyperarousal, reaching statistical significance on 10 of the 16 measures.

[Slide.]

Additional analyses were also conducted to look at potential gender differences in the treatment effects- The analyses I will be presenting are pooled analyses from the three general population studies as none of these trials

were individually powered to conduct these analyses.

[Slide.]

The efficacy results on the five efficacy measures, the CAPS, the Davidson, the IES, and the CGI ratings of improvement and severity are shown here for the pooled studies 640, 671, and 682.

In the women, there was a significant treatment effect on the CAPS-2, the Davidson, the CGII, and the CGI-S, and the women had improved numerically compared to the placebo group on all five of these ratings. The IES was the rating scale in Study 682 in which there was a significant effect in favor of placebo.

In contrast, for the men, there was not a significant between group treatment effect on any of the five ratings, and the mean change in the men did not appear to differ between the treatment groups.

The treatment by gender interaction effect was 0.02 for the Davidson Scale and at the 0.08 level for the CAPS-2.

[Slide.]

This slide shows the same five efficacy measures, but for the pooled positive trial 640 and 671 only, and here the effect in women is significant in all five of the efficacy measures and still there is no significant treatment effect emerging for the men.

[Slide.]

This slide shows the mean change at endpoint in he efficacy measures for only the women in the two positive rials, Study 640 and 671, looking at the CAPS, the Impact f Event Scale, and the DTS, the PTSD-specific symptom easures.

On these three measures in both studies, ertraline-treated women were significantly improved ompared to placebo-treated women in both trials. I want to mphasize here that although the treatment by gender nteraction was noted in a pooled analysis, on both trials ndividually, the sertraline-treated women were ignificantly improved compared to the placebo-treated omen.

[Slide. 1

The scores from the women from Study 640 on the hree clusters of PTSD symptoms are shown here, the reexperiencing/intrusion cluster to the left, then avoidance/numbing, and the hyperarousal.

On the symptom clusters, women treated with sertraline were significantly improved compared to placebo on the Impact of Event Scale and the DTS with a trend toward significance in the CAPS.

For the second cluster, avoidance/numbing, women treated with sertraline were significantly improved on the

ZAPS and the DTS compared to placebo, with a trend on the Impact of Event Scale, the IES.

In hyperarousal cluster, the sertraline-treated women were significantly improved compared to placebo on both ratings.

[Slide.]

This slide shows the results from Study 671, the second positive trial on the three symptom clusters, on the ZAPS, the IES, and the DTS.

Here, on all three of the symptom clusters, sertraline-treated subjects were significantly improved compared to placebo on all of the measurements.

[Slide.]

In two studies in the general population, women treated with sertraline were significantly improved on all efficacy measures compared to placebo. In addition, the sertraline-treated women in the two positive studies were improved on symptoms of all three symptom clusters, reexperiencing/intrusion, avoidance/numbing, and hyperarousal, reaching statistical significance on 14 of the 16 assessments.

[Slide.]

As stated earlier by Dr. Ryan, and Dr. Laughren, as well, one of the issues of this application is the potential of overlap of symptoms between PTSD and comorbid

depressive disorders.

Additional analyses were then conducted to valuate the relationship between PTSD and depressive isorders in terms of overlap of symptoms.

[Slide.]

This table shows the mean baseline HAM-D scores or the two positive trials, Studies 640 and 671 pooled. he HAM-D 24 item scale was the scaled used in these linical trials. Subjects were stratified by whether or not hey had a SCID-based diagnosis of a depressive disorder at aseline. On the HAM-D 24, the baseline score for subjects ho did have a diagnosis of a depressive disorder was 24 ompared to 19 for subjects who were not diagnosed with a omorbid depressive disorder

We have also calculated the baseline scores on the AM-D using the more traditional HAM-D 17 item score. In his case, subjects with a comorbid depressive disorder had mean at baseline of 18 compare to 15 for subjects with no comorbid depressive disorder.

Thus, patients with PTSD, whether or not they have a comorbid depressive disorder, have moderate scores on the HAM-D, which may be a reflection of the HAM-D's ability to register PTSD symptoms.

[Slide. 1

This table shows the correlation of the change in

the HAM-D from baseline to endpoint with the change on the three PTSD-specific symptom scales from baseline to endpoint.

This is again Studies 640 and 671 pooled, the two positive trials. There is a strong correlation on all three of the PTSD symptom measures between the HAM-D change from baseline to endpoint and the PTSD measure regardless of whether the subjects were treated with sertraline or placebo, so the effect seen here is not necessarily a sertraline-based effect.

[Slide': 1

Because of the issue of comorbidity with depression and PTSD, it was important for us to show that we have a specific effect on PTSD symptoms that can be distinguished from an effect on depressive disorders.

We conducted two types of analyses to address this i-pue. One was to stratify subjects by the presence or absence of a SCID-based diagnosis of a comorbid depressive disorder, and another was an analysis of the individual items of the CAPS-2, some of which are not common to subjects who have depressive. disorders.

[Slide.]

This slide represents the stratification with or without a comorbid depressive disorders of subjects in the two positive trials, Studies 640 and 671. The mean change

from baseline to endpoint on the CAPS, the Impact of Event Scale, and the DTS.

In both groups, with sertraline again represented in red, sertraline-treated subjects were significantly improved compared to placebo-treated subjects regardless of whether or not they had a comorbid diagnosis of a depressive disorder at study entry.

[Slide.]

This slide shows the same type of analysis, but conducted on the cohort of women in the two positive trials, Studies 640 and 671. Here, too, sertraline-treated subjects were significantly improved compared to placebo-treated subjects whether or not they had a comorbid diagnosis of, depressive disorder.

[Slide.]

Looking to the analysis of the 17 individual items of the CAPS-2, this is again the cohort of men and women in the two positive trials. Sertraline-treated subjects were numerically improved compared to placebo-treated subjects on most measures, but specifically, looking to numbers 5 and 6, avoiding thoughts of the traumatic event or situations, a significant improvement in the sertraline-treated group on these symptoms that are not like symptoms of a depressive disorder.

Similarly, items 15, hypervigilance, and 17,

physiologic reactivity, are also significantly improved in the sertraline treatment group.

[Slide.]

On this slide, we have the results of the 17 individual items of the CAPS-2 for the women in the pooled positive trials, 640 and 671.

Here, most of the symptoms were significantly improved in favor of the sertraline treatment group. Notably, items 1 and 2, intrusions and distress at reminders of the traumatic event, No. 6, avoiding situations, and No. 15, hypervigilance, all of which are not common symptoms that are commonly seen in subjects with depressive disorders alone.

[Slide.]

Sertraline then is effective in treating subjects with PTSD with and without a comorbid depressive disorder, and it is effective across the range of PTSD symptoms, including symptoms that are characteristic of PTSD, but not of depressive disorders.

[Slide.]

This table is a summary of the results from the three general population studies in all subjects and in women. The sertraline-treated subjects were improved compared to the placebo-treated subjects on five of the primary efficacy measures in Study 640, and four of the five

measures in Study 671 with a trend on the fifth measure,

In addition, in all patients in the two positive trials, sertraline-treated subjects were improved on 10 of the 16 measures of the symptom clusters of PTSD.

In the cohort of women in the positive trials, women treated with sertraline were significantly improved on all of the efficacy measures compared to placebo, and in the symptom cluster analysis, the women treated with sertraline were improved compared to placebo on 14 of the 16 assessments.

[Slide; 1

I would now like to present a brief review of the safety of sertraline in the treatment of PTSD. The safety was investigated in 757 subjects, and nothing that was found in this development program suggests a risk that has not already been identified in previous trials and indications, and is already not described in the labeling.

[Slide. 1

This table shows the incidence of the most frequent adverse events seen in the PTSD clinical program at an incidence level of at least 10 percent in the sertraline-treated group.

The most frequent adverse events were diarrhea, headache, nausea, insomnia; somnolence, dry mouth, malaise, fatigue, and ejaculation failure. Those with the asterisks,

iarrhea, nausea, insomnia, et cetera, are statistically ignificantly higher in the sertraline-treated group ompared to the placebo group.

[Slide.]

The incidence of adverse events associated with iscontinuation including laboratory abnormalities with dverse events are shown on this table. Ten percent of ertraline subjects and 5 percent of placebo subjects were liscontinued due to an adverse event or lab abnormality, and his difference was statistically significant. The two dverse events most commonly associated with treatment liscontinuation were nausea **and** headache.

[Slide. 1

Overall, the incidence of serious adverse events .n this program was low, 2 percent in the sertraline :reatment group and 1 percent in the placebo group, :epresenting 8 of 374 sertraline subjects and 5 of 376 placebo subjects.

None of the serious adverse events was considered :o be treatment related by the investigators.

[Slide.]

Hematology and chemistry profiles were conducted for each patient at baseline and during the study, as well as endpoint. We looked at the incidence of laboratory abnormalities exceeding defined criteria for each parameter.

This table shows the parameters with an incidence of at least 1 percent in the sertraline treatment group. Overall, the incidence of abnormalities on laboratory parameters was low and there was no statistically significant difference in the incidence between the treatment groups.

[Slide. 1

Overall, treatment with sertraline was found to be safe and generally well tolerated in this clinical program, and the safety profile of sertraline in the PTSD program was found to be consistent with that of the current labeling, and I would refer you to your Table 25 in your briefing document for a comparison with the other labeled indications.

[Slide. 1

To conclude, the efficacy of sertraline in PTSD was established in. two adequate and well-controlled clinical trials. The safety of sertraline in 757 patients with PTSD was-consistent with the current labeling for the two other approved indications.

I would now like to ask Dr. Gary Ryan to come up and provide a brief summation.

DR. TAMMINGA: Before you leave, I would like to ask the committee if anybody has any questions for You.

DR. DOMINGUEZ: Yes, I do.

How representative was your population in the sample that you collected versus the population with PTSD with regards to marital, status, with regards to race, and with regards to ethnic origin?

DR. FARFEL: We only collected marital status in two of the trials, and in my understanding, it seems to be representative, that a large number of the patient population was not married currently.

With regards to race, we had primarily Caucasians in these studies, primarily whites, I am not sure that the literature--I don't know if Dr. Marmar or Dr. Friedman want to address this--1 am not sure that the literature has established that this is not representative in any trial.

Do you have anything to add? No, I don't think that there is anything in the literature that would establish that this was not representative.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: The FDA review notes that you have a number of trials, of placebo-controlled trials ongoing of various kinds. I just wondered.if those contribute anything to the gender analysis in particular or anything else.

DR. FARFEL: No. Some of the trials are still undergoing data analysis currently, and to our knowledge, no.

DR. TEMPLE: And the long-term trial, does that

contribute?

DR. FARFEL: No, not in a considerable way, no.

DR. BREWERTON: When you refer to the PTSD patients with and without depressive disorder, are you referring specifically to major depressive disorder, or are you including other depressive disorders, such as dysthymia?

DR. FARFEL: Yes, we are including dysthymia in that categorization.

DR. BREWERTON: The HAM-D was 19 in your nondepressive group. It seems fairly high for a nondepressed group.

DR. FARFEL: The subjects with dysthymia were counted in the depressive disorder group.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: Are there any comments to be made about Trial 682, the third of the general population studies relative to the other two that showed significant differences?

DR. FARFEL: I am sorry?

DR. WINOKUR: Are there any comments to be made about analysis of the one general population study that did not show significant treatment differences, 682 relative to 640 and 671?

DR. FARFEL: In terms of understanding the results? No, we saw a relatively high placebo response

ompared to the other trials and a bit of a lower sertraline esponse compared to the other trials, and that seems to be he results.

DR. HAMER: In examining the relationship between epression or the effect on depression, the effect on PTSD, id you do an analysis in which you used the PTSD scale cores, the CAPS or the Davidson as the response variable nd covariate it out, either baseline Hamilton depression or hange in Hamilton depression?

DR. FARFEL: I will let Dr. Gaffney address that.

DR. TAMMINGA: Would you identify yourself before ou start.

DR. GAFFNEY: Good morning. Michael Gaffney. I as the statistician on this project for Pfizer.

To answer your question, we did both of those nalyses. Specifically we looked at the Hamilton depression aseline score as a covariate. It is a very weak predictor f response for the CAPS total and the Davidson total. lso, the Hamilton Depression Scales are fairly evenly alanced at baseline, too, so that the adjustment that one ould make in the covariate analysis is negligible and the significant results hold.

Regarding the changed score, though, the effect of sertraline on reducing the Hamilton Depression Scale is larger than the placebo group. There about an eight- to

ine-point drop on sertraline group compared to that of a hree- to four-point drop for placebo.

So, using the covariate in Hamilton Depression cale there, it is strongly related to the change in the APS total and the Davidson total, and you have this mbalance in the effect sertraline and placebo, so that here is a considerable adjustment there.

You change maybe a nine- or lo-point sertraline ffect on the CAPS-2, reduce it to about a five- or six- oint change, and that is statistically significant still oth for the CAPS and for the Davidson.

DR. HAMER: So, even though you covariate out hange in Hamilton Depression Scale in the studies in which ou did have positive results, you still had a significant ifference between drug and placebo on the CAPS or the avidson after covariating out change in Hamilton?

DR. GAFFNEY: That is true. I'also want to point ut that, as I am sure you are aware, if it is a very onservative approach because it's assuming that the change n the Hamilton Depression is somehow causing the change on he CAPS-2 when the results could be the opposite or neither, but you still have, after. covariating out the differential effect of sertraline on the Hamilton Depression Scale, you still have significance on the CAPS total and the Davidson.

DR. HAMER: Did you do those analyses also in just omen?

DR. GAFFNEY: Yes, the analysis that I am eferring to specifically is in just women. I did the nalysis also in the two positive studies, as well, and the esults, as I said, hold as well.

DR. HAMER: And if you do the analysis on the two ositive studies, you mean men and women pooled?

DR. GAFFNEY: Yes.

DR. HAMER: But, of course, those studies had more omen than men in them.

DR. GAFFNEY: It is dominated by women. The lumbers that I gave you were the numbers that are specific o the analysis in women from those two trials.

I do have a slide I could put out if it's helpful o the committee.

DR. HAMER: I would appreciate it.

DR. TAMMINGA: While we are waiting for the slide, I would like to ask Dr. Farfel to clarify sexual dysfunction. How did you assess sexual dysfunction in the patients, and did you do it differently in the men and the women, did you use a specific scale?

DR. FARFEL: No, we just used self-report from the patient or if the investigator chose to probe with questions, but we did not use a rating scale.

[Slide.]

DR. GAFFNEY: This slide summarizes the information I was giving verbally before. This is in the women pooled over the two positive trials, 640 and 671. These values here are the values of the response on all of the variables unadjusted for the change in the Hamilton Depression. One can see that there is statistical significance for the CAPS-2 total, the DTS, the IES, and the CGI improvement. These are basically the results that Dr. Farfel showed.

When we look at the adjusted analysis, these now again, to reiterate, are adjusted for the differential change in Hamilton Depression total. Again, sertraline effected about an eight- or nine-point change, placebo, about a three- or four-point change in this dataset, so adjusting for that larger effect on the Hamilton Depression scale, we reduce what we see for the sort of pure effect of sertraline and reduce it to the numbers that one sees here under the Adjusted column, however, the statistical significance still holds.

Again this is a very conservative analysis because it is taking two outcome variables. and adjusting one for the other in a sense of a causative way when that relationship doesn't need to be holding:

DR. HAMER: And this is in the model that had

enter effect in it?

DR. GAFFNEY: This was a model that had a center ithin study, as well as a study effect in it, so it is not compilation of the data over the study. It is using a orm of meta-analytical model for it.

DR. HAMER: Thanks.

DR. TAMMINGA: Dr. Southwick.

DR. SOUTHWICK: Were there any analyses directed t the relationship between duration of illness and reatment efficacy?

DR. GAFFNEY: Yes. I will put up a few slides to ddress that.

[Slide. 1

I will just take a second to orient you to the structure of the slides. This slide summarizes the analyses hat were done stratifying patients according to whether the ation of their symptoms of PTSD were greater than five ears or not.

Down the left column here, those that had their symptoms within five years, the results are summarized. Over on the righthand side, patients where the symptoms are longer than five years are summarized, as well.

The information that is given for the three general population studies; for the two comprehensive scales, the CAPS-2 and the patient-rated Davidson Scale.

These numbers are the mean responses, the mean changes from baseline within that particular strata. The sample size is given in parentheses, so one can see the distribution of patients according to the stratification.

Down at the bottom, again, in a sort of form of meta-analytical way of combining the information over the three general population trials, one sees the overall mean response versus placebo by strata.

This is for all patients, men and women, in the three general population studies.

If we go to the next slide, we can see this broken out by women.

[Slide.]

This information now is the same as was in the preceding slide, but just confined to women. I think that one thing to point out is that 682 in a sense, when one does these analyses, you can make the case that it really doesn't elucidate the point, it obscures it a bit because it's a study with no effect, and if one looks at 640 and 671, I think you can see that the significance is there for women in the strata which is symptoms less than five years versus those that are greater than five years.

The bottom line I think of this would be that within this dataset, women are responding sort of equally well whether or not their symptoms are within five years or

ot.

The next slide would be men, which shows that the on-effects seen in men is consistent regardless of strata. 'here may be a little bit of an effect here that one can see 'ith men whose symptoms are within five years, but we have roken this data according to many of these potential redictors of response, and one is always getting a little omething on one side or other, but I don't think there is uch to make out of it, but in general, the durations in his trial are not real predictors of response.

DR. SOUTHWICK: I have one other question.

Was there an attempt to compare single traumas to ultiple traumas in terms of efficacy?

DR. GAFFNEY: Yes.

[Slide. 1

This is the same structure to the slide as was own previously except now this is stratified by patients resenting with more than one trauma. Patients categorized ver here are those that present with.a single index trauma. atients categorized on the righthand side are patients who are presenting with the index trauma plus some additional rauma.

Again, this is for all patients in all three of the general population studies going down to the bottom line, which is probably the clearest way to view this

.nformation, in the composite, one sees significant sertraline effect versus placebo regardless of whether one presents with a single trauma'or with multiple traumas.

[Slide.]

This is again the effect in women alone, the same esults since the overall result is driven by women. Again, E you confine yourselves to 640 and 671, you even get I hink a clearer picture of the effectiveness of sertraline ithin both of these strata, and for the sake of ompleteness, let's put up the men after that.

I think we see here that again, regardless of 'resenting with a single or multiple trauma, there is no ignal for effectiveness of sertraline in the male opulation.

DR. SOUTHWICK: Thank you.

DR. TAMMINGA: Any other questions from the mittee? Dr. Geller.

DR. GELLER: Could you show analyses by substance se?

DR. GAFFNEY: Yes.

[Slide. 1

This is actually quite an interesting stratification because when I show it with men, it is very indicative of some effect of sertraline in the strata where men have had a history of drug abuse, but I am getting ahead

f myself a little bit, going back to all patients in the hree trials.

We have stratified again by whether they have resented with a history of drug abuse, no versus yes. This yes," of course, would have to be previous to six months nrollment in the study. I think Dr. Farfel mentioned that s an enrollment criteria.

In all patient population, we see that sertraline ffectiveness is smaller actually in those who are resenting without a history of drug abuse, quite a bit arger in those patients who present with a history of drug buse. The sample size is relatively small, these are not arge sample sizes, but the composite does give you this information and a somewhat larger effect in this subpopulation compared to those presenting without it.

If we go on women, we can see it is consistent within women, as well.

[Slide.]

Again, within women, you will see a larger effect of those small number of women presenting with a history of drug abuse relative to those who present without one, but again, there is diminished effects, but they are significantly in favor of sertraline versus placebo.

The interesting slide is the next one where we go on to men.

[Slide.]

There is no real signal in these three studies and n the VA study about the effectiveness in men except for his very small strata of men presenting with a history of .rug abuse, you actually do get statistical significance for ertraline versus placebo in this group, and it is confirmed lso in the DTS. This is nearly significant, there is just to asterisk up there. Nothing at all going on in the ajority of patients who are presenting without a history of lrug abuse.

I might add, although it is not up here, that in i41, the VA study, where you have more men with substance abuse, I believe there is probably 19 on sertraline and 10 on placebo, if I remember the numbers. This is confirmed. There is a 20-point drop in the GAPS total for men with a history of drug abuse, a lo-point drop for placebo. The numbers are reduced quite a bit, but the separation of a 10-point separation is there.

If you put all those numbers together, the four trials of men who have a history of drug abuse, you do get a significant effect in favor of sertraline.

DR. TAMMINGA: As I recall, Dr. Farfel, the exclusion criteria was six months of active drug abuse?

DR. FARFEL: Yes.

DR. TAMMINGA: Additional questions? Dr.

Dominguez.

DR. DOMINGUEZ: Yes. I would like to refer to your responder analysis, which I believe is the post hoc analysis. First, a clarification. In some of the pre-meeting materials that we received, it said 30 percent decrease in CAPS and/or a CGI of 1 or 2. I want to clarify that, is and a CGI score of 1 or 2, am I correct?

DR. FARFEL: That is correct, it is "and."

DR. DOMINGUEZ: The second question is and why 30 percent? What criteria did you use to establish that a 30 percent drop was a clinically significant decrease in the symptoms?

DR. FARFEL: In the 30 percent drop was a consensus of experts in PTSD. We originally developed responder criteria for one of our long-term protocols that had responder status as an entrance criteria, so the responder criteria were developed by this consensus group outside of analysis of these 12-week trials, and they felt that a 30 percent drop due to the chronicity and the effect on daily life function in PTSD subjects, PTSD patients, they felt that a 30 percent drop, which in other disorders might be considered a modest drop in symptoms, could actually be a profound drop in these highly chronic patients if it is also accompanied by an overall improvement on the CGI, and there was a minimum criteria that the 30 percent had to be at

east 15 points.

DR. DOMINGUEZ: Did you by chance conduct any nalysis using a higher percentage?

DR. FARFEL: Yes, we did.

[Slide. 1

These are the two positive trials, 640 and 671, oth men and women, and these are the calculations of ercent responders. When the criteria were varied using a GI improvement rating of 1 or 2 and either a CAPS decrease f 20 percent from baseline, 30 percent, which is what was hown, 40 percent, or 50 percent, and the difference between he treatment groups holds regardless of the CAPS criteria.

DR. DOMINGUEZ: Thank you.

DR. TAMMINGA: Any other questions by the committee? Dr. Brewerton.

DR. BREWERTON: Yes. Did you do any analyses that looked at the possible role of the age at the first trauma?

DR. FARFEL: Dr. Gaffney?

DR. GAFFNEY: Was it age or aged? No, we didn't do a specific analysis looking at that. We did look at age of the person, and I showed stratified by five years. I did also look at a multivariate analysis using both age and duration of symptoms which would in some way capture their age at the time of occurrence. In those cases, there was no significant--

DR. BREWERTON: How about presence of child abuse?

DR. GAFFNEY: I did a stratification by that as he index trauma, if you would like to see that information.

[Slide. 1

This is the results stratified by whether the atient presented with an index trauma of childhood hysical, sexual abuse. Those that did not are listed here n the left side, those who did are on the right side. One an see the distribution of patients in these three trials. 'here again are all patients.

One can see again here that patients presenting ith a childhood physical, sexual abuse, effectiveness with f sertraline is significant and quite a bit larger than one ees here in those that are presenting without a physical, exual abuse.

Again, I think that 682 maybe obscures a little t the effectiveness of sertraline in the strata for 671, and a little bit for 640.

If we go on to the women, I think we see the effectiveness shown a little bit better.

[Slide.]

This is in women. Again, we always see a stronger effect when we parse out the men because there really is no effectiveness in the men. 'Again, whether the women are presenting with childhood physical, sexual abuse or not, one

has overall significance, and I think if you look at the two positive trials, you will see that the effect of sertraline is not really dependent on this.

If we go on to the men, we will show that for the sake of completeness.

[Slide.]

Here, this is another indicator similar to what I had shown with the history of drug abuse, where if you look at the small numbers of patients--and again you can add them up as well as I can--there is only 10 patients on sertraline who came with a childhood physical, sexual abuse, 1322 on placebo, one does see a separation out and effectiveness of sertraline in this very small subpopulation. Again, these are all post hoc analyses, exploratory analyses to try and understand what is going with the data, particular as it regards men.

DR. TAMMINGA: Any more questions from the committee to Dr. Farfel? Dr. North.

DR. NORTH: Yes. I wonder if you have any data on the percent who had clinical remission from PTSD.

DR. GAFFNEY: We do not have data on that. We did not stratify or look at that as a response criteria.

DR. TAMMINGA: It appears as though the committee is finished with the questions for you, Dr. Farfel. Thank you.

**Conclusion**

DR. RYAN: As Dr. Farfel just reviewed, results rom Pfizer's PTSD clinical program revealed a significant ertraline treatment effect in two of the three studies onducted in the general patient population. No significant reatment difference was observed in the fourth trial onducted in the **VA** setting.

Some of the issues which will be discussed today ave been observed before in the development of drugs to reat psychiatric indications. One is the realization that oth positive and negative clinical trials have been reported in **NDAs** of marketed psychiatric drugs.

In addition, PTSD, **as** with other psychiatric illnesses, exhibits overlapping symptoms and comorbidities with other diagnoses including mood, anxiety, and substance abuse disorders, however, as just described, patients with PTSD also present with distinct symptoms for which a beneficial effect of sertraline has been observed.

Another point for discussion will relate to the difference in the treatment effect of sertraline in men and women in these data. An analysis by gender in these studies revealed a strong response in women who were randomized to sertraline compared to placebo.

This finding was -replicated in the two positive trials. In contrast, no significant treatment effect was

bserved in men. Clear answers to the observed gender ffect are not readily apparent, however, we will be happy oday to discuss the interpretation of these results with ou.

Thank you.

Are there any additional questions?

DR. TAMMINGA: Does the committee have any uestions for Dr. Ryan?

[No response.]

DR. TAMMINGA: I think the committee does not have ny additional questions for Dr. Ryan, and we thank Dr. Ryan nd his team at Pfizer for a clear and lucid presentation of he information to us and for answering many of our uestions.

I think we will take a break now and return at ten inutes after 10:00. We will restart the hearing at that ime.

Thank you.

[Recess.]

DR. TAMMINGA: I would like to call the meeting to order again for the continuation of our discussion of sertraline and PTSD. I would like to say that after the FDA presentation, we are going to have the open public hearing for those of the public speakers who are here.

Before the committee begins its deliberations for

both the company data and the FDA presentation, we will hear from the public speakers.

With that, I would like to call Dr. David Smith, who is the statistical reviewer from the Office of Biostatistics for the FDA. I would like to point out to the committee that Dr. Smith's slides are in your blue folder, if you would like to follow along.

Dr. Smith.

**FDA Presentation**

**Statistical Review**

DR. SMITH: Thanks very much.

[Slide. 1

I am David Smith. I am a statistical reviewer at the FDA. First, I would like to say that while I am speaking, I would like the committee to jump in and ask me for clarifications as we go through in case I don't make my point clearly or if you have a question 'about the tables, and things like that.

[Slide. 1

I am going to present the FDA's review experiences while reviewing sertraline for posttraumatic stress disorder. Here, of course, is the proposed indication, sertraline is indicated for the treatment of posttraumatic stress disorder.

I am not going to repeat the sponsor's

presentation. I thought they gave an excellent overview of some of the issues that we are facing. I am just going to present the FDA's perspective and a few of the issues that concern us as a regulatory agency.

[Slide. 1

As Dr. Laughren pointed out in his earlier comments, this is the FDA's first experience for posttraumatic stress disorder as an indication, and we invite the committee to give their perspective on some of the issues that we are going to present.

The issues that i would like to present, there is three of them, three main ones. The first is the relevance of Study 641, the veteran study, and Study 682.

The second issue is, of course, the gender difference, and the third is the issue of PTSD improvement being related to depression improvement.

I am going to go through each one of these in turn and then summarize the points after these three issues.

[Slide.]

Here, we see the demographic characteristics of the three studies. This is the veteran study here, and the other three studies are 640, 671, and 682. 640 and 671 again are the two pivotal studies.

The sponsor had a similar slide earlier. What I would like to show in this slide, and for 641, it appears on

ne surface that we are dealing with a different animal are, that gender ratio is different, the mean age of the atients is older, the duration of illness is older, 18 ears versus 11 to 12 years. Of course, combat is the rimary triggering event, and time since traumatic event is uch longer in the veterans population. Dr. Gaffney from fizer addressed this question, time since traumatic event nd how that affects PTSD outcome.

The other three studies hang together much better, hough. 640, 671, and 682 are similar demographically, at east on the surface. So, one of the concerns that FDA has s, as I think Dr. Laughren mentioned earlier, is that of eproducibility or robustness of the results.

640 and 641 had identical protocols. 671 and 682 tad identical protocols.

[Slide. 1

Here, are mean changes from baseline on the three primary endpoints - CAPS-2, IES, and CGI-S. Again, we see that 640 and 671 showed statistical significance on these three endpoints. 641, This is striking to me that the improvement in the PTSD scales aren't even in the same ballpark as the other three studies.

I have to say that the way we interpret these scales is that large negative differences imply patient benefit. so, here, for CAPS+2 and 33, this says sertraline

s better than placebo, because sertraline is much more negative in magnitude.

So, one concern is, of course, that the veterans just don't seem to have the same type of response on PTSD. The other concern again is the lack of reproducibility or robustness in 682. Even though the scores are in the same ballpark, it has been mentioned that this could be just a large placebo effect that washes out any difference and it makes the p-values not significant.

What is interesting is that on the Impact of Event Scale, Dr. Farfel mentioned that placebo patients improve more than sertraline patients on the Impact of Event Scale, and that is statistically significant.

[Slide. 1

Again, for 641 and 682, one issue that we have is the lack of confirmation for these two studies. Given that the demographics for 640, 671, and 682 are mostly women enrolled, 641 may be the best evidence that we have for a sertraline effect in males, however, there was no difference, but there is lots of other things that come along with the veteran study, as well, and I have mentioned some of them, that it could be a different biochemistry going on--I am just guessing--or it could be an older population or more duration of PTSD.

How would FDA interpret? We would like

uggestions from the committee for their perspective on how e should interpret 640 and 671 in light of these two upportive, yet not significant studies. That is the first ssue.

[Slide. 1

The second issue is the gender difference. The ponsor showed that there was a significant gender by reatment interaction. The way I interpret that is that the reatment isn't consistent across genders, and it is tatistically significant, and that was tested.

A question that I have is do we have enough data o evaluate efficacy in men. This is more of a power uestion, do we have enough information to detect ifferences to begin with.

Finally, a gender difference issue gets us into he area of subgroup analyses, and subgroup analyses are icky sometimes to work with due to the fact that often studies are powered for specific subgroup type analyses.

[Slide.]

I would like to present the FDA's perspective on subgroup analyses, and some of this information comes from he ICH guideline.

Subgroup analyses are easy enough to understand. If you have an entire population, you may split this population into two different subgroups, so, for example, we

have all patients in this study, we can split it by gender, male and female.

What might be happening here, one could hypothesize, let's just assume sertraline works in females; but doesn't work in males, the overall effect that we are seeing of sertraline overall, an entire population, is significant, but since more women were enrolled in these studies, the women could be driving the overall analysis. That is subgroup analysis.

To get into this question, FDA has some guidelines, and-that is what I would like to talk about right now. If this type of difference, this sort of differential subgroup analysis effect is known before the study is begun, then, there are ways to design the study around the subgroups, so that, for example, you may stratify and then you can perform a stratified analyses whenever the study is completed.

This idea is from the ICH guideline, Volume No. 9, the. statistical volume. Neither the sponsor nor we expected this differential gender effect, so this first one doesn't really apply. Instead, we are in the realm of the second one here.

We found a subgroup differential, males and females. The ICH guidelines then say to test'interaction first, and this is what the sponsor did, and they found a

ignificant gender interaction.

What happens then? Well, given that the ertraline effect isn't consistent across genders, we move o the last thing, which is where things get a little bit ricky. What we are now faced with are post hoc analyses on he subgroups.

They are necessary post hoc because we didn't xpect these coming up through the course of the trial or in he design stage of the trial, but remember that to draw onclusions about subgroups, we have to recognize that ubgroup conclusions weren't specified in the protocol, and o we don't have fundamentally enough power sometimes to raw striking conclusions about subgroup analyses.

I am going to suggest that we examine the subgroup analyses, but consider them exploratory and interpret them with caution.

[Slide. 1

This is a table that is similar to the sponsor's. What we have here are specific gender by treatment effects for the two pivotal studies, 640 and 641. What I want you to get from this study is look at the significant effects for women and the lack of significance in men.

The final column here are the interactions on all of the types of clusters that were measured. Again, we see, of course, that women are in the majority here. This is why

we have to be careful of the subgroup analyses because we have so few men, and to jump to conclusions about men is not recommended. We have somewhat tenuous conclusions whenever we make judgments about men.

However, you can see that there is a big difference between the women's effects, the differential between women scores and the difference in men. Recall again that for all of these scales, large negative differences imply patient benefit. So, whenever sertraline is much more negative than placebo, that implies a win for sertraline. .

The exception to that is the CGI improvement row here. CGI improvement is a scale type question, so the closer that you get to 1, that implies patient benefit. The closer that you get to 7, that implies a worsening in patient symptoms. So, again, the smaller numbers for CGI are good for the patient.

Again, what I wanted to show you is that even though the men and the women are in the same ballpark in terms of their improvement, either we don't have enough power to detect the difference in men, and that is why the p-values are significant, or perhaps more likely, that there just doesn't seem to be anything going on in men whenever they are administered sertraline versus placebo.

That is our perspeative on the gender effect.

[Slide.]

Finally, the last issue that we would like to invite the committee to address is that of the relationship between depression and PTSD, and we have already talked about that. I have a few analyses to add to the discussion perhaps and we would invite your feedback.

Just to reiterate that PTSD does have similar clinical features to depression, and we saw that the patient populations do have quite a bit of comorbid depression, anywhere from a third to a half. These actually, the 36 and the 49 are both-extremes, and both of them came from the pivotal trials. The veteran study was in between, and the 682 was in the middle there somewhere, too.

What we asked ourselves at the FDA is can we quantify how depression improvement contributes to PTSD improvement. Now, this is a different question I think that that we have seen earlier, namely, that we are talking in terms of improvement now. That is the difference between baseline and the last visit.

Before, we were talking about baseline, just baseline depression, are you diagnosed as depressed at baseline and how that does that affect your PTSD. Now, we are talking in terms of improvement in depression over time.

There are two analyses that I would like to present, and I am going to call them Analysis 1 and Analysis

[Slide. 1

Again, here is the question: Can we measure PTSD improvement in the presence of an antidepressive effect?

One way that we can get at this question, it has already been discussed, is we can consider PTSD-specific symptoms, and if I can go back, this is an example of that.

[Slide.]

We already saw some slides by the sponsor. One could argue that these are unique somehow to PTSD, not necessarily, but it does at least give us evidence that at least in women on PTSD-specific symptoms, there is an improvement. So, this is where depression can't get at PTSD, for those specific symptoms, those aren't shared with PTSD.

Another way to get at this question is to exploit the fact that the sponsor measured HAM-D throughout the course of the study, and so we can use that data perhaps to monitor HAM-D improvement, which is a-surrogate for depression improvement, and PTSD improvement, which we have as measured by the PTSD scales.

However, again, this gets us into the arena of subgroup analyses. Now, instead of having males and females, we have depression improvers perhaps and depression non-improvers. This is necessary post hoc again because

nything with improvement in depression is outcome based, so e have to wait until the end of the study to see how epression improved.

Again, I have to caution you to take these esults, consider them very carefully, and don't make snap udgments about them, because we don't have the power in ome cases to draw striking conclusion about this, but what e are trying to do is just do an exploratory analysis and ry to augment what has already been done in terms of epression improvement.

[Slide. 1

Let me set up Analysis No. 1. We tried to get a lepression improvement based on the HAM-D total scores. lhat we did was we took our entire population and we split .t into two groups, those we call HAM-D Improvers, those who .mproved with their total HAM-D scores, and HAM-D Non-.-&rovers, which were those'whom I think of as that either stayed the same or got worse as measured by the HAM-D.

HAM-D is a similar type of instrument as the ›revious ones, the CAPS-2 and the IES, in that large ıegative differences implied patient benefit.

So, what we did was we split the patients into :heir baseline HAM-D scores, and the difference was around 20 for the baseline. We tried to make it fair, so that we didn't require patients who didn't have high HAM-D scores,

they didn't have to improve quite as dramatically as those who were more depressed and had larger HAM-D scores.

This is how we split the data. In this arbitrary way, this arbitrary split, we tried to quantify our ideas about depression improvement using what we had available to us. Even though this is arbitrary, the idea is to relate depression to PTSD based on the scales that we have available.

Instead of doing more like a covariate analysis, we looked at the question in terms of subgroups instead. So, it would be two subgroups, improvers and non-improvers, as surrogates for depression improvers and depression non-improvers.

[Slide. 1

This is Analysis No. 1. What we tried to get at here is how does improvement in depression affect improvement in PTSD. So, let's walk through this slide.

Here are the results for 640 and 671, males, females, and males plus females here, and for all four studies combined. This is the column for HAM-D improvers, this is the column for HAM-D non-improvers. Again large negative differences imply patient benefit, so this column is much more negative, which means much more patient benefit than this column right here, and all those columns are statistically significant.

Now, I only showed this CAPS-2, but I can assure you that for IES and the other primary endpoints, the table is pretty much the same. HAM-D improvers, as defined by our little arbitrary designation by the previous slide, do much better in PTSD symptoms than HAM-D non-improvers.

What is somewhat striking to me is that HAM-D improvers show--let's see, how shall we say this--HAM-D improvers have a much larger magnitude of improvement over non-improvers than sertraline versus placebo.

If I go back three slides, here is CAPS-2 total, here is the sertraline versus placebo difference, that is one way to split up the data, and compare that to the HAM-D improvers and the HAM-D non-improvers.

If we didn't expect to see any difference between the improvers, the little arbitrary designation between improvers and non-improvers, we would expect this number to be the same as this number across the board, and there is no statistical significance. Instead, what we have is a kind of dramatic improvement in CAPS-2 based on our little arbitrary split of the data.

So, this is evidence that we think that says that depression and PTSD are related rather intrinsically. I have a note down here at the bottom this is inclusive of both treatments. What we were trying to get at here is not both HAM-D improvement and treatment differences. We just

ried to get at depression type differences instead of reatment type differences. That is Analysis No. 1.

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Let me show you Analysis No. 2. Analysis No. 2 as based on HAM-D Question 1, which is specifically ailored to get at depressed mood. So, the patients, as hey made their first visit, were given these states to escribe themselves, and how they answered was zero, 1, 2, , or 4, was their *score* for HAM-D Question 1.

We took this score at baseline and we took the core at the end of the study, and that is how we did our ext subgroups. You can see the progression. You get a core of zero if you don't relate any of these states, and hen versus at 4, this is the only state that you report to he interviewer.

So, large scores here imply that a patient has pressed mood. This is the second slice of the data that we lid. Instead of doing HAM-D type totals, we did HAM-D Question 1, and we called these HAM-D Question 1 improvement.

So, between baseline and end of the study, we showed if you improved on the HAM-D Question 1, you were a HAM-D Question 1 improver, if your score was either zero or increased until the end of 'the study, then, you were a HAM-D Question 1 non-improver. So: this is another way to split

up the data.

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This is Analysis No. 2. This is a rather busy slide, but let me try to walk you through it.

The first thing that I notice is that for me, again, we don't see any differences really between sertraline and placebo. Each of these p-values are sertraline versus placebo. Nonsignificant p-values mean there is no sertraline advantage. In men, there doesn't seem to be any sertraline advantage whether or not you improve with your HAM-D Question 1 or not.

The same is true for HAM-D Question 1 improvers in women. This is another, sort of hand-fisted way to get at the filtering out of depression, removing depression from the equation, and seeing what raw PTSD effect sort of shines through.

If you are a woman and you improve in depression, there really isn't any advantage to receiving sertraline. However, you do see a lot of effect up here in women non-improvers. if you didn't improve in depressed mood as measured by the HAM-D Question 1, you do see a sertraline advantage.

So, it is difficult to sort of interpret these data, but one thing that I can say is that it seems like depression and PTSD are related, and we have quite a bit of

evidence to make that statement, not only this type of analysis, but the sponsor's correlation type analysis.

[Slide. 1

Let's look specifically at women in 640 and 671. This is the population you will recall that shows the most sertraline efficacy. So, what I have here are the specific scores on the PTSD instruments and whether or not they improved on HAM-D Question 1.

The most improved group is the women who received sertraline and also improved in Question 1. The next group is those who improved in Question 1, but were given placebo. The last two groups are those women who didn't improve in Question 1 and got sertraline, and then those who got placebo and didn't improve on Question 1.

Down at the bottom we see the p-values. This 0.002 is the comparison between minus 14.3 and minus 25.3, and that is significant. That is a significant difference in favor of sertraline. This 0.255 is the difference between 39.8 and minus 44.6. That is consistent across the board for the other endpoints, as well.

Again, what we are trying to get at is filtering out depression improvement and seeing whether or not if PTSD-specific type symptoms can shine through even if depression tends to improve.

[Slide.]

Let me recap for the committee. These are the issues that we would invite the committee to engage in and discuss.

The first is how would FDA interpret Study 641 and 682. We agree with the sponsor across the board with the efficacy shown in 640 and 671. At least in females there does seem to be a sertraline effect.

However, we don't really see a robustness of an effect in Study 682 even though it has similar demographics and a similar design. There is no efficacy difference, and in the veterans study, there is no efficacy difference.

Unfortunately, we have a minority of men in the other three studies. The veteran study may be the best evidence that we have for the efficacy of sertraline, so it is valuable, I think, but it doesn't make our job really any easier in interpreting the results for men.

[Slide. 1

The second is the differential PTSD gender effect. Can anyone think of some of the reasons for this effect is what we would like to ask - is it because of the triggering event? The gender by treatment interaction is shown and established, but could women, for example, be diagnosed with PTSD more readily than men. Is there anything hiding behind the gender variable that would explain the sort of differential results of sertraline?

Finally, do we have enough evidence, enough nformation to detect any difference in males, or is it imply just a lack of effect?

[Slide.]

Finally, for the depression type question, how TSD improvement in depression are related, we do see that emales improved on PTSD-specific symptoms, however, men do .ot improve on the same symptoms, so that also makes it a ittle bit difficult to interpret.

The final thing is PTSD and depression are :onfounded in some way, and it is hard to find a PTSD-:pecific effect in some cases whenever we filter out lepression.

That's it for me. If anyone has any questions, my :olleagues and I would enjoy discussing it with you or :rying to answer them.

DR. TAMMINGA: Anyone is welcome to address clarifying questions to Dr. Smith. I would like us to save our discussion until just a little bit later, but any clarifying questions for the statistical analysis of the FDA?

DR. COOK: I am going to ask a difficult question, and that is, was there any attempt to look at the issue of whether the depression drives the change in PTSD, or the PTSD change precedes the change in depression since this

hould have been secondary depression allowed in the study?

DR. SMITH: That is an excellent question. All we id was we split into subgroups, and our working hypothesis as that depression was driving the PTSD, because Zoloft is pproved as an antidepressant, and that is where we came rom.

DR. BREWERTON: One of the important questions I ave--I am not sure if it is appropriate now or later--but n the materials we received before, you indicated the bsence of any kind of post hoc corrections for all of the tatistical comparisons, and I am surprised that you didn't ote that in your presentation.

I am wondering what precedents there are in other rugs that have been approved for FDA indications in using hese kind of post hoc corrections, and I would like some direction about that, because it seems to be an important ssue.

DR. SMITH: I can share my background. I generally work in the oncology area, and when you are faced with a life-threatenin; disease, you still might have a few andpoints, such as survival or progression-free survival. Those questions tend to be less important than whether or not you do show an effect at all.

So, even though you have multiple endpoints, the multiple endpoints adjustment is secondary. In this case,

ne only thing I might be able to add is that in women, it seems that the trend is so strong, that even if you were to djust, they would still tend to be significant almost cross the board.

So, we kind of lucked out in this case, I guess ou should say. We didn't really have to face this issue ecause it wasn't that close. I would invite any of my ther colleagues to comment on that.

DR. BREWERTON: That seems to be true for the otal CAPS, for example, but when you break down for the lusters, you have much larger numbers and where it would be ignificant it seems.

DR. SMITH: Right.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: I would say historically, we have Despaired of being able to affix true p-values in these settings, but as David said; there is a requirement in regulations that the effects of gender, race, and age be Looked at, so those three are sort of.number limited, and are always expected, and a finding in those areas is somewhat more credible with respect to multiplicity at least than all of the others one might imagine, but much of what you have seen we would call exploratory and throw up our hands with respect to trying to put a p-value on it.

Fair enough, Dave?

DR. SMITH: Yes,

DR. TAMMINGA: Any more questions of the committee or Dr. Smith?

[No response.

DR. TAMMINGA: Thank you, Dr. Smith, for your presentation.

DR. SMITH: Thanks for the opportunity.

DR. TAMMINGA: We will proceed now to the public hearing part of our schedule. It is slightly out of order. We have two of our public speakers here.

The first one that we would like to invite forward to talk to the committee is Esther Giller from The Sidran Foundation.

**Open Public Hearing**

MS. GILLER: Good morning and thank you for the opportunity to attend this meeting and to present information about posttraumatic stress conditions and the need for increased understanding and treatment.

I am the president of The Sidran Foundation, which is a national nonprofit organization devoted to advocacy, education, and research in support of people with traumatic stress conditions. One of our primary focuses is on education of front-line professionals and the public about posttraumatic stress and other traumatic stress conditions.

A lot of the comments that I was going to make

ere covered very beautifully by Dr. Marmar, so I am going o sort of skip around and hit some of the high points that e didn't mention, that I thought were important.

I wanted to mention the NIH National Comorbidity tudy, which found that childhood sexual abuse was a very trong predictor of the lifetime likelihood of PTSD. The rauma most likely to produce PTSD was found to be rape, rith 65 percent of men and 45.9 percent of women who had been raped developed PTSD. This study also shows that PTSD .s associated with nearly the highest rate of service use nd possibly the highest per-capita cost of any mental .llness.

In regard to chronicity, 1998 and 1999, 1995 studies showed that PTSD is also associated with high levels of use of non-mental health services. An HMO study in 1999 reported substantially increased health care costs among atients who reported childhood trauma.

Hidden costs include the medical costs for suicidal and parasuicidal behaviors, as well as other somatoform and psychophysiological disorders. These are commonly reported by trauma survivors.

Child sexual and physical abuse may not only produce PTSD in some, but may increase PTSD susceptibility in response to later, adult stressors.

People who have experienced assaultive violence

(interpersonal victimization) at home and in the community have also been shown to have very high risk for PTSD, as much as 21 percent.

The moderating effects of PTSD can significantly complicate any other co-occurring disorders including developmental disorders. People with PTSD are likely to have at least one other mental health diagnosis. Even in the most conservative studies, people with PTSD were two to four times more likely than those without PTSD to have almost any other psychiatric diagnosis.

Somatization was found to be 90 times more likely in those with PTSD than in those without PTSD. This shows an important but frequently overlooked connection between PTSD and physical complaints.

As was mentioned before, many people with PTSD turn to alcohol or drugs in an attempt to escape their symptoms by self-medication. People who are dually diagnosed with substance abuse and PTSD may benefit from trauma treatment instead of or in addition to traditional model substance abuse programs.

When we think about the costs of these various kinds of treatment which are often misdirected or unspecific, we realize the kind of impact that appropriate treatment can make.

In a study of rapevictims in 1990, Koss, et al.

found that severely victimized female members in an HMO had outpatient medical costs double those of control HMO members, and findings also suggest that from 3.1 to 4.7 million crime victims received mental health treatment in 1991, for an estimated total of $8.3 to 9.7 billion.

These recipients represent only a small portion of the trauma victims in need of treatment, since people with PTSD are typically reluctant to seek professional help.

I would like to talk a little bit about the marginalized populations, as well. There has been increasing attention paid to PTSD resulting from high-profile "single blow" traumas, such as school shootings, transportation disasters, earthquakes, but PTSD resulting from chronic trauma, such as experiencing or witnessing childhood abuse, domestic violence, and interpersonal victimizations in the community is not well known in the general population, among primary health care providers, and even among mental health care providers in many settings.

Also, male survivors of abuse, perhaps the most marginalized subgroup of all, are frequently overlooked even within trauma-focused programs, specialized treatment units, and survivor empowerment programs.,

Misdiagnosis and incorrect or inadequate treatment is not unusual for adults and children with PTSD. For example, refractory depression, substance abuse, eating

isorders, among others, often mask underlying but ndiagnosed PTSD.

Flashbacks and other dissociative episodes can requently be mistaken for psychosis, and especially chizophrenia, and unnecessary antipsychotic medication can ndermine treatment.

Schools increasingly report disciplinary problems rith no understanding at all that some of the children may e suffering from violence-related trauma disorders rather han ADHD or ADD. Consequently, they are improperly Diagnosed, treated with medications for a disorder that they lon't have, and their real problems remain unaddressed.

Because my organization is very much involved with education, I would like to conclude my remarks with some information about the need for education around PTSD.

Most treatment providers have not been adequately trained to recognize and treat PTSD, especially the complex chronic types. The topic is rarely address in universities and. professional schools. Public education about PTSD is Lacking, as well, and most lay people commonly associate PTSD with combat and little else.

These data clearly indicate the critical need for recognition and application treatment of survivors of traumatic experiences. An FDA indication for PTSD drug treatment will focus health care attention on this critical