public health problem.

Successful intervention depends on pharmaceutical and psychotherapeutic treatment approaches', as well as a two fold approach to education in professional and treatment settings, as well as in the patient population and general public.

Since primary care physicians and community mental health staffs are most likely to see people with PTSD first, they must learn to ask about trauma exposure, recognize the symptoms, and treat or refer patients appropriately.

Educating professionals first is paramount to managing the influx of clients that will certainly follow the public awareness programming that might come with this indication for PTSD medicine.

Thank you.

DR. TAMMINGA: The committee appreciates your remarks, Ms. Giller, and thank you for appearing before us.

The second public speaker we have is Ms. Bonnie Green, who is representing the International Society for Traumatic Stress.

Ms. Green.

DR. GREEN: Good morning. My name is Bonnie Green. I am a Professor of Psychiatry at Georgetown University Medical School.' I am here today as president-elect of the International Society for Traumatic Stress

Studies, the ISTSS, which is an international organization of approximately 2,500 mental health professionals who study and treat survivors of traumatic events.

I am here to speak today on behalf of the ISTSS to the importance to posttraumatic stress disorder, PTSD, as a public health issue, and of the necessity of identifying treatments for this potentially debilitating disorder.

PTSD is an anxiety disorder that is experienced following a traumatic life event. An event that can precipitate PTSD is usually a direct or indirect confrontation with death, or with serious bodily injury, which produces an overwhelming experience of fear, helplessness, or horror.

Traumatic events, such as rape, assault, domestic violence, accidents, and disasters are, unfortunately, relatively common in the general population. Estimates are that one-half to three-quarters of Americans have experienced a traumatic event in their lifetime.

Individuals with a PTSD diagnosis following such events reexperience the traumatic event in a number of ways including intrusive recollections, having disturbing dreams about the event, and becoming very upset when they are reminded of the event.

Trauma survivors with PTSD also try to avoid reminders of the event, they feel emotionally numb, and they

have difficulty being close to others. Finally, PTSD involves symptoms of physiological arousal, such as difficulty with sleep and concentration, exaggerated startle response, and hypervigilance. These symptoms can cause substantial disability and disruption of interpersonal relationships.

PTSD is a relatively frequent disorder in the general population. There have now been several studies in general community samples including a very large epidemiologic study of over 8,000 people between the ages of 15 and 54 in the United States, the National Comorbidity Survey, which I am sure you have already heard about this morning, that have assessed exposure to traumatic events and to PTSD.

In spite of very different methodologies, these studies have produced remarkably similar estimates of the prevalence of PTSD in the general population. Specifically, this diagnosis occurs on a lifetime basis in about 10 to 12 percent of women and 5 to 6 percent of men.

Point prevalence estimates, estimates of who would have PTSD at any given time are about 5 percent for women and 2 to 3 percent for men in the United States.

Heidi Resnick and her colleagues, in their national study of women, estimated that nearly 10 million women would have PTSD at some point in their lives, and that

over 4 million had PTSD at the time of the study.

If left untreated, PTSD can last for decades. Recent studies have found high prevalence of PTSD half a century later in Holocaust survivors, World War II combatants, and prisoners of war. The National Comorbidity Survey found that among those people who developed PTSD following a traumatic event, one-third of them continued to have the diagnosis 10 years later.

In addition to the mental anguish that PTSD causes, it also contributes significantly to problems with physical health, as Esther just mentioned. Studies have been accumulating for the past decade that have documented the relationship between exposure to traumatic events and increased levels of physical health complaints, physical illness conditions, physician diagnosis, visits to physicians, and cost of health care.

Only in the past few years, however, have researchers begun to investigate the mechanisms for these relationships. It turns out that there is convincing support for PTSD as an important link between trauma and poor physical health.

This means that among those traumatized in various ways, it is the development of PTSD that predicts poor health and higher utilization of care. PTSD also impact in the economic realm, with findings from a recent study

.ndicating that having PTSD is associated with high rates of inemployment and with significantly lower wages. The :ombined impact of PTSD on emotional, physical, and economic tell-being, therefore, makes it a significant public health >roblem.

While PTSD has been associated historically with :ombat trauma, studies in the past decade have clarified its frequency in non-military populations, indeed, PTSD occurs nost often outside of military settings.

In the National Comorbidity Survey and in other studies, PTSD was most likely to develop in both women and nen following rape. Physical abuse was very likely to lead :o PTSD in both genders, as well.

For women, being sexually molested and being :hreatened with a weapon were also important predictors of ?TSD. Since PTSD is more common in women than in men, it is ..ear that PTSD is an important concern, not only for nilitary veterans, but for civilians in all walks of life.

PTSD often coexists with other psychiatric disorders. The National Comorbidity Survey found, for example, that half of men and women with a lifetime history of PTSD also had a lifetime history of major depression. However, although anxiety and depression often coexist with PTSD, in recent years, it has become increasingly cleat that PTSD has a distinct neurobiology that can been

differentiated from depression.

Some of the more compelling evidence includes the observation that levels of the stress hormone cortisol are lower than normal in PTSD, whereas, they are consistently higher than normal in major depression.

Moreover, in PTSD, the negative feedback inhibition of cortisol, which regulates the sensitivity of the stress response mechanism in humans and animals, is altered in such a way as to produce an increase responsiveness to stress.

This has been established with numerous studies demonstrating an increased sensitivity of the glucocorticoid receptor, evidenced by an exaggerated cortisol suppression following dexamethasone administration, and an augmented ACTH response to the cortisol inhibitor, metyrapone, in PTSD.

In contrast, depressed individuals typically show a decreased sensitivity of the glucocorticoid receptor as evidenced by escape from dexamethasone suppression. This evidence strongly suggests that PTSD is a distinct psychiatric disorder.

Although PTSD first appeared in the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association as'recently as 1980, there is already enough preliminary information about potentially

efficacious strategies to warrant publication of a Treatment Guideline for PTSD, spearheaded by our organization, the ISTSS.

This guideline reviews different treatment options for PTSD including both psychotherapeutic and pharmacologic approaches. As the guidelines indicate, there are indeed efficacious treatments for PTSD.

With regard to medications, the SSRIs, in particular, appear to be frequently used in clinical practice and are well tolerated by patients. Medication trials have indicated that the SSRIs are associated with reduction of symptoms in all of the PTSD symptom clusters, reexperiencing symptoms, numbing symptoms, and physiological arousal.

In closing, the ISTSS wishes to be present today to speak to PTSD as a significant public health problem, and to underscore the importance of developing effective treatments for it.

We believe an approved medication for PTSD would serve to encourage the public to seek and receive treatment for this disorder, and would add significantly to our treatment options when we treat patients suffering from this serious health condition.

Thank you.

DR. TAMMINGA: Thank you, Ms. Green, for speaking

to the committee and sharing your concerns with us.

We have a third speaker here this morning, Ms. Jerilyn Ross from the Anxiety Disorders Association of America.

Ms. Ross.

MS. ROSS: I am Jerilyn Ross. I am president of the Anxiety Disorders Association of America, or ADAA. I am director of the Ross Center for Anxiety and Related Disorders here in Washington, and I am author of a book called "Triumph Over Fear."

Thank you, Mr. Chairman, and members of the Advisory Committee for the opportunity to speak to you here this morning.

For those of you who don't know us, the ADAA is a national nonprofit organization, and we are dedicated to the early prevention, identification, and treatment of anxiety disorders. We were established in 1980, and we are a partnership of researchers, clinicians, patients with anxiety disorders, and their family members and other interested individuals.

Together, we work towards the prevention and the cure of anxiety disorders by supporting research and by helping consumers gain early access to diagnosis and treatment. We also seek to reduce stigma, we stimulate ongoing research, and we educate health care professionals

and consumers about effective treatment.

Increasing access to safe and effective treatment for people with posttraumatic stress disorder, as well as with other anxiety disorders, is a major concern of our organization, and therefore we hope for a positive outcome to your deliberations today.

I am here on behalf of more than 19 million Americans who suffer from an anxiety disorder, specifically, today, the 8 million Americans who suffer from PTSD, posttraumatic stress disorder, which is a severe and potentially debilitating mental health problem.

People with PTSD come from every walk of life, every social class, every educational level, and every professional achievement. These are people who have been exposed to an extreme trauma, maybe an accident, a natural disaster, been raped, criminally assaulted, or exposed to c &at or physical or sexual abuse.

And these are people who may at one time have been healthy, productive individuals, who now, following exposure to this trauma, are suffering real life-altering, but treatable disorders.

People suffering from PTSD reexperience the traumatic event in the form of flashbacks, nightmares, intrusive, distressing recollections, and they develop avoidance behavior, they develop increased arousal, and

numbing, where they can't feel anything, positive or negative, emotionally.

They become vulnerable also to secondary problems, panic attacks, depression, substance abuse and suicidal thoughts and attempts, just to name a few, and many of them, most of them are unable to receive an accurate diagnosis for their illness, and many of them end up being dismissed as hypochondriacs or eccentrics or malingerers without getting of the help that they need and so desperately deserve.

Each year at ADAA, we receive tens of thousands of requests for information from people with anxiety disorders. As a matter of fact, we are currently experiencing more than 43,000 people per month who spend a minimum of 10 minutes on our web site seeking information, and we also get letters and phone calls from people who describe their heart-wrenching pain, their suffering, as well as their fear, their confusion, and their despair.

What we hear, what we find most frustrating from these people is that they are not able to find health professionals in their communities who are both knowledgeable about anxiety disorders, and able to provide effective treatment. Sadly, at this time, particularly for PTSD patients, there'are no approved medications and millions of people with PTSD are suffering, Oftentimes silently in the dark, with ignorance, frustration, and

shame.

According to a study that we published recently in the Journal of Clinical Psychiatry, called "The Economic Burden of Anxiety Disorders in the 1990s," PTSD was found to be one of the two anxiety disorders with the highest rates of risk factors for psychiatric service usage. PTSD was also among the anxiety disorders associated with most substantial impairment in workplace performance.

The good news is that thanks to new scientific understandings of the biochemical component of PTSD, and studies demonstrating the efficacy of specific biological and psychological treatment, things are beginning to change for the better.

Our association has joined with other mental health professional, as well as with other advocacy groups, in hopes of spreading the word, getting the word out that PTSD is a bio-psycho-social disorder that is real, that is serious, and that it is treatable.

Improving physician e&cation about PTSD and increasing the availability of safe and effective medications, as well as of psychological treatments, are vitally necessary, so that those suffering from PTSD are better able to manage their illness and go on to lead full and productive lives.

We have seen the difference that this has made as

effective treatments have become available for other anxiety disorders , like panic disorder, obsessive compulsive disorder, most recently for social anxiety disorder, and I believe that your deliberations here today can contribute greatly to achieving the objective that all people with anxiety disorders can get the diagnosis and the treatment that they need and deserve.

I thank you very much for your consideration today.

DR. **TAMMINGA: Ms. Ross,** thank you very much for your remarks to the committee.

Advisory Committee Discussion and Deliberations

With this presentation, we conclude the open public hearing portion of our meeting, and we begin the Advisory Committee deliberations about sertraline for **PTSD.**

We have heard this morning from Pfizer, who produced the data about sertraline, you had **an** opportunity to ask them some questions. We have heard from the **FDA** about their analysis.

We have a number of questions in front of us by the FDA, and the questions that the committee has in front of us today are questions that are not only about safety and efficacy of the compound for the indication, but actually questions about the indication itself, those questions that Dr. Laughren posed to us earlier.

I would like to suggest that the committee begin its deliberations by addressing some of those questions about the diagnosis that Dr. Laughren put to us, about PTSD as a new indication, how widely recognized and accepted is the entity, can PTSD be considered an independent diagnosis, and then more practical questions about actually doing studies in PTSD.

I would like to invite the committee to begin a discussion on that.

DR. DOMINGUEZ: I will make a very general statement to begin with. It is a disorder that is hard to ignore, although I think refinements will continue to take place in the definition of the disorder. I think that there are clusters of symptoms that are distinct enough that indeed it is recognized within our field.

So, I would like to immediately begin by expressing my opinion that yes, this is a distinct disorder where we should be seeking specific forms of therapy, both psychosocial and pharmacotherapy. I have no problem with that.

DR. TAMMINGA: Thanks. We have three PTSD experts here, and perhaps the committee could hear from them.

Dr. Southwick.

DR. SOUTHWICK: I also feel this is a distinct disorder that has had a very long history and gone by many

different names throughout history, and many of the early names were derived from combat experiences like shell-shock, irritable heart of soldiers, combat fatigue, et cetera, and as DSM was formed in 1980, PTSD became a formal diagnosis, and I think what we have seen, although some of the symptoms have changed since DSM-III, they are relatively stable between DSM-III-R and IV.

There has been really very little change with the core symptoms, suggesting that with experience and research and clinical input, that the disorder has been more carefully and rigorously defined over the last number of years.

Also, as mentioned earlier, there are a number of very distinct PTSD symptoms, I think there are eight, that are specific to the trauma, which helps to differentiate from other comorbid diagnoses.

DR. TAMMINGA: Thank you.

Dr. Brewerton.

DR. BREWERTON: Yes. I think among the questions that are posed to us today, this is probably the easiest one. In my mind, there is no doubt that PTSD exists. It certainly fits with all of my clinical experience, and I think also the science is at a point now that does, in fact, confirm its existence and distinction from depression.

I would add, among the comments made already, that

there are several psychiatric disorders that have significant overlaps with major depression. Certainly PTSD is just one of many.

We think about the anxiety disorders, eating disorders, substance use disorders, somatoform disorders, dissociative disorders, personality disorders, all of those have strong and important links to depression, but yet remain as fairly distinct entities, and I think PTSD is just yet another that fits that bill.

So, I would think that this is the easiest question and I think the overwhelming evidence is in favor of its independent existence.

DR. TAMMINGA: Dr. Brewerton, would you comment a little bit more on the nature of the evidence that it is an independent disorder?

DR. BREWERTON: Well, I know at the Medical University of South Carolina, in the National Crime Victims Research and Treatment Center dataset, which is in reference to one of the studies mentioned today by Heidi Resnick, which is the National Women's Study, which included over 4,000 women randomly selected across the United States, there have been detailed cluster analyses of the symptoms generated from this study, clearly again showing the links between PTSD and depression, but that they do, in fact, separate out in terms of factor analyses as clustering

together and separately.

I know that there are a number of other studies like that, that show its independence.

DR. NORTH: There is considerable controversy regarding the diagnosis of PTSD among clinicians, and I think part of the force responsible for that is the comorbidities and confusion among diagnoses and the preexisting disorders, but I myself come from epidemiology of disasters, and I can say that what we see after disasters often appears very different from much of what we see in other populations, and that is because we can study PTSD in a more pure form after disasters because in other populations, PTSD is confounded with vulnerability to a traumatic event, whereas, disasters select populations actually unselected for previous psychopathology.

In this setting, I can say after interviewing very many disaster survivors, that I have seen many people with PTSD without any previous or coexisting comorbidity, and I am--definitely a believer in PTSD from my own research experience, and I believe that PTSD looks different in different populations, and that may be a source of the disbelief among many clinicians, but in my experience as a researcher and a clinician, it is apparent to me from the data and from clinical experience that this is an important disorder.

DR. KATZ: I have a related question. Everything or most everything we have seen today, both in terms of the literature, the previous literature that was discussed, and the data that we have had presented from this application suggests that veterans, people whose particular traumatic event was war or combat, don't seem to respond to treatments that perhaps others do respond to, raising the question as to whether or not that is a fundamentally different thing, whether that is a variant of PTSD, and it raises the sort of generic question of does the event, does the specific traumatic event 'have anything to do with what we are calling PTSD. I just wonder what people think.

DR. HAMER: That is an interesting question, and I think it relates directly to what happened in the clinical trials here. There a number of events or characteristics that are clearly very confounded, at least in the databases we have - being a veteran, being male, the type of trauma, the age of exposure to trauma, and the length of time since trauma and the duration of reported PTSD.

We are focusing, you are focusing at the moment on the veteran versus non-veteran issue. Pfizer and the reviewers tended to focus on the gender issue, but to some extent it could be any of them. I mean it could be that if we had the data to find a cohort of males who had been sexually assaulted at roughly the same age as the women in

our cohorts have, and it has been that duration of time since the assaults, we could find a similar pattern in terms of response to medication or we might not, but given the data that we have at hand, trying to separate out gender effect, trauma effect, veteran, duration, age, and all that sort of material seems to me to be fundamentally difficult.

DR. TAMMINGA: I am wondering if people who have had experience with treating PTSD veterans versus non-veterans, or combat trauma, could speak to that.

Dr. Southwick.

DR. SOUTHWICK: I think it is a complicated issue. One factor is in combat, one is typically exposed to multiple repetitive traumas that may last, go on for years or a year or whatever, so that one of the most important questions I think is looking at the nature of the trauma, how repetitive it is, that sort of thing.

It is also true that how you sample, which patients you select, I think is very important because if the patients are selected from the VA.now, 30 years later, as opposed to a community sample, advertising for veterans who may have some of these symptoms, you may see a different response because most of the veterans who are coming to the hospital now have very severe PTSD and have been coming for a long period of time, and have probably been in treatment, and that sort of thing.

So, I think sampling is very important issue. I am not totally convinced that veterans do not respond to medications. For example, 15 years ago, there were some studies done on veterans at outreach centers, and so forth, and they had not been in treatment for as long a period of time, and I think some of those results were more promising.

DR. BREWERTON: I definitely agree it's a most complicated issue, and another factor that I wonder about is the issue of service-connected disability and what percentage of the veterans had service-connected disability, which becomes a disincentive to improvement.

DR. HAMER: That is another confound. I would actually be curious to ask Pfizer, since I haven't seen the protocol, what kind of exclusion criteria there were for either involvement in some sort of a legal process, that is, whether a lawsuit was ongoing, or whether the subject was receiving or about to receive some sort of disability payment that would be an incentive to continue to report PTSD symptoms.

DR. TAMMINGA: I would like to broaden that question just a little bit to include the question of whether these veterans were, like Dr. Southwick implied, recruited from a VA hospital or were they veterans recruited generally from the community.

DR. FARFEL: The exclusion criteria for all four

of the trials, which include the veteran study, excluded subjects who were currently in litigation, but did not exclude veterans or anyone who was currently receiving disability benefits related to their PTSD, only if it was in terms of litigation.

DR. HAMER: And, in fact, was there a higher rate of people receiving disability payments for PTSD in the veterans sample as opposed to the community sample?

DR. FARFEL: That would be somewhat of a logical conclusion, but we did not actually collect the data.

I am sorry, could you repeat your question?

DR. TAMMINGA: Where did you recruit from, did you recruit from the hospital?

DR. FARFEL: Primarily, as I understand it, the VA medical centers recruited from their hospital patient base, but they were permitted to advertise and, in some cases, they did. In addition, several of the VA medical centers were allowed to enroll subjects who were not veterans that they found through their recruitment, so there are approximately, if I am correct, about 20 percent of subjects who met that criteria.

DR. WINOKUR: While we are on this tack, were there differences in this study with respect to prior treatment attempts and also treatment failures as compared to the other studies?

DR. FARFEL: From what we could determine, there was no difference in the prior treatments' success or failure in Study 641 compared to the two positive general population trials, however, as noted in your briefing document, we did not in the most rigorous way collect the prior treatment history data, so we backed into it looking at using the data that we did collect regard the patient self-report of psychiatric medication or psychotherapy administered within the past five years, and we used the indications of PTSD, depression, sleep, and I believe anxiety to approximate those who might have been treated for symptoms related to this disorder, so it was not the most rigorous collection of prior treatment history.

DR. BREWERTON: In response to your question, Dr. Katz, regarding the type of trauma and what might account for the differences in the males, in the veterans, there has been a number of studies that have shown that life threat is a powerful predictor of PTSD and the degree of life threat, and I think, by definition, combat-related PTSD is probably in general--certainly there are exceptions--but in general, a more life-threatening situation and trauma than assault even though they certainly can be life-threatening, but not necessarily so. That is one possible explanation for the findings that we hear today.

DR. TAMMINGA: Do we know anything about whether

the dose of life threat is related to the severity of the illness as related to the treatment outcome?

DR. SOUTHWICK: There are many studies that clearly show that level of traumatic exposure is related to development of PTSD symptoms., so the more combat, the more life-threatening experiences, the more likely one is to develop PTSD, and not just combat, but other civilian traumas, as well.

DR. TAMMINGA: Is that related to treatment response?

DR. SOUTHWICK: I am not sure. I assume that it is related to treatment response. I can't think of specific studies, but that is my impression.

DR. HAMER: I also have a question for Dr. Southwick. One fundamental difference between combat and civilian assault or rape is that in combat, you are part of a-cohort which is being assaulted somewhat impersonally. By and large there is not a specific individual out there trying specifically to hurt you; while an individual assaults or rape, there is.

Do you think that relates, do you have any data to think that relates in any way to the potential difference in efficacy that we have seen in these trials?

DR. SOUTHWICK: I don't know data specifically to answer your question. I think that one of the variables

;hat is felt to be very important with regard to stress disorders is how uncontrollable the stress is, and combat is highly uncontrollable. If you are sitting in a foxhole, you cannot control whether the mortar around is going to hit you or not.

So, there is a huge literature on the effects of uncontrollable stress on later development of symptoms, and t think combat is the perfect example of stress that you cannot in any way control or have very little control over it, at least at times.

DR. COOK: I would just like to point out that Erom the data that we are looking at in terms of efficacy today, most of it that is positive seems to not be the combat related,' and a very large group seems to be post-child and sexual abuse.

This may be something different, so I have no question about the existence of PTSD, but having seen lots of victims of child physical and sexual abuse at the time, it---is remarkable that there is quite a bit of disconnect between the literature;;

What I see are--again, not knowing which factor is which and perhaps from a skewed perspective--it seems like there may be a relationship between onset and later treatment.

Now, this is worth'pursuing because many times

people would assume, well, if the onset is early, it may be harder to treat. It is actually possible that the assault during a different time, the nervous system may have a different consequence that may have a relationship to this treatment, and not to the other.

In terms of the specific question in terms of the data, I am not sure that we have evidence that postcombat-related PTSD responds to Zoloft. It may respond better to something else. I don't know that we could say that yes or no, but I raise the question.

DR. BREWERTON: Along those same lines, I thought that the data were interesting that showed that the men who were physically or sexually abused as children did respond to sertraline versus the men who had non-childhood sexual or physical abuse. So, I think it supports the notion that the type of trauma is important in response and perhaps more important than gender.

DR. TAMMINGA: You are suggesting that the gender effect may be an epiphenomenon about the type of trauma.

DR. BREWERTON: That's right. You know, they are embedded within each other. Clearly, the males have much more combat related, and the females have much more civilian related.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: It just seems worth mentioning, as

Pfizer pointed out, that that is a tiny number of patients, I think maybe eight in the treated group.

DR. TAMMINGA: It is a good point remembering what Dr. Smith cautioned us about.

In addition to the more general discussion of PTSD and its status as an independent entity, the FDA also would like us to comment about the specific study of PTSD, the kinds of protocols, the duration of studies, the need for long-term studies, the appropriateness of the outcome measures.

I would invite some comment on those practical issues now. Dr. Southwick.

DR. SOUTHWICK: With regard to duration of treatment, I think there is mounting evidence that the trials need to be perhaps somewhat longer than in other conditions or some other conditions anyway, and I would think a minimum of eight weeks and more, as we saw in the sertraline, 12 weeks, there was a difference in their other pharmacologic studies that seem to have shown similar results, that the effects may take a while to be seen.

DR. TAMMINGA: Dr. Brewerton.

DR. BREWERTON: I would very much like to second that. I know from the Yale group, there was a study by Goodman and Price, I believe, about OCD and fluoxetine, and if you followed out the patients to 16 and maybe even 20

weeks, I think, you have gotten a significant amount of responders out at that end, whereas, if you just cut it off at 8 or 12 weeks, you don't get as much of a response, and it may very well be true with this anxiety disorder, as well. When you have got patients being ill for 12, 18 Tears, it may be unreasonable to expect them to improve in such a short time.

DR. TAMMINGA: Surely, if PTSD is a chronic condition, one would ask the question whether the acute symptom response to drug treatment predicts long-term response. One would want to have some information about that. The treating physician would want-to have some information about that.

DR. NORTH: Along those lines, it would be important to have data on acute PTSD as opposed to chronic PTSD as defined as DSM-IV.

DR. TAMMINGA: You might suggest how one would get those data. They may only come from the kind of PTSD populations that you run into.'. Would-that be true?

DR. NORTH: I don't have the exact statistics on what percent of people showing up for treatment show up shortly after a trauma, but the data seem to indicate that a considerable majority of people have onset of symptoms acutely after trauma, but that might be one way of obtaining subjects short of going to a'disaster and doing a study

here.

DR. WINOKUR: In this study, as I recall the data, it was, of course, a dose titration study, and the dose gradually crept up, as would be expected, to about 150 mg in all four studies, and also it was at 12 weeks that some of the measures started to be clearly different, so it does raise the possibility that perhaps a higher dose for a longer period of time may have brought out even more clearly some differences that were apparent at 12 weeks, but clearly might have been more evident with a more continued period of treatment.

DR. TEMPLE: Actually, I was curious about the titration design. Here is a condition that seems to actually respond very late and people are titrating every couple of weeks in terms of response. It doesn't make a whole lot of sense.

I would be curious as to why that design was chosen. If it was chosen to avoid adverse effect, that would make some sense, but ordinarily I think you would learn more from a randomization to fixed doses even if you inched your way up to those doses, and you didn't really get any of that kind of information here.

Now, of course, you could analyze this to see if there is a dose/response hidden in there, but I would be curious about that.

DR. HAMER: Actually, I think it is unfortunate that there were no fixed dose studies done as part of the set, because it makes it really utterly impossible to discern in any decent way a dose/response effect.

Given a particular side effect profile, it is more than possible that the people in whom there is a lack of efficacy could be the ones who get inched up to the higher dose, so you wind up showing an inverse dose/response effect if you analyze these data naively.

So, I would have a hard time leaving dose/response out of any set of purely flexible dose trials unfortunately.

DR. TEMPLE: You would say then that we should be advising people to utilize fixed dose designs in this situation as we do in most others, of course, frequently ignored?

DR. HAMER: Yes, I was really surprised that there was not one flexible dose and one fixed dose study in terms of the set we were really asked to examine, because it is true, in almost all of the other things you do, you strongly advise people to do both types of studies, and there is a good reason for that, so that you get a handle on dose and dose/response, and this makes it more difficult.

DR. TAMMINGA: In the current clinical research climate, one would have to recognize there is some skew against doing dose/response studies and going to doses that

are most efficacious for most people to be compared with placebo. I was just trying to state the other point of view.

Dr. Dominguez.

DR. DOMINGUEZ: I would like to make two points. Again, I was also surprised at the absence of fixed dose studies. I think that the excuse that previous applications for other indications have not found a relationship between dose and response is a very weak excuse not to do it.

So, even though previous applications have not shown that, that does not justify not having that information available.

One more comment regarding the duration of treatment or the duration of the acute phase of a study. I personally believe that 12 weeks may be the optimal, and I disagree with you. Having considerable experience in the treatment of OCD, the vast majority of patients, if you treat them aggressively with pharmacotherapy, will respond well within 12 weeks of treatment. You only get the outliers at week 8, week 10 or week 12.

You have to balance that against the human subjects issue, the continued exposure of the individual to placebo for an extended period of time. So, I personally believe that a 12-week trial, and when I received the information initially, was optimal in duration.

DR. TAMMINGA: Dr. Temple.

DR. TEMPLE: Just an observation. I am sure any sponsor that is interested in pursuing this sort of claim will note that one of the two favorable studies would have been much less persuasive if it had stopped prior to 12 weeks. That is an important lesson I think people will pick up very quickly.

DR. TAMMINGA: Would any of the PTSD experts like to comment on the dose/response question?

DR. BREWERTON: I would tend to agree with the sentiment about 'having fixed dose studies. I think that are some, even though not with Zoloft, there are precedents with other SSRIs, notably OCD tending to respond at higher doses in depression, and bulimia nervosa, as well, tending to respond at higher doses than normal antidepressant doses.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: I want to get back'slightly to the issue earlier of gender difference, type of combat difference, and so forth.

We haven't seen them in our handouts, but you did Phase I trials prior to this, and furthermore, did you collect blood levels during the Phase III trials? Was there any sort of a difference in pharmacology, pharmacokinetics, pharmacodynamics between men and women, and were there different dose blood level curves which might explain a

piece of whatever gender differences we see here?

DR. RYAN: We did not collect plasma samples during our Phase III clinical program with sertraline, however, if my memory serves me correct, for the panic disorder program in a randomized fixed dose design, patients randomized to 50, 100, and 200 mg at steady state, when trough levels were taken, and when we evaluated the levels in males versus females, there were no significant differences in those concentrations.

DR. HAMER: What about the Phase I, even though we are going back a while, pharmacokinetics and pharmacodynamics data, does anyone remember those?

DR. RYAN: Dr. Alderman, could you come forward and speak to that, please.

DR. TAMMINGA: Could you identify yourself, please, and your relationship to Zoloft.

DR. ALDERMAN: My name is Jeff Alderman. I am with Clinical Pharmacology in Pfizer.

We did have one Phase I study that looked at differences in gender and age as it happened. If I could have Slide No. 6, please.

[Slide.]

These are results from 11 subjects in each group, young and elderly, as you see, the young being 18 to 45, elderly 65 and over. In each case, male and female, equal

numbers were looked at. If you look across the pharmacokinetic parameters, you can see some differences, but if you look only for statistically significant ones, the young males were somewhat less than any of the other groups. There were no gender-specific differences.

DR. TAMMINGA: Could you tell us what young and elderly are in terms of years?

DR. ALDERMAN: 18 to 45 for young, and 65 and older for elderly. All of these, by the way, I don't think I mentioned, this was the top dose of sertraline 200 mg per day for more than two weeks.

DR. TAMMINGA: And these Phase I data are similarly manifest in your other studies with sertraline, your depression studies or whatever?

DR. ALDERMAN: These levels are consistent, yes.

DR. HAMER: So, to interpret this correctly, you have an area in the young, you have an area under the curve that is 50 percent higher in the females, and you have a half-life that looks like it's about 50 percent longer.

DR. ALDERMAN: In this particular group of 11 each, yes.

DR. HAMER: Which, with a little bit of interpretation, would mean that there is sort of far more sertraline hanging around in the blood of the females than the males.

DR. ALDERMAN: There is the difference that you pointed out.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: I was interested in any information from the depression clinical trials with Zoloft in terms of even hints of gender differences in terms of either magnitude of response or rate of response or different doses, anything that we can kind of think about in considering this issue here.

DR. RYAN: Yes. For the other three currently approved indications for Zoloft, depression, obsessive compulsive disorder, and panic disorder, there was no hint of this sort of gender by treatment interaction in any of those pivotal studies which supported those indications.

DR. TAMMINGA: Has the company done any dose analysis of the PTSD effect?

DR. GAFFNEY: Are you asking whether we attempted to do a dose/response within these four studies?

DR. TAMMINGA: Yes.

DR. GAFFNEY: No, we did not do that for the reasons that were pointed out, that it is very difficult to yet a dose/response effect when you are doing a titration study such as this.

DR. TAMMINGA: Thank you.

Dr. Lacey.

DR. LACEY: Part of the inclusion criteria equired young women to be on contraceptives or practicing ome form of birth control. In raising the question about he pharmacological kind of differences and seeing the ender differences, I am curious as to whether or not--well, hen I looked at the medication list, contraceptives were ot listed either place as an included or excluded edication, so I am just curious as to whether any look was ade at those types of medications in terms of effect?

DR. FARFEL: Oral contraceptives were permitted, nd, no, we have not looked at any analysis&f subjects who ere *or* were not on oral contraceptives.

DR. WINOKUR: I wanted to ask Dr. Farfel, since, as we talked about before, the doses did creep up in all four of the studies pretty much to the same level, and I think that is acceptable, do you have a sense or I am not sure what kind of instructions the clinical investigators had in terms of was dose increase, especially later, primarily driven by lack of or Inadequate response, or do you have any other sense about why dose was continually. upward titrated to the end of the study?

DR. FARFEL: No, I do not have a specific sense of uhy the dose continued to be moved upward. They were only instructed, the investigators, to titrate in terms of considering both efficacy and tolerability.

DR. TAMMINGA: One of the questions that the FDA sked us to consider is the kind of trial designs that might e optimal to use to suggest long-term efficacy and whether r not those trial designs should be required before pproval or whether we need those data eventually, but not t the time of approval, and what kind of trial designs ight be optimal.

Any comments on those kinds of questions from the ommittee?

DR. DOMINGUEZ: Just briefly, I think that any ype of crossover trial carries with it so much baggage, hat I was even surprised to see it as a question in this ight as a possibility for a chronic disorder.

I cannot think of any sort of crossover design hat would be convincing.

DR. SOUTHWICK: I think one of the other problems ith a crossover design in PTSD is that the symptoms do wax and wane, for example, people talk about anniversary reactions where their symptoms are worse at a particular time of year, and it would be really impossible to factor that out.

DR. TEMPLE: I guess that was a reference to the initial study being crossover design, and certainly what everybody said makes sense. A maintenance trial in which there is a withdrawal is, technically speaking, a crossover

esign although it is not a randomized order crossover, and hose are commonly used now to show there are persistent ffects in depression, and we eventually see those for most rugs.

Actually, Pfizer does have a trial of that design ere. I guess the question is how do you feel about those, nd we are still interested in whether you think that is so mportant it ought to be done prior to approval, which is ot the normal standard in this country although it is in urope actually.

DR. HAMER: First of all, I want to say how much I ppreciate seeing a physician argue eloquently against the rse of crossovers, because they do carry with them so much statistical and methodological baggage that it is really difficult to figure out just what your generalizing to and ow you are generalizing.

In terms of Dr. Temple's comments, the kinds of sustained efficacy/relapse prevention trials that we get with these re-randomizations, they are not crossovers in the same sense, because we are really restricting the generalizations we make to the population in some sense that we are using, and so there really is much less difficulty in those in making those generalizations.

DR. WINOKUR: I think longer term studies for the treatment of PTSD will be important eventually certainly in

light of the chronicity of the illness, but I think in fairness, the same points and issues apply to so many of the disorders that we treat, and such longer term studies for us and our colleagues clinically have been very important in establishing guidelines for once treatment and remission of symptoms has been established, how to best manage patients in the longer term, but I think it was pointed out very nicely in the introduction, I think by Dr. Marmar, that there have been so few studies even looking at acute treatment under controlled conditions, that for this disorder, this seems like a very key point to establish before going on to longer and more complex designs.

DR. TAMMINGA: I think the committee may be ready to move on to the specific questions of sertraline in PTSD.

We have had several quite specific parts of this question addressed to us by Dr. Smith. I could just summarize a couple of those, that we have two out of three studies in the general population that show an effect, but one. that doesn't show an effect, and we could have some discussion of that, some additional discussion, although we have had a lot about the gender by treatment interaction, and then just a carrying on of our more general discussion.

Dr. Cook.

DR. COOK: As far as the general question we didn't address, there is one that I thought was very

important, particularly based on the data today, is the question of is PTSD found in pediatric populations and should sponsors of drug products be encouraged to study this disorder in pediatric patients.

I think we have already made those comments, but I wanted to have that fully discussed, because in a sense, more than 40 percent of the population is being treated as adults, when they should have been treated as children or were treated as children, but without this.

DR. TAMMINGA: So, the committee certainly supports early and aggressive studies of PTSD treatment in children. Yes, Dr. Dominguez.

DR. DOMINGUEZ: I know that the Agency can do just so much in the encouragement of development of a product or an agent for a specific indication, but as I was reading the materials that were provided prior to the meeting, I thought to myself wouldn't it be nice to have been able to dissect the pharmacologic effect of the drug in the context of a study which would include at some well-established psychosocial intervention to run concurrently with either medication or placebo.

I think this is particular germane to a disorder with so much comorbidity and where psychosocial interventions have been shown, in my opinion, to have a more robust response than the pharmacologic response that I am

itnessing from this application.

DR. TAMMINGA: There may be some psychosocial reatment buried in the design of the trial. In other ords, if you have a newly diagnosed PTSD person that hasn't one through the list of symptom response, talked to omebody extensively about their trauma, it seems that just he conduct of the study itself will include some sychosocial treatment.

Dr. Southwick.

DR. SOUTHWICK: I think this is a very important ssue. It has to deal with recruitment and how subjects are ecruited, are they recruited from a clinic where a person s accustomed to the idea of PTSD, are they recruited by advertising, someone who has never been in treatment, and as ou said, part of the response--and we saw some pretty big lacebo responses--may be education.

The person becomes educated, perhaps they have lever been in a relationship with a therapist who is really ttending to them, and in some ways you could see the repetitive asking of questions about PTSD as a form of exposure.

So, it seems to me it is important to really nderstand how recruitment is done and exactly who the patients are, and how closely the patients that are being studied will match the patients that you are actually going

0 treat.

DR. DOMINGUEZ: Let me also add that that is my eeling, that the sociodemographic profile of the population hat was studied, it does not appear to be representative of he individuals with PTSD. It is representative of those ndividuals who will sign an informed consent for a double-lind trial.

In general, outreach must take place in order to nclude a more mixed racial population, a more mixed inority population, and yet let me just personalize this or a second.

It is quite different to have gone through urricane Andrew in Miami in 1992, and have your roof blown ff, knowing that you have insurance, knowing that they are oing to put you up, knowing that you have a mother who has home, that you can stay there for a while, versus various ckets of the population in South Florida which did not ave the social support system, did not have these recourses, and you may indeed get a differential response to harmacotherapy when you factor in those social demographic ariables.

Again, it is an issue of average. It is an issue of getting out there and expending more effort to try to recruit those populations into studies that many of these populations are very wary to participate in for various

easons, but they are absolutely necessary and certain postmarketing, they are necessary.

DR. TAMMINGA: Dr. Lacey.

DR. LACEY: I would like to I guess follow up on r. Dominguez's comment there about the recruitment of opulations. Race, as we heard, is mandated as a onsideration in these studies, but at the same time, as we aw the analysis of the data, the number ended up being so mall that we got no meaningful differences there, eaningful findings there.

As we discussed posttraumatic stress disorder, we talk about sort of like the combative disorders in males, on the one hand, as has been pointed out here, and the sexual assault, on the other, and we also talked about disaster things, yet, we know within this society,. for all of this century at least, there is a type of violence that is perpetrated and has been perpetrated and continues to be that causes some of the same kinds of things, and they end up showing up in people of various racial makeup other than the white majority.

So, I am once again just saying that as we recruit for persons in studies, I think those kind of considerations need to go into the formula. Otherwise, we end up with a definition that says we have something that works, but we haven't studied it in various parts of our population, yet,

hen those persons with that definition come in, they may ot respond at all to what is going on.

So, I would want to follow that as much as ossible.

DR. TAMMINGA: Thanks, Dr. Lacey.

Dr. Hamer.

DR. HAMER: I also what to emphasize that for iological reasons, that is, we know that there are ometimes vast ethnic and racial difference in etabolization and processing by the cytochrome P450 soenzyme systems, and it is entirely possible that lifferent doses **may** be required in different subgroups, and .t is important that we know that.

DR. TAMMINGA: Any ideas or opinions about Study 382? That was the study in the general population which showed no difference between placebo and drug. Any comments about it? Dr. Brewerton.

DR. BREWERTON: One of the things that I noticed was that it had a lower rate of assault in terms of the percentages. The other two were 62, 63 percent physical, sexual assault, whereas, this one I think was 54 percent, so I am not sure how significant that difference is, but that is one thing that jumped out at me.

Again, it gets back to the issue of type of trauma and the role that that plays.

DR. TAMMINGA: Dr. Smith, we are not giving you very much help on this one.

Dr. Hamer.

DR. HAMER: Well, as a statistician, then, I will give Dr. Smith some help. You know, things happen.

[Laughter.]

DR. TAMMINGA: We need more than that.

DR. HAMER: No, but it is true, sometimes clinical trials fail. Sometimes placebo groups respond, sometimes drug groups especially in psychiatry trials tend to fail to respond. You know, a failed clinical trial is not particularly unusual, and not particularly really disconcerting.

You know, if we saw a pattern of eight clinical trials of which only two were successful and six failed, that would be very different, but I don't have any--I know that that is not real help, but, you know, probability is such that sometimes these things happen.

DR. TAMMINGA: Dr. Katz. . .

DR. KATZ: I just want point out, just sort of maybe enlarge the context, we have asked the question about how do we reconcile 682 with the other two positive studies, but the reality is there are two negative studies out of four, and we have sort of assumed--I am sure we will have more discussion about this later--that that is because it is

. different population, it is not the general population, but, you know, that is an explanation after the fact even though it seems sort of fairly obvious, but reality is just looking at the results, two out of four are positive, two out of four are not, so it is not really two out of three.

DR. HAMER: I didn't say it was two out of three. I just concentrated on the one in the general population if for no other reason than in some psychological sense, we have sort of pushed the other one off the books.

DR. KATZ: Right. I just sort of. want to put it back on the page.

DR. WINOKUR: But for a perspective with the two out of four, what we have clearly heard is there appears to be a significant gender effect, or at least that is connected to something else that we need to try to understand better, and there is something very strikingly different about the veteran population study.

So, at least on the face of it, the gender effect is as robust as the data we have, we have reason to focus primarily on the three studies that would have more of a chance of being evaluable in terms of a response.

DR. SMITH: If I might follow up to Dr. Hamer's comment that things also don't happen, as well, so what our concern is, is that could the trend be in the other direction in which we have two unusual results in 640 and

71, as a regulatory agency, we want to protect the public rom something that doesn't work.

DR. HAMER: Although, of course, since we attempt o rig statistics so that we don't say something happened nless there is a whole lot of evidence that it did, to some xtent there is a difference in weight between two things hat happened and two things that didn't happen or failed to rove that they happened.

DR. TAMMINGA: We have already said a lot about he gender issues. Is there anything more that we have to omment on about the gender issue? I am sure. Yes, Dr. eller.

DR. GELLER This actually is a question for the DA. Are there any rules about the ratio of positive to egative studies that are desirable at approval time?

DR. LAUGHREN: There are no strict rules about at. One thing that we like to see for an indication that s more mature in some sense than this is, from a regulatory standpoint, we like to see an active control arm in a trial o help us in interpreting it, so that if an active standard rug, which is believed to work, also fails, we are more inclined to discount that study.

That obviously is not a strategy that you can use arly on in the development of a new indication, but there are no strict rules about what the ratio has to be.

DR. TAMMINGA: Dr. Geller.

DR. GELLER: What in the experience would be a desirable ratio?

DR. LAUGHREN: Are you asking what is the worst case?

DR. GELLER: Or the best case.

DR. LAUGHREN: I really can't give a number. It is always a judgment based on the entire set of evidence provided. You can look at individual studies, even those in which you don't have an active standard to rely on, as is being done here with the veteran study, to try and explain why that study might have failed. But there isn't any precise number that one can rely on. It is always a judgment based on the entire set of evidence.

DR. TAMMINGA: The phrase I recall is a preponderance of evidence?

DR. LAUGHREN: Yes, it's an art more than a science.

DR. TAMMINGA: Dr. Brewerton.

DR. BREWERTON: Along those same lines, are there any guidelines in terms of sample sizes or sheer numbers in the studies, however many they are?

DR. KATZ: No, not in terms of determining effectiveness in any event, that we often say that the trials need to be as big as they need to be, and it is going

o depend on the variability, of course, it is going to epend on the treatment effect, the population, the placebo, ou know, presumed placebo response.

It is hard to say. Certainly, there are onditions where we have considered studies positive or pproved drugs on the basis of fairly small studies, but in hich the treatment has been shown to be statistically ignificantly different from the control.

Of course, the smaller the studies, the more ikelihood that there is some bias creeping in or that there s some imbalance in important characteristics that you lon't really know how to test for, you don't even know what hey are necessarily.

So, we like to see larger studies, but there is no specific requirement for numbers. The standard in law for letermining effectiveness is substantial evidence of ffectiveness, which is ordinarily considered to be at least wo trials.

I am not even sure the standard is preponderance. It is just that the presumption is if two adequate and well-designed trials give you statistical significance, that is pretty unlikely by chance that the drugs actually don't work. So, how many studies out of how many? At least two ordinarily.

DR. TAMMINGA: Sertraline is a little different

rom some of the other drugs that come before the FDA, that ave broad safety database and other indications available, hich we didn't see, but which we can understand is solid nd reasonable.

Dr. Geller.

DR. GELLER: This bears on the question that you ad raised, that actually I was indirectly addressing in erms of gender. Are there precedents in a case like this or recommending approval just for one gender or the other?

DR. KATZ: Apparently, there are cases in which a pecific indication has.been approved for one sex, but we ave no personal experience in the Division as far as I know ith that, and in those cases, I think it is usually because nly one sex has been studied. This is a different ituation.

DR. LAUGHREN: If I can just add a comment on t, it is a little bit problematic in my view from a regulatory standpoint to entertain approving a claim on what ould essentially be a subgroup analysis if we were to focus nly on the women even though it is obvious after you see he overall effect, and you go back and subgroups, it appears that the effect is coming largely from women.

There are ways of handling that in labeling. This is the situation we faced before. We have a drug Luvox, which is now approved for use in children with OCD based on

study which stratified on the basis of age, children and adolescents. The study was positive overall, but again if you go back and look at the subgroups, it appears that the effect is coming virtually entirely from the children in that sample even though it is not a power question. There were more adolescents in that trial.

We ended up approving that claim, but went on in the clinical trial section to describe where the effects appeared to be coming from, but more descriptively, but again, the question is whether the Agency wants to approve a very specific indication that is based, on a subgroup analysis.

DR. TAMMINGA: But I would wonder whether the committee would even want to recommend that. I was somewhat impressed listening to the data presentation, the efficacy data presentation this morning, that, in fact, there were male subgroups, there were subgroups within the male population that responded significantly, the males with a history of drug abuse, although they are very small and it's an early analysis and exploratory and all that.

In my opinion, it would be a bit rash to say that the drug is only active in women, even though the preponderance of its effect, it seems to be most active there.

DR. KATZ: We are actually very interested in the

committee's view on this question, because we are always concerned about what is the label going to look like, what is the actual indication going to be. It is a critical question for us.

Just to sort of close the loop, there is no prohibition against indicating a drug for one sex or another, or one subgroup or another. It is just that particular subgroup, it would be very unusual to do that.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: However, I think I would personally have some difficulty with concluding really that this drug was only effective in women, simply because of the fact that gender was so confounded with so many other things that it might be connected to, and it would be--you know, I would strongly urge the sponsor to do some clinical trials to attempt to address those issues.

I would like to see clinical trials of males with childhood sexual abuse. I would like to see clinical trials, powered appropriately, in females with and without histories of drug abuse, and so on, and so forth, to attempt to get a handle on what may be driving this in addition to, or instead of, sex itself.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Again, I would be very interested to know what the committee thinks about whether or not there is

any hint of anything going on in men and what the basis for granting a global claim, if the committee decides to recommend that the drug ought to be approved, I would be interested to know what the evidence would be that it should be indicated for everybody, and beyond that, as we have heard, there are other studies ongoing, and the question I put to you is whether or not you think it would be necessary to have one or another of those studies in hand before you recommend approval, so maybe they will shed light on the male/female question.

DR. TAMMINGA: Dr. Geller.

DR. GELLER: This goes back to what Dr. Cook was saying before about the importance of child studies. Another reason is you can study males before the onset of drug abuse, take out some of the confounds.

DR. LAUGHREN: Can I raise a question that has come up at several points during our discussion. My impression is'that the sponsor has data from a relapse prevention trial, and we have not seen those data yet, and ordinarily, we wouldn't have those discussed at this meeting if we hadn't had a chance to candle them in some sense, but I am wondering if it would be useful to take a peek at those data from the standpoint of this gender issue..

I mean, for example, if there were another source of evidence, even if it was in a relapse prevention context

that addressed possibly efficacy in men versus women. Maybe that would be helpful to the committee.

DR. TAMMINGA: The committee would be interested in seeing whatever we were allowed to see.

[Laughter.]

DR. LAUGHREN: Well, I think it is in sort of an exploratory nature, you know, given that we haven't had a chance to candle it, but it may shed some light on this burning question about men versus women.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: I just want to make a caveat about that, which is that, as Tom pointed out, we haven't looked at it, and the question that I am interested in is whether or not, if we do see some preliminary discussion of it here, whether or not it would be critical, whether or not the committee thinks it would be critical for us to look at that closely and establish that there is or is not an effect on males, let's say, from that study before we take an action.

In other words, we need to know whether or not you think that data would be critical for an action or for a specific indication.

DR. TAMMINGA: So, the company should understand when it shows it to us that we could recommend that you be given the data and take a careful look at it.

DR. KATZ: Right, and that anything you recommend

bout ultimate action on the application, whether it should e approved at all or whether or not it should be approved or a specific subgroup would depend upon what we think of he data when we actually look at it closely. Is that lear?

DR. TAMMINGA: Under those conditions, would the ompany like to present any additional data?

DR. RYAN: Dr. Farfel will present a very brief verview of these additional studies.

[Slide. 1

DR. FARFEL: Pfizer conducted two long-term extension trials. They were extension studies of two of the four double-blind, placebo-controlled 12-week trials. The initial studies that fed into the long-term studies were studies 671 and 682, and I will remind you that Study 671 showed a treatment effect in favor of sertraline while Study 682 did not.

Subjects who completed Study 671 or 682, regardless of treatment group or response data', were entitled to enroll in an extension study 672, which was a six-month open label study with open label treatment of sertraline in a flexible dose format.

At the end of the six months in Study 672, subjects 'who met response criteria,which I will elaborate in a minute, were allowed to enroll in the relapse

revention study 703, in which subjects were re-randomized o either sertraline or placebo.

[Slide.]

It is important to note that in these two feeder tudies, 671 and 682, there were 380 randomized subjects and 75 completed, so were eligible to enter open label reatment. Of the 275 completed, 252 entered the open label rial. 155 completed the six months of open label reatment, and of those 155 completers, 139 met the esponder criteria, so were eligible to enroll in the re-. andomization trial.

Of the 139 who enrolled in the re-randomization rial, 96 actually chose to enroll in the re-randomization rial, and so 50 were randomized to placebo and 46 were randomized to sertraline.

[Slide. 1

Just to restate, the eligibility criteria for ntering the six-month open label trial was simply completion of one of the double-blind feeder studies. The eligibility criteria for entering the re-randomization study, the additional six months, was to meet responder criteria for two consecutive visits, the subject's last two consecutive visits, and this is where the responder criteria, as we discussed earlier, were developed, a 30 percent decrease in the CAPS-2 total severity score from the

subject's initial baseline from the double-blind studies, from the first visit that they came to this investigator.

In addition, the subject had to have a CGI improvement score of 1 or 2 at both of the final visits.

[Slide.]

This slide shows the mean daily dose by selected visit week, it was a long trial, in Study 672 for the safety analyzable subjects. Again, we start with 252 subjects and end with 158 subjects.

Because subjects coming into the open label trial were either on sertraline or placebo, all subjects began again at 25 mg per day at week 1, and then were flexibly titrated between 50 and 200 mg, and the mean dose at week 14 was 138 mg, which is consistent, which was also seen as the mean dose in the 12-week studies.

[Slide.]

This slide shows the mean change on the CAPS total severity score during the six-month open label trial, and this point here, about 74, represents the mean on the CAPS for these same subjects when they entered the initial double-blind, 12-week study, Study 671 and 682.

So, at the beginning of the 12-week trial, they had CAP scores of about 74. After 12 weeks of treatment, and this is the placebo and sertraline groups I believe, Or just sertraline--1 am sorry, we will clarify that in a

inute--they had a mean CAPS of about 45, and then this was heir improvement over the six months of open label reatment. This is the observed cases, and then this is the OCF at endpoint.

[Slide.]

The readings on the Davidson Scale and the CGI mprovement Scale followed the same pattern.

In Study 703, which was the re-randomization study, the double-blinded continuation trial, the primary efficacy parameters were the time to relapse, so that the Kaplan-Meier estimates of the time to relapse, and then the proportion of subjects who actually met relapse criteria.

Relapse criteria had to be met for the last two consecutive visits in order to be called a relapse patient, and then the other primary endpoint was a combination of subjects who met relapse criteria, as well as discontinuing due to insufficient clinical response, which is the ICR abbreviation, because some subjects, when suspecting they were on placebo and beginning to relapse, may have chosen to exit the study after one week of meeting relapse criteria or one visit rather than two.

The secondary efficacy measures for these trials were the mean changes from baseline to endpoint on the efficacy rating scales.

For two consecutive visits, subjects had to have a

GI improvement rating of 3 or greater. We had considered a esponder one who had a CGI improvement of 1 or 2, so all ubjects in Study 703 began the trial with CGI ratings of 1 r 2. In addition, they had to have had their CAPS-2 score ncreased by at least 30 percent, which was a minimum of 15 oints, from the baseline of the relapse trial, not the baseline of the original feeder study, but they had been onsidered responders when they entered the relapse trial if hey had their CAPS increase by 30 percent in addition to he CGI change, that was considered relapsing, and the nvestigator had to concur with the rating scale.

[Slide. 1

This slide shows the doses across selected visit reeks in the study for sertraline and placebo. In this ase, subjects began the trial on the same doses that they had been on at the end of the open label trial, and the mean ose at endpoint is similar to what we have been seeing in the'-other studies.

You can also note here the decrease in N's from 46 to 28 in the sertraline-treated group and from 50 to 20 in the placebo-treated group.

[Slide. 1

This is a slide of the first primary efficacy parameter, the Kaplan-Meier estimate of the probability of not relapsing, and the red line indicates the sertraline-

reated subjects who had an extremely low probability or elapsing during the course of this trial, and the subjects n placebo had a significantly greater probability of elapsing.

[Slide.]

The proportion of subjects who actually did iscontinue--and discontinuation if you met relapse riteria, you were required to be discontinued from the tudy--the proportion of subjects who discontinued due to eeting relapse criteria, there were 2 of 38 in the ;ertraline-treated group and 12 of 46 in the placebo-treated roup, and this difference was statistically significant.

[Slide. 1

This is the probability of two things, not relapsing and not discontinuing due to insufficient clinical response, and again, the sertraline-treated subjects had gnificantly lower probability of these events than the placebo-treated subjects.

[Slide.]

This slide shows the proportion of subjects who discontinued for either of these two reasons in both groups. Six of 38 sertraline-treated subjects compared to 21 of 46 placebo-treated subjects, and again this difference is statistically significant.'

[Slide.]

These are the main changes in some of the efficacy parameters, the CAPS, the DTS, and the IES. Sertraline-treated subjects are in the red bars, placebo-treated subjects are the blue bars, and some of you may be realizing that the fact that the change is always positive indicates that, in general, all of the subjects were having a worsening of their symptoms at endpoint--the mean, the mean change was a worsening of symptoms at endpoint.

I would like to go to the next slide and put this in perspective for you.

[Slide; 1

At the beginning of Study 703, subjects had CAPS scores of about 74. When they finished 12 weeks of double-blind treatment and entered the six-month open label trial, they had CAPS scores of about 38.

For those who elected the double-blinded continuation study, their CAPS scores at the beginning of that--and all of them were de facto defined as responders--their CAPS scores here were below 20.

So, what you see here is the fluctuation in the CAPS scores over the course of this additional six months of treatment including those who might have discontinued due to relapsing on placebo, and then who were responding on placebo, who continued in the trial.

So, although there was an increase in symptom

scores for the group as a mean in both cases, relative to how they were when they came to the trial, is in not remarkable.

[Slide.]

To conclude from these two trials, we feel that sertraline was shown to be safe and effective in maintaining a response in PTSD symptoms over the course of a year and that it was more effective than placebo in relapse.

Dr. Katz.

DR. KATZ: I thought the reason we wanted to see preliminary results of this related to the gender question.

DR. FARFEL: We felt it was hard to skip right to the gender question without the trial that we have.

DR. KATZ: Well, again, as I say, my concern or the question that we need to have answered from the committee is whether or not additional data on the gender question from this trial or some other trial, is critical for us to have in hand before we make a final decision on the application.

That is really the question, not whether or not the study is positive or negative. The committee has already said that long-term data may not be necessary for an approval, but it's the gender question we thought this was trying to get at.

DR. FARFEL: We have that. Do you have the slide

f the-men, the change over the course of 672 and 703?

[Slide.]

This is for Study 672, the six-month open label reatment study. Is this men? This is not men. Okay.

In Study 672, of the 244 subjects who entered, 67 ere male. Their baseline CAPS score was a 42, which was imilar to the baseline of the females who chose to enter he study, and their endpoint mean CAPS score was a 27 ompared to a 28 in the female cohort.

So, the mean point change for the males compared o the females was comparable, and in this somewhat enriched opulation, the mean percentage change of the males who were n this six-month open label trial, compared to the females as also comparable, approximately a 36 percent change.

DR. KATZ: Maybe you will get to it, but this is pen label data.

DR. FARFEL: The next slide.

DR. KATZ: I want to make it clear that this doesn't address the question that we are asking.

DR. FARFEL: Do you have the similar slide for Study 703 by gender?

[Slide. 1

In Study 703, the discontinuation study, there were nine males in the sertraline group and 18 males in the placebo group. The mean change from baseline to endpoint in

he sertraline-treated group for the males was a decrease in core of 12.8 points, so that is improvement in symptoms to he tune of 13 points, whereas, on the placebo group, the 18 ales had an increase in score of 17.5 points.

DR. KATZ: What about the primary outcome, which as time to relapse or proportion of relapse?

DR. FARFEL: Could you bring up the Kaplan-Meier or the males in 703?

DR. GELLER: Could go back to the slide you just ad?

DR. FARFEL: Bring the slide back up.

DR. GELLER: On this slide, it may just be I am ooking at it quickly, but there is a negative change for ales and a positive change for females?

DR. FARFEL: Yes. That goes to the females, as a roup mean, were actually increasing slightly in symptoms. ain, the mean score on the CAPS for the study cohorts when they entered at the beginning of the double-blind trials was about a 75.

When they began after six months of open label treatment and were called responders, they had a CAPS score of about 18, so they are fluctuating now around what may be floor effect.

DR. HAMER: While we have the slide up, those p-values, exactly what are they testing?

DR. FARFEL: This is quite a back-up slide. It's a, significant difference in terms of the sertraline group compared to the placebo group. I am not sure which analysis was used. But the asterisks next to the placebo numbers are extra.

DR. TAMMINGA: So, in both of these genders, male and female genders, placebo causes relapse significantly different from sertraline, which causes less relapse.

DR. FARFEL: Yes.

DR. TAMMINGA: Dr. Winokur.

DR. WI-NOKUR: Where were the males at the start of this, that they improved or they had a further decrease of 12.8 points? This was at the point that they were responders and then went into the--

DR. FARFEL: Could you back up to the slide previous to this one? They were not in order. Because these were males who elected to enter the double-blinded continuation, their levels of symptoms on the CAPS were roughly the same, so they had mean scores of about 20 when they entered this double-blinded continuation study, and then they decreased further by 12 points compared to increasing by 17 points on placebo.

DR. WINOKUR: So, in effect, they were almost super-responders, they improved to close to zero,

DR. FARFEL: Yes. The numbers of subjects in the

1 ıale sertraline group was 9.
2 DR. KATZ: I really hate to sound like a broken
3 :ecord, but we are not going to be able to adequately
4 ınalyze these data here. That is why we ordinarily don't
5 ıave a sponsor present data. This just is not the
6 tppropriate forum to do that.
7 I will ask it again. What we really need to know
8 is whether or not data of this sort are necessary in order
9 :or you to be able to recommend a particular action. If you
10 :hink it is necessary, we will have the sponsor submit it,
11 se will review it, and if we confirm what they say, then, we
12 will take an appropriate action.
13 That is really the question that we need to have
14 addressed by the committee, not so much whether or not at
15 the moment we think this study is positive or negative. We
16 are not going to be able to do that.
17 DR. TAMMINGA: But thank Pfizer for your
18 presentation on the spot.
19 So, the committee needs to really continue talking
20 about the gender question. We have seen what additional
21 kinds of data the company has and can submit.
22 The issue that I would like to see the committee
23 discuss is gender issue, to what extent gender is a factor
24 in drug action as we see it in the data presented here. We
25 have said a lot about it already.

Dr. Hamer.

DR. HAMER: Gee, I wasn't going to say very much today. I have got two small pieces of slightly opposing information, if you will. One is whatever difference we saw in the pharmacology leading to different blood levels, different areas under the curve, and different half-lives between the two sexes, and not knowing how that might be related to differential response rates, but it is something that bears investigating, and then the other is the confound between sex and all of these other things which may well be related to differential response rates.

The only way to get at those is to do some studies with sufficient sample sizes in various subgroups, so you can ask the questions. As I said earlier, I would have a hard time concluding that this drug is effective in women, and not effective in men in the absence of being able to attribute that difference to these other'confounders.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: But in the absence of that additional information which we would all love to have, what evidence is there that it should be indicated in men?

DR. TAMMINGA: We have, in fact, seen data from several subgroups of men that showed significant--in exploratory analysis, showed significant responses. I wouldn't guess that clinicians would like to have their male

patients denied this. I don't know if any of our experts want to speak to that.

DR. HAMER: But it's all a matter of labeling. They could approve it, but put in the appropriate clinical trial information, so that the physicians had information that there was more evidence currently in females than males, which would then perhaps provide some motivation to the pharmaceutical company to provide other evidence.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: In his presentation and analysis, Dr. Smith advised us or questioned us about making conclusions about subgroups for which studies were not adequately powered, and I am struck that we are needing to make calls, if we do get down to the gender difference, on sample sizes that are strikingly low.

DR. KATZ: Of course. I am we certainly are very wary about doing that, as Tom said, and lots of others have said. There is one slide that Dave showed, that I think that is interesting in this regard, whatever you make of it, which was a slide I guess that looked at the men, not in the VA study, but maybe it was just the men in the two studies that were positive.

If you look at that slide, there was.--it could still be, I suppose theoretically it could still be a power question-- there are I think 50 men on drug and 50 men on

placebo or something like that. The scores on sertraline and placebo were identical except for the global, which actually had the same response as the women did, but all the others were right on top of each other.

It was suggesting that it's not really a power question. They didn't have the same treatment size effect, it just wasn't significant. Really, nothing was going on in that analysis anyway. I just throw that out, and I would be interested what people think about that.

DR. TAMMINGA: Dr. Smith.

DR. SMITH: If I might just clarify, the slide that Dr. Katz is referring to is the slide titled women versus men, PTSD-specific symptoms 640-671.

It is lots of columns of p-values. If I might repeat what Dr. Katz said, it sounded like the column for women did show an improvement, the column for men were essentially the same, so if you go across the rows for each of the specific symptoms, women showed an improvement, men were essentially the same for sertraline versus placebo. I think that was his point.

DR. KATZ: Right. In fact, in some cases, it goes in the wrong direction. That would just suggest then to me that it is not really a power question, it's maybe something else is going on.

DR. TAMMINGA: Dr. Cook.

DR. COOK: This relates to the way that I was aught that things happen in statistics, meaning that you et different results when you pull different samples out of he barrel, so I am still reluctant to call that a gender ffect knowing that genders don't have the same--there is a ood chance that we have sampled different populations.

So, if we had, let's say, a pathologically defined lisorder in the, sense of under the microscope, a very pecific condition, sampled from exactly the same clinics, or exactly the same problems, exactly the same histories, tge of onset, then, I might say yes, these are the same.

I get a strong sense of apples and oranges by Tender.

DR. TAMMINGA: Thank you.

I am going to ask one more question first. Is there anybody on the committee who would take the opposite position to the one just articulated by Dr. Cook?

DR. DOMINGUEZ: I am not going to take the opposite position, but I wonder if perhaps this is the time to make a motion for the committee to consider the question whether indeed the gender issue has been inadequately studied versus whether the study drug has failed to show an effect in men, and I submit that motion to the chairperson.

DR. TAMMINGA: In my opinion, we are not quite ready to address that motion/yet since I would like some

more discussion on both sides of the question first.

There are a number of people on the committee that would suggest that with the data at hand, these is not enough data to suggest that this drug would only be effective in PTSD in women.

Is that a proposition that is shared by the committee?

DR. HAMER: Just one other point about the subgroup analyses which applies less of an extent to the gender issue simply because that is really mandated beforehand, so to some extent, it's a planned hypothesis, but there is a multiplicity issue, and in addition to the power. issue in subgroups, the more subgroups we have, the more tests we do, and the more tests we do, the more likely we are to pop one up by chance alone. So, we need to filter that issue in, as well as the power issue.

DR. TAMMINGA: Dr. Smith.

DR. SMITH: I understand what Dr. Hamer said. Because of the multiplicity issue, the results that we are seeing would be diluted essentially, is that correct? Okay.

DR. TAMMINGA: Dr. Katz.

DR. KATZ: Certainly, multiplicity is a concern, but this is a difference. It seems to be fairly robust in the sense that wherever you look for it almost, certainly at least in the positive studies, it is clearly there.

I am wondering what are the differences, what makes us think that there is lots else going on besides lender. is it the type of initiating event? If you look at the slide that we just talked about, that Dave put up, those were men who, again small numbers, but those were men, who had not been in combat. Those are men who had the same sorts of initiating trauma largely as the women did.

So, duration of the disease in men, I don't think it is really much different, certainly the non-traumatic men, so I am just sort of wondering what the differences are that would suggest to people that there is really--we really can't say anything about the difference.

DR. TAMMINGA: Dr. Brewerton.

DR. BREWERTON: Is there, in fact, a data slide that shows us what exactly the types of trauma are in the by-gender?

DR. TAMMINGA: We haven't seen it.

DR. BREWERTON: I don't think we have.

DR. TAMMINGA: I have a procedural question for the committee. I am trying to gauge whether we ought to move forward or stop for a lunch break. If people could make a slight nod of their heads one way or the other.

Move forward? We will move forward.

We do have one issue that we haven't approached yet, and that is the independence of Zoloft's antidepressant

effect, the independence of the sertraline effect on PTSD from depression.

Nobody really responded to Dr. Katz's last question, and I am not sure that we have anymore to say to that question than we have already said. I would like to have us focus some on whether the committee saw this PTSD effect as an independent effect on PTSD symptoms separate from its antidepressant effect.

Dr. Southwick.

DR. SOUTHWICK: Obviously, that is a very complicated question as the data suggests. I think that because of the overlap, for example, the HAM-D, I think is obviously picking up a lot of PTSD sorts of symptoms.

I found one of the analyses to be illuminating, and that was to look at PTSD with major depression compared to PTSD without major depression, and which showed that the PTSD without major depression responded as well.

I also think it is important that PTSD-specific symptoms responded, but I think to pull them apart is obviously very complicated.

DR. WINOKUR: One other point that at least would make me cautious about some of the analysis that Dr. Smith provided, and I did feel that some of the presentation from the Pfizer investigators in terms of separating out patients diagnosed with primary or significant major depression and

Lso the improvement being across the spectrum of including more, quote, unquote, "PTSD-specific symptoms," some of the analysis that you presented took the item from the Hamilton spression Scale, the depressed mood, and I think one needs o be very cautious about using that item as clinical epression.

There are so many circumstances in which people ight acknowledge points on that particular item, where they ould not be, by most clinician's or researcher's judgment, ignificantly clinically depressed, and I think that it ould also be expected that with overall improvement in the rimary disorder, that that item might well be expected to hange.

So, I think that some caution in terms of eneralizing from data with that item to depression per se n proving is crucial to PTSD responding would really be in der, and my overall weight of things was to feel that the vidence more supported specific'effect.

We heard from several people including Dr. lrewerton on our committee that anxiety disorders tend to be mportantly overlapping with.depression commonly, so I think his is a challenging issue that is difficult to sort out, not just with PTSD, but with virtually all of the anxiety disorders that have been ldoked at in terms of drug efficacy.

DR. SOUTHWICK: I just want to make it clear, if I didn't, that is what I was actually trying to say, that I feel that, reading and listening to all the data, to me it would appear that sertraline has an independent effect on PTSD symptoms.

DR. HAMER: I have two comments about that issue. The first is that when we looked at the slide with the correlations between the Hamilton Depression Scale scores and the various PTSD indices, they were all correlations in the 0.6 range, which means that in terms of shared variants between the two scales, the R-squares for those are about 01.36.

So, to put it another way, even though there is some overlap between at least the scales that measure the severities of the two diagnoses, there is two-thirds non-overlap, so that is to me some evidence that, in fact, there is at least a difference between depression and PTSD. There is an awful lot of non-shared variation.

The other was that the analysis in which you looked at the difference between the two treatments on the PTSD scales after covariating out the Hamilton, there still remained a significant sertraline effect, and I find that to be reasonably convincing that there is a sertraline effect on PTSD above and beyond that which may be due to depression.

Now, I may be wrong. One of the things about statisticians is that statisticians demand the right to be wrong 5 percent of the time, and so I could be wrong, but what I see is that it certainly looks like it is not just depression.

DR. TAMMINGA: Any more discussion or comment on this question?

I think, Dr. Dominguez, we may be ready to consider what your question was, if you could restate it for us.

DR. DOMINGUEZ: I would like to make the motion for the chairperson to consider that based only on the acute data, the 12-week data, whether the issue of the gender differences were either inadequately studied or whether indeed that was a failure to show a response based only on the 12-week acute studies, the positive studies.

DR. TAMMINGA: So, perhaps the committee can discuss the proposition that we cannot fully answer the gender question from the data presented. Is that it?

DR. DOMINGUEZ: It's one opinion versus another, whether it was again inadequately studied, in other words, there have to be more studies to answer the question, or whether indeed the data that was presented failed to show an effect in men

DR. TAMMINGA: Can we have some discussion on Dr.

Dominguez's proposition? I understand that these studies were not powered to separately demonstrate a PTSD effect in men and women, so the idea that that be studied gave us independent information on sertraline effect in men and women is true.

DR. DOMINGUEZ: Yes, I agree with you. On the other hand, as I understand it, it's a free country, and the Agency may indeed wish to hear the opinion of the committee with regards to those two questions.

In fact, I think that the question was presented as such in Dr. Smith's presentation, correct? Okay. Wasn't that a question in your presentation?

DR. KATZ: I am sorry. Could you repeat that? I would appreciate it.

DR. DOMINGUEZ: Versus whether it was inadequately studied versus whether it failed to show an effect in men.

DR. KATZ: To answer the question whether or not the committee thinks the drug can be approved, and if it can be approved, what would the committee propose as an indication, in other words--and I think we have sort of been talking about this a lot, whether or not it should be approved, if you believe it should be approved as a general treatment for PTSD, and then some statement later on about where the data came from, or whether it should be restricted to approval in women only, if you think it should be

approved, whether or not you think more data of any kind, but specifically with regard to the gender question needs to be reviewed before you can even recommend an action.

DR. TAMMINGA: I think it is important for the committee to keep in mind, I think that everybody here would recommend more data in gender, more information since all of us are of that bent in any case.'

The question that you want our opinion on is whether or not they need more data before approval. Is that correct?

I think it is time for me to address the first question, which actually requires a vote and take some discussion on this:

Has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that Zoloft is effective for the treatment of posttraumatic stress disorder?

Do we have any additional discussion around this question?

[No response.]

DR. TAMMINGA: Then, I would like to call for a vote on the question. There is three non-voting members of the committee - Dr. Brewerton, Dr. North, and Dr. Southwick, so I think we should just go around the table and vote on the question: Has the sponsor provided evidence that Zoloft

is effective for the treatment of posttraumatic stress disorder?

Dr. Geller, might you start?

DR. GELLER: I think yes with some label consideration to the need for further studies in certain areas, types and gender.

DR. TAMMINGA: Dr. Cook.

DR. COOK: Yes with the caveat that it is only in the age groups studied.

DR. TAMMINGA: Dr. Lacey.

DR. LACEY: I think the sponsor ha&provided evidence from more than one adequate study, but I don't feel comfortable voting that there is sufficient data in the studies presented, so I would be no.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: I would vote yes overall for demonstration of efficacy, and I agree with the need to discuss labeling guidelines in light of the limitations of the information that we have.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: I vote yes also with the trust that the FDA will be judicial and careful in its labeling.

DR. TAMMINGA: Dr. Dominguez.

DR. DOMINGUEZ: My vote is yes, as well. My bias is toward my belief that the sponsor failed to show efficacy

n men.

DR. TAMMINGA: My vote is also yes, that the ponsor has showed that sertraline is effective for the reatment of PTSD with all the caveats that people have lready submitted.

Dr. Katz.

DR. KATZ: I take to heart Dr. Hamer's hope and ish that we will do the right thing, and we will try. But gain, is there a general sense from the committee--I don't now that this needs a formal vote--that the specific ndication should not be limited to women?

I just want to sort of make this explicit. There re ways that labeling can be written. The indication tself could say approved for PTSD in women or it could just ay approved for PTSD as a treatment for PTSD, and then in nother place describe where the data come from.

I am just trying to get a sense from the committee which of those two or perhaps some other option would be preferable.

DR. TAMMINGA: What I would say is that we just voted on the general efficacy of sertraline in posttraumatic stress disorder and previously had a discussion about the gender question, and that in the gender discussion, although there was a universal call for more data, the majority of the group was not willing to exclude men from the efficacy

question. If I am misstating that, would somebody from the committee--

DR. BREWERTON: I don't think that we really took a formal vote on that.

DR. TAMMINGA: We didn't take a vote on it. .I said that was the gist of the discussion.

DR. BREWERTON: I would feel more comfortable Limiting it to women personally. I see absolutely nothing in the data that would supports its efficacy in men.

DR. TAMMINGA: More discussion on this issue?

DR. LAUGHREN: If I can just clarify, the question that I framed in my mind clearly was focused on the **claim** generally, not limited to men or women or any other subgroup.

Again, we have great flexibility in writing labeling to describe the findings in the clinical trial section, but the question that everyone voted on in my mind was a question on a general claim for PTSD.

DR. TAMMINGA: Dr. Katz. . .

DR. KATZ: That is I think what we meant when we wrote the question, but again, it is useful to us to know explicitly how people feel about that, because I am not sure that everybody, when they vote on it, voted on it the way it was technically worded.

For example, Dr. Brewerton suggested he would like

t to be restricted, the indication itself to be restricted ust to women.

DR. TAMMINGA: Would you like us to take a formal ote on that/

DR. KATZ: *Or* at least poll the committee, I don't are really about a vote, but if you could poll the ndividual members of the committee, this way we would have t on the record, we would know what people think.

DR. TAMMINGA: I would like to then repeat this in equence, not taking a vote, but having a statement from ach member of the committee on their position on the lender.

Dr. Geller, could you start?

DR. GELLER: I would like it not restricted by render because my experience is the FDA will do its usual outstanding job of including information on the trials in .e labeling.

DR. TAMMINGA: Dr. Cook.

DR. COOK: I would agree that it should be labeled and obviously, data needs to come in. I really want to emphasize that although we aren't presented with anything that suggests stratification by previous history, age of onset, that this should be looked for, maybe more important in terms of getting the truth of what should be labeled.

So, for example, women with combat experience, we

don't know that they respond any better than men with child abuse. So, it's just a little caveat. We can't say what we don't know, and I guess we have to label for what is presented.

DR. TAMMINGA: Dr. Lacey, would you like to make a statement?

DR. LACEY: I certainly strongly recommend that the differentiation be clearly specified about differences in populations even though we might leave it open.

DR. TAMMINGA: Dr. Winokur.

DR. WINOKUR: Taking literally or as expressed, the question that we were asked to address, I, as others, felt that we have been presented with convincing data from two good, well-controlled studies that support the general efficacy question.

I feel personally, as a committee member, unable at this point, with the information available to address or project whether in the long run, men will be shown to respond differently or other factors will come out, as well, but to me, this is an issue that we commonly face in our field where we are dealing with disorders that were primarily describing syndromally or phenotypically, there is heterogeneity in response, I think having treatments that are well studied and shown to respond in at least a fair percentage of individuals gives us a chance then to go

forward and do more specific studies to factor that out, so gender or age of exposure or type of exposure may well down the road turn out to be very important dimensions for further research, but I don't feel that we have the information at this point to. really make appropriate decisions about that.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: One of the first things we learn in statistics is to not over-interpret a null hypothesis that we failed to reject. We certainly failed to reject the null hypothesis that there is no difference between sertraline and placebo in males here.

I will make the statement that in my opinion, the sponsor has failed to show us that sertraline is effective in males, but that is a vastly different thing from saying that we were shown that it is not effective in males.

So, however the labeling gets written, whether the labeling is written in such a way that says the indication is only given in females or whether the labeling is written with the indication saying the indication is for PTSD in general and then appropriate labeling saying the sponsor failed to demonstrate that it was effective in males, again, I leave up to the FDA.

They do a wonderful job of this sort of thing, in negotiating with the pharmaceutical company, and then just

as long as you are asking for opinions, if I were constructing an ideal world, I would want to construct the world 'in such a way that the sponsor was motivated to investigate the issue of effectiveness in males.

DR. TAMMINGA: Dr. Dominguez.

DR. DOMINGUEZ: Deleting that very, very last statement that you made, since English is not my primary language, I will ditto everything that Dr. Hamer said. I think the sponsor has failed to show an effect in men.

DR. TAMMINGA: And I also, adding my opinion in as the chair of the committee, think that this indication ought to be in PTSD without reference to gender, but that the data, as it has been presented, go into the labeling.

The next question that we have to consider is the safety question. The voting committee can assume that the safety question of sertraline as a treatment in humans has been already answered by the FDA, and we need to consider the safety question of sertraline in PTSD.

Is there any discussion, any specific discussion by anybody about safety concerns of sertraline in PTSD? Comments by the voting and the non-voting members of the committee.

Any concerns that any committee member has of sertraline's safety in PTSD other than the concerns that we might have about human use in general?

[No response.]

DR. TAMMINGA: I think I would like to go around again and then take the final vote on has the sponsor provided evidence that sertraline is safe when used in the treatment of PTSD.

Dr. Geller.

DR. GELLER: Yes.

DR. TAMMINGA: Dr. Cook.

DR. COOK: Yes.

DR. TAMMINGA: Dr. Lacey.

DR. LACEY: Yes.

DR. TAMMINGA:' Dr. Winokur.

DR. WINOKUR: Yes.

DR. TAMMINGA: Dr. Hamer.

DR. HAMER: Yes.

DR. TAMMINGA: Dr. Dominguez.

DR. DOMINGUEZ: Yes.

DR. TAMMINGA: Dr. Tamminga. Yes.

I cannot believe it, we had-no additional discussion.

With answering these two questions for the FDA and providing additional and extensive, if you will, or at least some discussion of PTSD as an independent diagnosis worthy of an indication, I would like to thank the committee, both the voting and the, non-voting members, for their

participation in this discussion, and wonder if the FDA has any final comments.

DR. KATZ: I also would like to thank everybody very much. I think it was an interesting discussion, some tough issues, and I appreciate it very much. We will take our advice to heart.

DR. TAMMINGA: I would like to bring the meeting to a close and thank everybody very much.

[Whereupon, at 1:15 p.m., the meeting was adjourned.]

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C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO