Statistical Review and Evaluation

NDA Number:	19-839	SEP 27 1999
Applicant:	Pfizer Pharmaceuticals	
Name of Drug:	Zoloft (Sertraline HCl)	
Indication:	Treatment of posttraumatic stress disorder.	
Documents Reviewed:	Vols. S98.1, S98.5-S98.8, S98.15-S98.18, S98.21-S98.36 dated 7 Oct 1998	
Statistical Reviewer:	David Smith, Ph.D.	

1. Background and Overview

In order to support labeling for the indication of posttraumatic stress disorder (heretofore abbreviated PTSD), the sponsor submitted an NDA which is comprised of four Phase III trials. The sponsor's submission included efficacy and safety reports of the four Phase III trials.

A brief summary of the four studies appears below.

Study	Type	Arms	N
93CE21-0640 (Study 640)	Randomized Ph III	Zoloft / Placebo	98 / 104
93CE21-0641 (Study 641)	Randomized Ph III	Zoloft / Placebo	93 / 90
95CE21-0671 (Study 671)	Randomized Ph III	Zoloft / Placebo	84 / 82
96CE21-0682 (Study 682)	Randomized Ph III	Zoloft / Placebo	94 / 94

The sponsor submitted two studies in support of the efficacy of sertraline in PTSD (Studies 640 and 671), and all four studies were submitted to provide evidence for the safety and toleration of sertraline in PTSD. The next section includes relevant statistical issues for these studies. The following sections will discuss these studies, first individually, and then collectively. The last two sections will include overall conclusions and recommendations for the submission.

References will follow the review.

2. Statistical Issues

- There was a statistically significant gender imbalance in study 640 at baseline. Fewer males were enrolled on the sertraline group compared to the placebo group ($p = 0.041$). The sponsor performed numerous analyses to quantify the effect of gender on sertraline efficacy in PTSD and these analyses suggest that there may be a gender interaction with treatment apart from the gender imbalance at baseline in Study 640.

- There were no Type I Error adjustments specified for the number of comparisons of the primary endpoints.

- In the sponsor's analyses, there were few analyses that examined the effect of sertraline on PTSD in those patients that do not show improvement in depression symptoms. The issue is whether the data suggest that PTSD should be considered as an entirely separate indication from depression. Sertraline is approved in the United States in the treatment of depression, but there is evidence that improvement in depression is correlated with improvement in PTSD.

3. Pivotal Phase III Trials

3.1 Description of Study 640

Study Objective: To evaluate the efficacy and safety of sertraline in outpatients with posttraumatic stress disorder (PTSD).

Study Dates: 26 May 1994 - 25 March 1996

Study Design: This was a multicenter, double-blind, parallel-group, flexible-dose study designed to evaluate the comparative safety and efficacy of sertraline and placebo in the t reatment of outpatients with PTSD.

In this study, a one-week, single-blind, placebo run-in was followed by 12 weeks of double-blind

treatment. During the double-blind period, subjects returned to the study site at the end of Weeks 1, 2, 3, 4, 6, 8, 10, and 12. A total of 160 subjects were to be randomized, with an equal number of subjects assigned to sertraline and placebo. Subjects randomized to sertraline received 25 mg/day for one week and, in the absence of dose-limiting adverse events, were increased to 50 mg/day at Week 2. Subjects who failed to respond satisfactorily to 50 mg/day could, in the absence of dose-limiting adverse events, be titrated in weekly 50 mg increments to a maximum dose of 200 mg/day.

Sample Size: The sample sizes planned for this study were computed to be 80 subjects per treament group based on a two sample t-test. The sample size estimates were based on detecting a difference of ten units at endpoint in the CAPS-2 total severity score between sertraline and placebo treatment groups. A standard deviation of 20 units in the CAPS-2 total severity score was assumed. With this standard deviation and sample size, a difference of 10 units could be detected with power greater than 80%. The randomization list was generated using a blocking factor of four. Randomization was performed at each study site.

Criteria for Evaluation: During the study, a series of efficacy assessments were completed to rate the subject's progress. The primary efficacy parameters specified in the protocol were the Clinician-Administered PTSD Scale Part 2 (CAPS-2) and the Impact of Event Scale (IES), as well as the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) ratings. Additionally, scores for each symptom cluster of the CAPS-2 and IES, and the individual items in each cluster, were analyzed.

Secondary assessments included the total scores of the Davidson Self-Rating PTSD Scale, the 24-item Hamilton Depression Scale (HAM-D), the Hamilton Anxiety Scale (HAM-A), the Civilian Mississippi Scale for PTSD, the Disorders of Extreme Stress Scale – Not Otherwise Specified (DES-NOS), and the Pittsburgh Sleep Quality Index (PSQI).

Primary efficacy analyses assessed change from baseline to endpoint. Additional analyses included a summary of primary efficacy variables at each visit using the last observation carried forward, and a post-hoc analysis of responders, subjects with at least a 30% decrease in the CAPS-2 score and a CGI Improvement score of 1 or 2.

For all variables except CGI Improvement, a numerical decrease in the ratings at endpoint compared to baseline indicated an improvement in status. For CGI Improvement, a lower numerical value indicated a greater improvement in status.

Primary Endpoints

Clinician-Administered PTSD Scale, Part 2 (CAPS-2): The investigator rated the subject's condition since the previous visit based on the frequency and intensity (greater with higher numbers) of the following 17 items within three symptom clusters (Re-experiencing/Intrusion, Avoidance/Numbing, Arousal). When visits were spaced two weeks apart, the rater determined a weekly average for the frequency and intensity scores. The CAPS-2 was administered at baseline (end of washout) and at the end of double-blind treatment Weeks 1, 2, 3, 4, 6, 8, 10, and 12 (or at the time of discontinuation if prior to the end of Week 12).

Impact of Event Scale (IES): The subject responded to a series of 15 statements consisting of seven intrusion items and eight avoidance items by assigning numeric values of 0, 1,3 or 5 to each one (0 = not at all, 1 = mild, 3 = moderate, or 5 = severe) to describe his or her symptoms during the past week. These 15 items constitute the total score of the IES. The IES scale for PTSD was completed by the subject at screening, baseline, and at the end of Weeks 1, 2, 3, 4, 6, 8, 10, and 12 (or at the time of discontinuation prior to the end of Week 12).

Clinical Global Impressions (CGI): For **CGI Severity of Illness**, the investigator rated the subject in response to the following question, "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" The ratings were: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most severely ill. For **CGI Global Improvement** (whether or not due to drug treatment), the investigator rated the subject in response to the following question, "Compared to the subject's condition at the beginning of the study, how much has he/she changed?" The ratings were: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The CGI was administered at baseline and at the end of double-blind treatment Weeks 1, 2, 3, 4, 6, 8, 10, and 12 (or at the time of discontinuation prior to the end of Week 12). However, **CGI improvement** was not rated at baseline.

Although there were multiple primary endpoints, there was no adjustment in Type I error for multiple comparisons.

Secondary Endpoints

Davidson Self-Rating PTSD Scale: The subject responded to 17 questions about his or her PTSD symptoms during the past week. The subject assigned numeric values to frequency (0 = not at all, 1 = once, 2 = 2-3 times, 3 = 4-6 times, and 4 = every day) and severity (0 = not at all distressing, 1 = minimally distressing, 2 = moderately distressing, 3 = markedly distressing, and 4 = extremely distressing). The Davidson Self-Rating PTSD scale was completed by the subject at screening (Day 1 of washout), baseline, and at the end of double-blind Weeks 1, 2, 3, 4, 6, 8, 10, and 12 (or at the time of discontinuation prior to the end of Week 12).

Hamilton Depression Scale (HAM-D): The investigator rated the subject's condition at the time of the visit in regard to 24 different items on the HAM-D scale describing states, symptoms, or groups of symptoms (e.g., depressed mood, agitation, somatic symptoms). Items were scored on scales of either 0-2 or 0-4, with 0 = absent or none. The HAM-D was administered at baseline and at the end of double-blind Week 12 (or at the time of discontinuation prior to the end of Week 12).

Hamilton Anxiety Scale (HAM-A): The investigator rated the subject's condition at the time of the visit in regard to 14 different items on the HAM-A scale describing states and groups of symptoms (e.g., anxious mood, tension, cardiovascular symptoms). Each item on the rating scale was scored as 0 = not present, 1 = mild, 2 = moderate, 3 = severe, or 4 = very severe. The HAM-A was administered at baseline and at the end of double-blind Week 12 (or at the time of discontinuation prior to the end of Week 12).

Civilian Mississippi Scale for PTSD: The subject responded to 39 statements probing four clusters of PTSD symptoms at the current time: re-experiencing; withdrawal/numbing; arousal and self-persecution. Subjects responded on a scale of 1 = never to 5 = very frequently/true to statements such as "I am able to get emotionally close to others" and "I lose my cool and explode over minor, every-day things." The Civilian Mississippi Scale was completed by the subject at baseline and at the end of double-blind Week 12 (or at the time of discontinuation prior to the end of Week 12).

Disorders of Extreme Stress – Not Otherwise Specified Scale (DES-NOS): The investigator rated the subject on 48 questions from seven categories of PTSD symptoms and associated features. Symptoms were evaluated since the trauma, and at current severity. Subjects were rated as to whether the item was present or absent in the past month, and if present, severity was rated on a scale of 1 = minor to 3 = extremely serious. The DES-NOS scale was administered by the investigator at baseline and at the end of Week 12 (or when a subject was discontinued prior to the end of Week 12).

Pittsburgh Sleep Quality Index (PSQI): The subject answered a series of questions on sleep habits and sleep quality during the previous month. The PSQI was performed by the subject at baseline and at the end of Week 12 (or when a subject was discontinued prior to the end of Week 12).

3.2 Description of Study 641

Study Objective: To evaluate the efficacy and safety of sertraline in outpatients with posttraumatic stress disorder (PTSD).

Study Dates: 16 May 1994 - 12 September 1996

Study Design: This was a multicenter, double-blind, parallel-group, flexible-dose study designed to evaluate the comparative safety and efficacy of sertraline and placebo in the treatment of outpatients with PTSD.

In this study, a one-week, single-blind, placebo run-in was followed by 12 weeks of double-blind treatment. The study was conducted at 10 Veterans Administration (VA) Medical Center sites. During the double-blind period, subjects returned to the study site at the end of Weeks 1, 2, 3, 4, 6, 8, 10, and 12. A total of 160 subjects were to be randomized, with an equal number of subjects assigned to sertraline and placebo. Subjects randomized to sertraline received 25 mg/day for one week and, in the absence of dose-limiting adverse events, were increased to 50 mg/day at Week 2. Subjects who failed to respond satisfactorily to 50 mg/day could, in the absence of dose-limiting adverse events, be titrated in weekly 50 mg increments to a maximum dose of 200 mg/day.

Sample Size: The sample sizes planned for this study were computed to be 80 subjects per treatment group based on a two sample t-test. The sample size estimates were based on detecting a difference of ten units at endpoint in the CAPS-2 total severity score between sertraline and placebo treatment groups. A standard deviation of 20 units in the CAPS-2 total severity score was assumed. With this standard deviation and sample size, a difference of 10 units could be detected with power greater than 80%. The randomization list was derived from a computer-generated schedule using a blocking factor of four. Randomization was performed at each study site.

Criteria for Evaluation: See **Criteria for Evaluation, Study 640.**

3.3 Description of Study 671

Study Objective: To evaluate the efficacy and safety of sertraline in outpatients with posttraumatic stress disorder (PTSD).

Study Dates: 1 May 1996 - 12 June 1997

Study Design: This was a multicenter, double-blind, parallel-group, flexible-dose study designed to evaluate the comparative safety and efficacy of sertraline and placebo in the treatment of outpatients with PTSD.

In this study, a 2-week, single-blind, placebo run-in was followed by 12 weeks of double-blind treatment. During the double-blind period, subjects returned to the study site at the end of Weeks 1, 2, 3, 4, 6, 8, 10, and 12. A total of 160 subjects were to be randomized, with an equal number of subjects assigned to sertraline and placebo. Subjects randomized to sertraline received 25 mg/day for one week followed, in the absence of dose-limiting adverse events, by one week of 50 mg/day. Subjects who failed to respond satisfactorily to 50 mg/day could, in the absence of dose-limiting adverse events, be titrated in weekly 50 mg increments to a maximum dose of 200 mg/day.

Sample Size: The sample sizes planned for this study were computed to be 80 subjects per treatment group based on a two-sample t-test. The sample size estimates were based on detecting a difference of ten units at endpoint in the CAPS-2 total severity score between sertraline and placebo treatment groups, which was assumed to be clinically relevant based upon a study of fluoxetine and placebo in which the between group difference was 12.6 + S.D.17 on the CAPS-2. A standard deviation of 20 units in the CAPS-2 total severity score was assumed. With this standard deviation and sample size, a difference of 10 units could be detected with power greater than 80%. The randomization list was derived according to a computer-generated schedule using a blocking factor of four. Randomization was performed at each study site.

Criteria for Evaluation:

Quality of Life Enjoyment and Satisfaction (Q-LES-Q) Questionnaire: The Quality of Life Scale assesses health perception, health transition, daily role functioning, feelings about symptoms, interference of PTSD with daily activities, interpersonal relationships, effect of PTSD on daily function, and overall quality of life. The Quality of Life Scale was administered at Visit 3 (baseline) and at the end of double-blind Week 12 (or at the time of discontinuation prior to the end of Week 12). An increase on the Q-LES-Q reflects improvement.

For the additional endpoints, see **Criteria for Evaluation, Study 640.**

3.4 Description of Study 682

Study Objective: To evaluate the comparative safety and efficacy of sertraline and placebo in the treatment of outpatients with PTSD.

Study Dates: 31 July 1996 - 7 January 1998

Study Design: This was a multicenter, double-blind, parallel-group, flexible-dose study designed to evaluate the comparative safety and efficacy of sertraline and placebo in the treatment of outpatients with posttraumatic stress disorder (PTSD).

In this study, a 2-week, single-blind, placebo run-in was followed by 12 weeks of double-blind treatment. During the double-blind period, subjects returned to the study site at the end of Weeks 1, 2, 3, 4, 6, 8, 10, and 12. A total of 160 subjects were to be randomized, with an equal number of subjects assigned to sertraline and placebo. Subjects randomized to sertraline received 25 mg/day for one week followed, in the absence of dose-limiting adverse events, by one week of 50 mg/day. Subjects who failed to respond satisfactorily to 50 mg/day could, in the absence of dose-limiting adverse events, be titrated in weekly 50 mg increments to a maximum dose of 200 mg/day.

Sample Size: The sample sizes planned for this study were computed to be 80 subjects per treatment group based on a two sample t-test. The sample size estimates were based on detecting a difference of ten units at endpoint in the CAPS-2 total score between sertraline and placebo treatment groups. A standard deviation of 22 units in the CAPS-2 total severity score was assumed, based on the results of the interim analysis of Protocol 93CE21-0640. With this standard deviation and sample size, a difference of 10 units could be detected with power greater than 80%. The randomization list was derived from a computer-generated schedule using a blocking factor of four. Randomization was performed at each study site.

Criteria for Evaluation: See Criteria for Evaluation, Study 640.

4. General Overview of the Phase III Studies

The designs of all four completed trials were similar; further, Protocols 640 and 641 were identical to each other, as were Protocols 671 and 682. Subjects in all four studies were required to meet DSM-III-R criteria for a principal diagnosis of PTSD and were not allowed to have a primary diagnosis meeting DSM-III-R criteria for most other mood, anxiety or psychotic disorders, as determined by Structured Clinical Interview for DSM-III-R (SCID). All studies were conducted at U.S. research centers. Protocols 640, 671 and 682 were conducted primarily at civilian sites, while Protocol 641 was conducted at Veterans Administration (VA) medical centers. There were no protocol restrictions as to the type of subject (civilian or veteran) that could be enrolled at a site. The intent-to-treat efficacy population included all randomized subjects who had at least one dose of study medication and one post baseline efficacy evaluation. Table 4.1 shows the demographics characteristics of the four Phase III studies.

Table 4.1. Demographic characteristics of the four Phase III studies for sertraline vs. placebo in patients with PTSD. Studies 640 and 671 are the two pivotal studies.

Demographic Characteristics				
	640	671	641	682
Gender Ratio female:male	3:1	3:1	1:4	3:1
% white	84	84	71	89
Mean age (yrs)	37	40	45	37
Duration of illness (yrs)	12	12	18	11
Most common traumatic event	physical/sexual assault (62%)	physical/sexual assault (61%)	war or combat (71%)	physical/sexual assault (54%)
Time (yrs) since traumatic event	18	18	23	15
% Comorbid Depression	49	36	46	45

A one-week single-blind placebo run-in preceded Protocols 640 and 641, while a two-week single-blind-placebo run-in preceded Protocols 671 and 682 in order to better allow for washout of ongoing psychotropic medications and to increase the time available to receive baseline laboratory reports. At the baseline visit, subjects in all four studies were required to have a score on the Clinician-Administered PTSD Scale Part 2 (CAPS-2) of at least 50 in order to be randomized.

Efficacy Endpoints

The primary efficacy variables in the study were the CAPS-2 total severity score, IES total, and CGI Improvement and Severity ratings. The CAPS-2 total severity score, the analysis method validated by the scale authors, was computed as the sum of the frequency and intensity of each of the first 17 items, corresponding to the DSM diagnostic symptom criteria for PTSD. The reexperiencing cluster contained items 1-4; the avoidance/numbing cluster contained items 5-11; the hyperarousal cluster contained items 12-17; and Associated Features contained items 23-30. On the IES, items 1-7 contributed to the reexperiencing cluster, and items 8-15 contributed to the avoidance/numbing cluster. The Davidson Self-Rating PTSD Scale total was computed as the sum of the frequency and intensity of each item. As with the CAPS-2, the reexperiencing cluster contained items 1-4; the avoidance/numbing cluster contained items 5-11; and the hyperarousal cluster contained items 12-17.

There was sufficient documentation provided to support the validity of the scales considered in the primary efficacy analyses.

Scores on CAPS-2 total severity and variables, IES total and symptom clusters, CGI Severity, Davidson Self-Rating PTSD Scale, DES-NOS Scale, Civilian Mississippi Scale, HAM-A, HAM-D, and PSQI were analyzed at baseline using analysis of variance with terms for treatment group and center. In Study 640, statistically significantly fewer males were enrolled at baseline in the sertraline group when compared to enrollment in the placebo group ($p = 0.041$).

Analysis of covariance models which included terms for treatment, site, treatment-by-site, and baseline effects were used to analyze the change from baseline to the last observation in the intent-to-treat population. The model used to analyze CGI Improvement did not include baseline values since CGI Improvement measured change from baseline and was not defined at baseline. Adjusted means and standard errors were reported. Responder analysis for CAPS-2 total severity and CGI Improvement used a Mantel-Haenszel chi-square statistic, stratified by site.

Table 4.2 shows the mean change on the primary efficacy variables for all four studies.

Table 4.2. The mean changes from baseline on all four studies for the primary endpoints. Statistically significant differences are in bold text. The pivotal studies for efficacy are Studies 640 and 671.

Mean Change from Baseline on Primary Efficacy Variables												
	640			671			641			682		
	Sert	Pbo	p-val.	Sert	Pbo	p-val.	Sert	Pbo	p-val.	Sert	Pbo	p-val.
CAPS-2	-33.0	-26.2	**0.043**	-33.0	-23.2	**0.016**	-13.1	-15.4	0.587	-27.4	-27.9	0.896
IES	-19.2	-14.1	**0.018**	-16.2	-12.1	0.071	-8.7	-8.1	0.799	-13.6	-19.7	**0.017**
CGI-S	-1.3	-1.0	**0.037**	-1.2	-0.8	**0.012**	-0.5	-0.6	0.468	-1.0	-0.9	0.798
CGI-I	2.3	2.8	**0.014**	2.5	3.0	**0.016**	3.0	3.0	0.879	2.6	2.6	0.891

Note that the veterans in Study 641 had similar scores from baseline to study completion across all questionnaires. It has been hypothesized that "American Vietnam veterans who have served as patients in most published randomized clinical trials may be the most severely impaired, chronic, and treatment-refractory cohorts...[and they are] available subjects for drug trials because they are still enrolled in VA treatment programs" [1]. Therefore, there is an inherent selection bias in this cohort which may explain the lack of response in either the sertraline or placebo arms compared to the other three studies.

The sponsor submitted two studies in support of the efficacy of sertraline in PTSD. These were Studies 640 and 671, and we briefly discuss their results below.

Results of Study 640

Study 640 was a double-blind, 12-week comparison of flexible doses of sertraline and matching placebo conducted at 12 study sites. All sertraline-treated subjects received one week of treatment with 25 mg sertraline after which dosage was titrated to 50 mg, followed by a flexible titration of dose between 50 and 200 mg/day in accordance with the subject's clinical response and in the absence of dose limiting side effects.

Ninety-eight subjects in the sertraline group and 104 in the placebo group were included in the intent-to-treat analysis. Subjects were primarily white females, with significantly fewer males in the sertraline group compared to the placebo group (16/100 v. 30/108; $p = 0.041$). The most common traumatic event was physical/sexual assault, with an approximate time since traumatic event of 18 years. Forty-nine percent of subjects had been diagnosed with a comorbid secondary depression.

The mean scores of the primary efficacy variables (CAPS-2 total severity score, IES total score, CGI-S and CGI-I) did not differ between arms at baseline. The mean changes between the baseline and the end of the study on the primary efficacy variables are presented above in Table 4.2. Subjects treated with sertraline were significantly improved on all four primary efficacy endpoints compared to placebo-treated subjects, although there was no Type I Error adjustment for multiple comparisons.

Sertraline-treated subjects had greater reductions in score on symptoms from all three clusters on the CAPS-2 and IES, with a statistically significant result on the CAPS-2 avoidance/numbing cluster and on both the intrusion and avoidance clusters on the IES. Results from the CGI Severity and Improvement ratings (Table 4.2) show that sertraline-treated subjects improved significantly on these global measures compared to placebo subjects.

Figure 1. CAPS-2 graph for Study 640

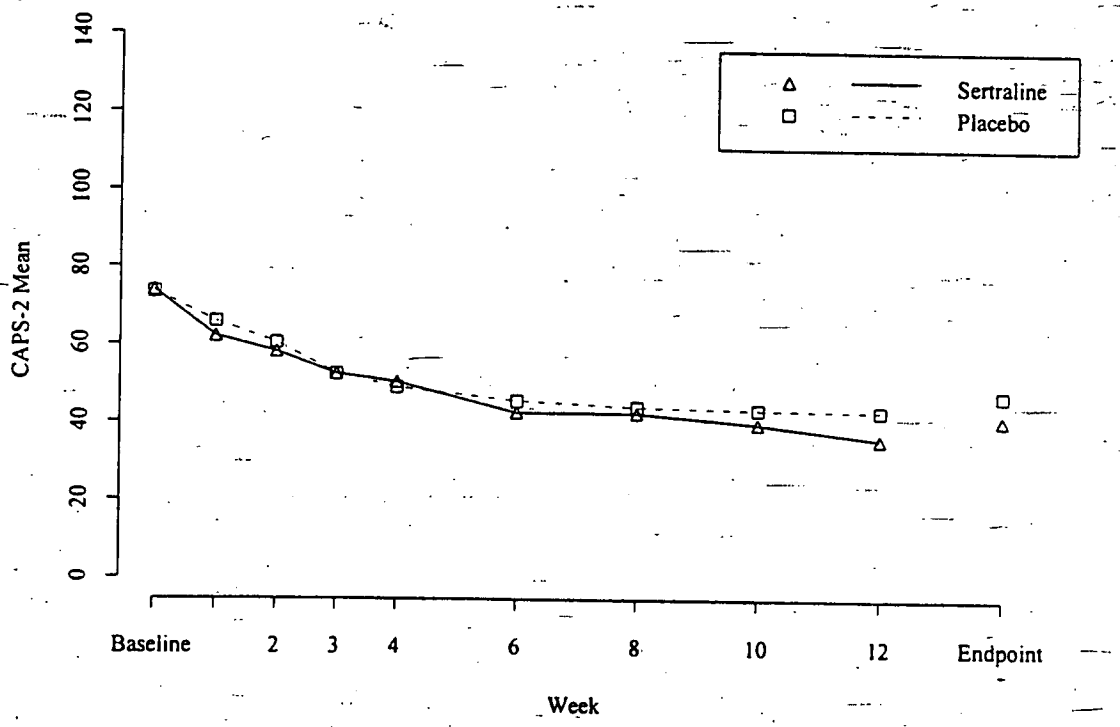

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Figure 2. IES graph for Study 640

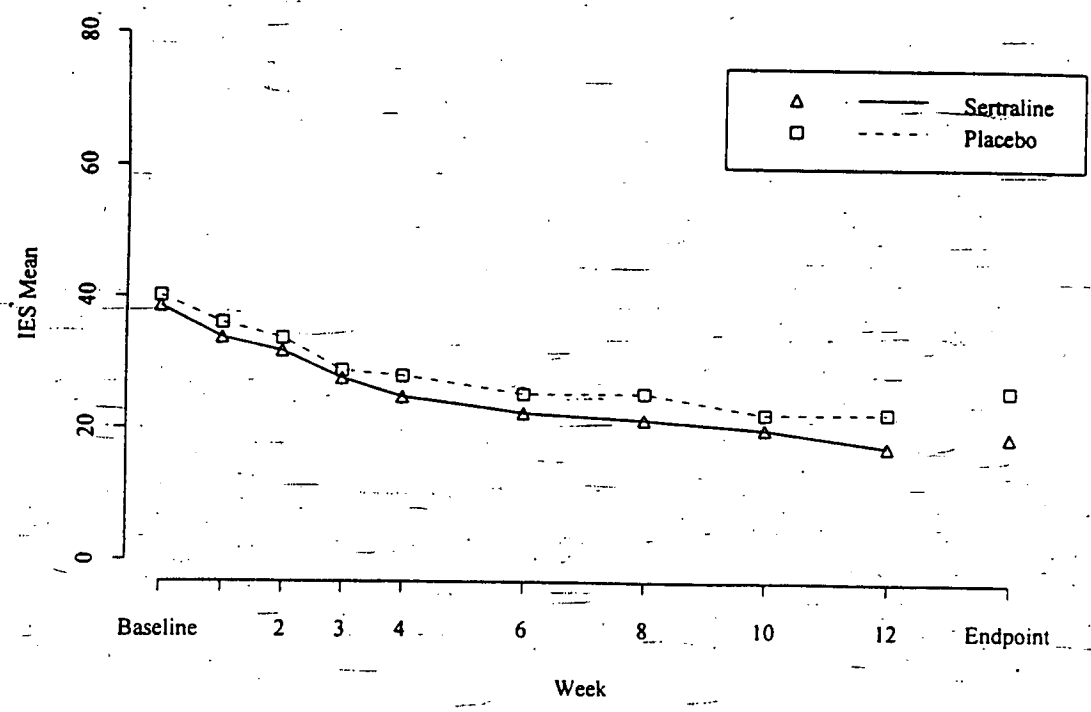


Figure 3. CGI-S graph for Study 640

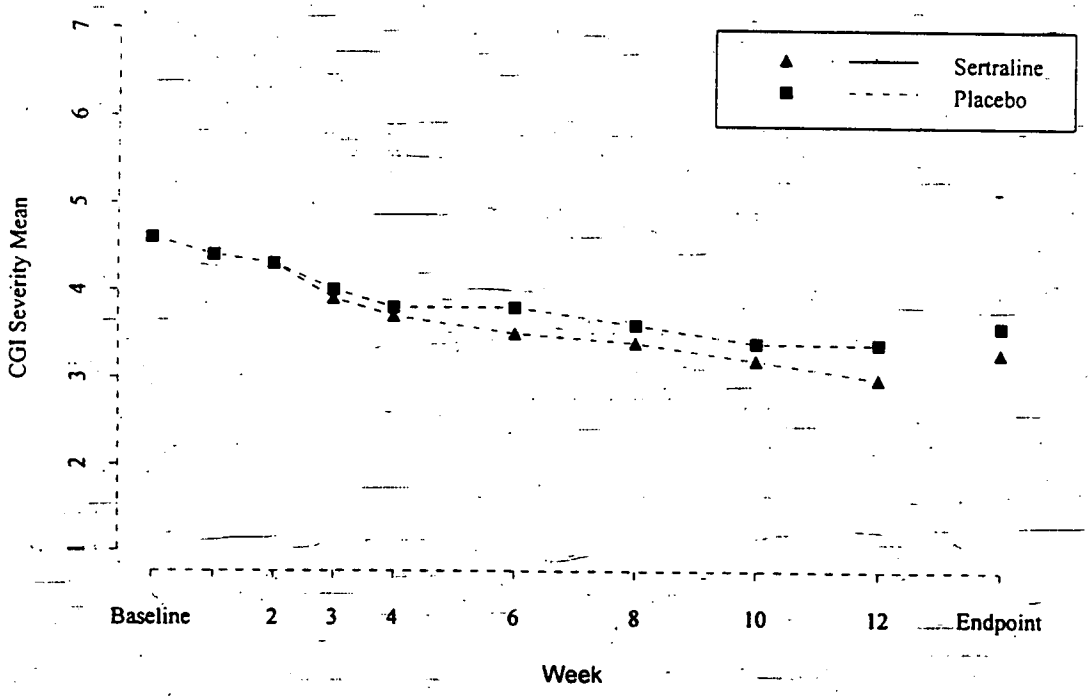
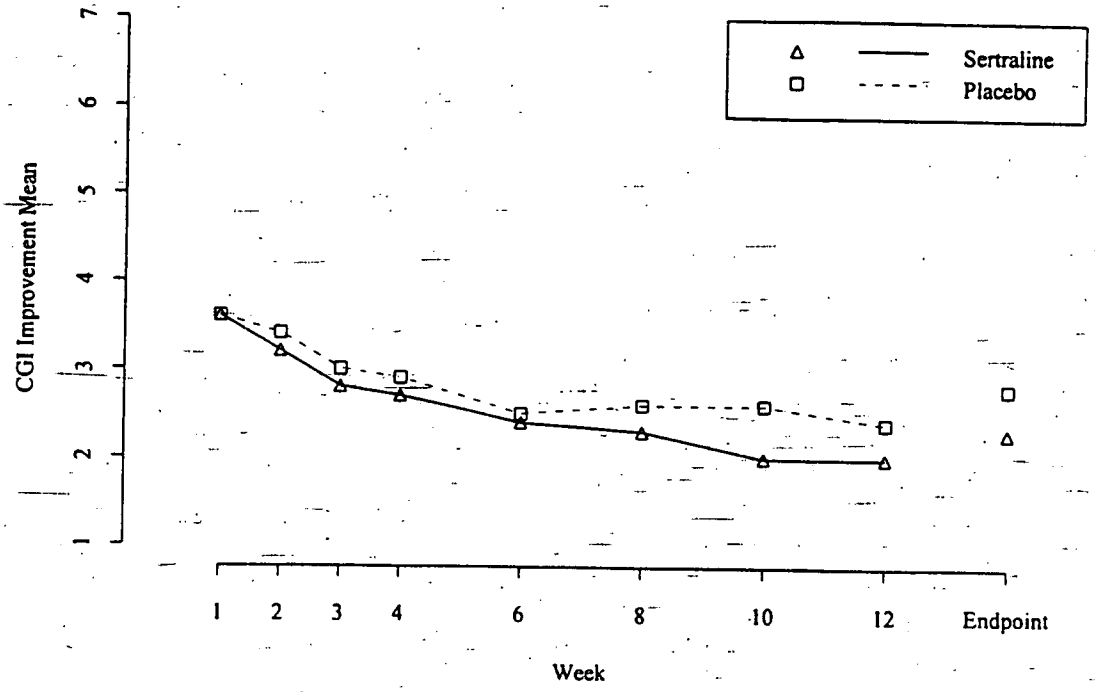


Figure 4. CGI-I graph for Study 640



Other (secondary) endpoints that were measured in Study 640 were Davidson Self-Rating PTSD Scale, DES-NOS, Mississippi Civilian PTSD, HAM-A, HAM-D, and Pittsburgh Sleep Quality Index. The mean differences from baseline for these endpoints appear in Table 4.3. The Davidson scale is the only secondary efficacy parameter that shows a statistically significant improvement for sertraline over to placebo.

Table 4.3. Mean differences from baseline in the secondary efficacy endpoints for 640.

Secondary Efficacy Parameters			
	Sert	Pbo	p-value
Davidson	-32.3	-20.0	0.002
DES-NOS	-23.1	-19.1	0.247
Mississippi	-11.9	-9.4	0.235
HAM-A	-7.8	-6.4	0.260
HAM-D	-7.7	-6.3	0.330
PSQI	-3.0	-2.5	0.451

Results of Study 671

Study 671 was a double-blind, 12-week comparison of flexible doses of sertraline and matching placebo conducted at 14 study sites. All sertraline-treated subjects received one week of treatment with 25 mg sertraline after which dosage was titrated to 50 mg, followed by a flexible titration of dose between 50 and 200 mg/day in accordance with the subject's clinical response and in the absence of dose limiting side effects.

Ninety-three subjects in the sertraline group and 90 in the placebo group were included in the intent-to-treat analysis. Subjects were primarily white females, approximately 40 years old with a mean duration of illness of approximately 12 years. The most common traumatic event was physical/sexual assault, with time since traumatic event approximately 18 years. Thirty-six percent of subjects had been diagnosed with a comorbid secondary depression.

Subjects treated with sertraline improved on all four primary efficacy measures compared to placebo-treated subjects, reaching statistical significance on the CAPS-2, CGI-I and CGI-S (see Table 4.2). There were significant reductions in favor of the sertraline treatment group in the avoidance/numbing and hyperarousal symptom clusters on both the CAPS-2 and Davidson ratings (see Tables 4.5-4.7). The primary efficacy variables (CAPS-2 total severity score, IES total score, CGI-I and CGI-S) did not differ between treatment groups at baseline. The mean changes on primary efficacy variables are presented above and in Table 4.2.

Figure 5. CAPS-2 graph for Study 671

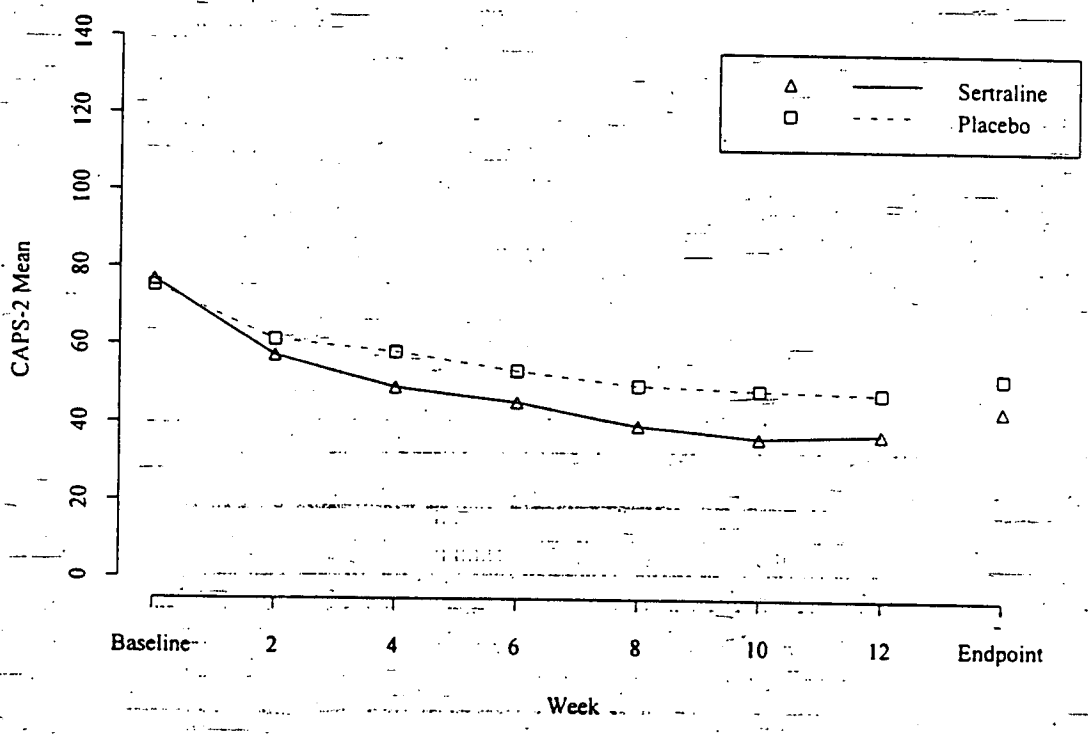


Figure 6. IES graph for Study 671

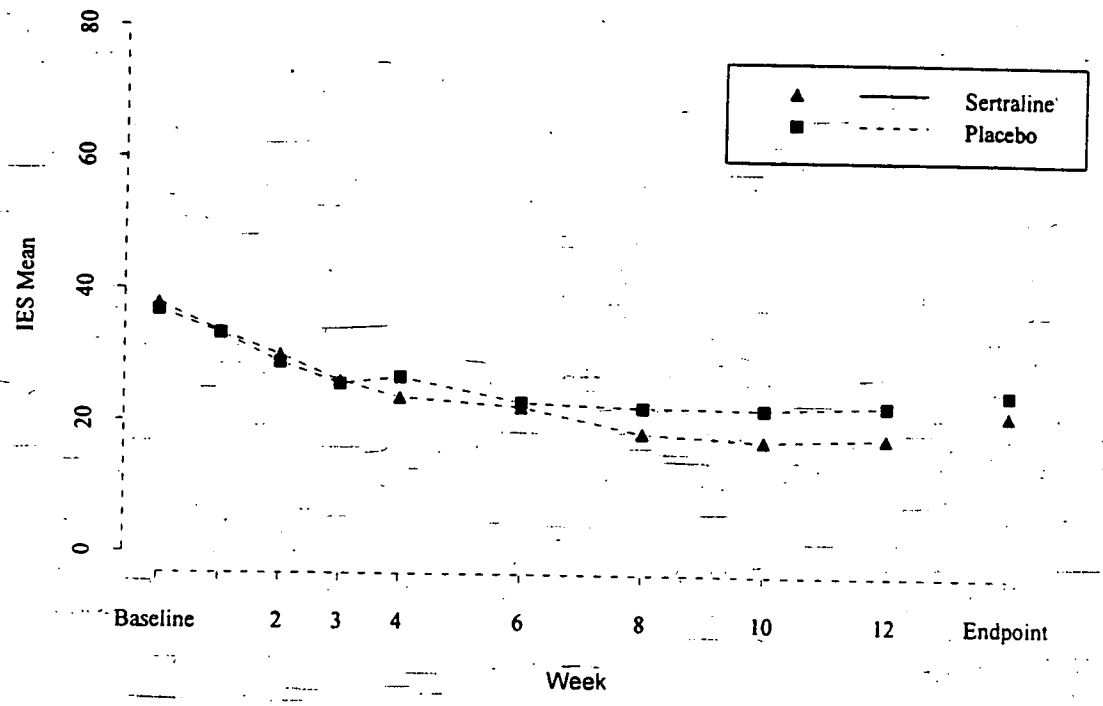


Figure 7. CGI-S graph for Study 671

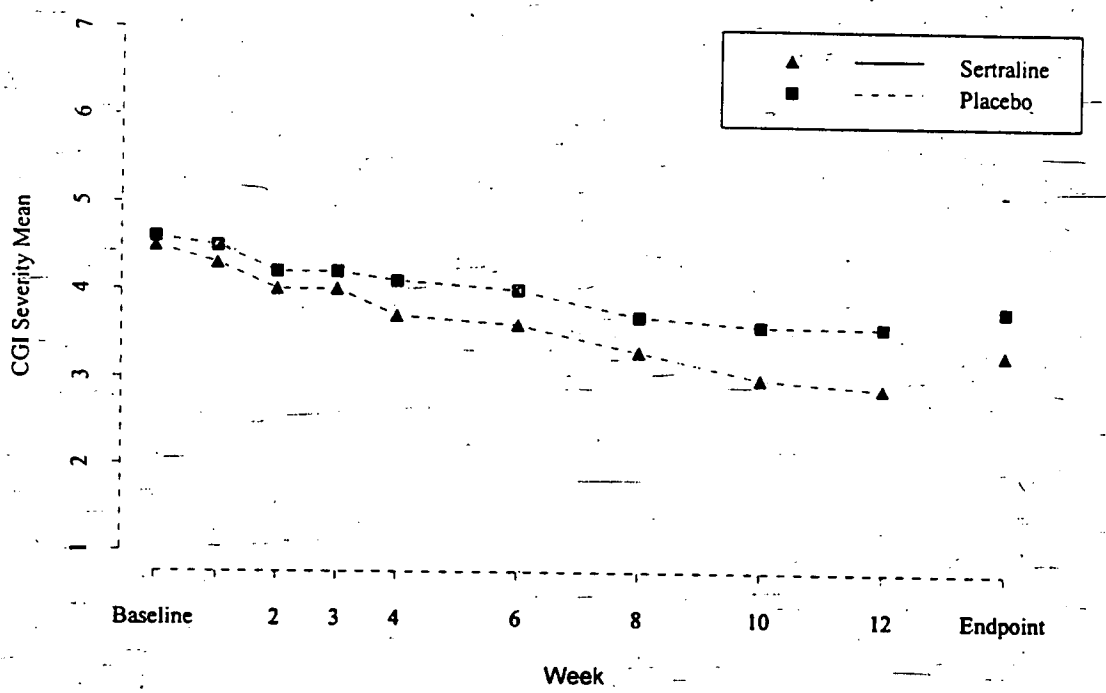
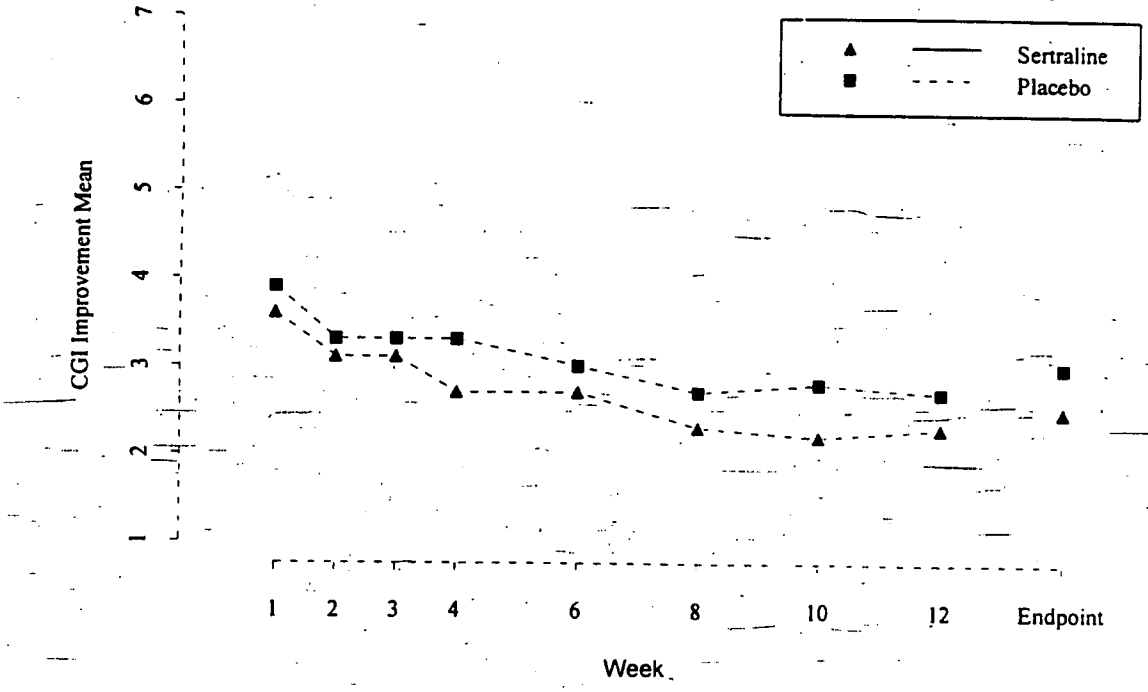


Figure 8. CGI-I graph for Study 671



Other (secondary) endpoints that were measured in Study 640 were Davidson Self-Rating PTSD Scale, HAM-D, and the total and response to item 16 on the Q-LES-Q. The mean differences from baseline for these endpoints appear in Table 4.4. Results from each of these instruments show a statistically significant improvement for sertraline compared to placebo.

Table 4.4. Mean differences from baseline in the secondary efficacy endpoints for 671.

Secondary Efficacy Parameters			
	Sert	Pbo	p-value
Davidson	-28.1	-16.1	0.003
HAM-D	-8.6	-5.0	0.042
Q-LES-Q Total	11.7	3.3	0.004
Q-LES-Q Item 16	0.7	0.2	0.048

Pooled Results of Studies 640 and 671

The PTSD symptoms comprising the clusters from DSM-III-R (and having one-to-one correspondence with items of the CAPS-2 and Davidson scales) are listed below:

Reexperiencing/Intrusion:
1. intrusive thoughts
2. distressing dreams of the event
3. flashbacks, reliving the event
4. intense psychological distress at exposure to reminders of the event

Avoidance/Numbing:
5. efforts to avoid thoughts, feelings, conversations about the trauma

6. efforts to avoid places that arouse recollections of the trauma
7. inability to recall aspects of the trauma
8. diminished interest in activities
9. feelings of detachment or estrangement
10. restricted affect
11. sense of foreshortened future

Hyperarousal:
12. difficulty falling or staying asleep
13. irritability/anger
14. difficulty concentrating
15. hypervigilance
16. exaggerated startle response
17. physiological reactivity to reminders of the trauma

The sponsor presented the pooled results of Studies 640 and 671 based on these three divisions. Tables 4.5, 4.6 and 4.7 show the mean change from baseline for reexperiencing/intrusion, avoidance/numbing, and hyperarousal, respectively.

Table 4.5. Results for Studies 640 and 671 on the Reexperiencing/Intrusion clusters.

Reexperiencing/Intrusion Mean Change							
	640			671			640 & 671
	Sert	Pbo	p-val.	Sert	Pbo	p-val.	Pooled p-val.
CAPS-2	-7.5	-6.5	0.297	-6.9	-5.4	0.143	0.056
IES	-9.6	-6.9	0.027	-7.1	-5.4	0.158	0.019
Davidson	-6.7	-4.4	0.029	-4.9	-3.1	0.102	0.008

Table 4.6. Results for Studies 640 and 671 on the Avoidance/Numbing clusters.

Avoidance/Numbing Mean Change							
	640			671			640 & 671
	Sert	Pbo	p-val.	Sert	Pbo	p-val.	Pooled p-val.
CAPS-2	-14.7	-10.6	0.016	-14.6	-10.0	0.015	< 0.001
IES	-9.6	-7.1	0.048	-9.0	-6.8	0.085	0.004
Davidson	-12.8	-7.2	0.003	-11.1	-6.7	0.013	< 0.001

Table 4.7. Results for Studies 640 and 671 on the Hyperarousal clusters.

Hyperarousal Mean Change							
	640			671			640 & 671
	Sert	Pbo	p-val.	Sert	Pbo	p-val.	Pooled p-val.
CAPS-2	-10.8	-8.9	0.123	-11.4	-8.0	0.027	0.007
Davidson	-11.8	-7.8	0.007	-11.3	-6.1	0.002	< 0.001

Although Study 671 does not show a statistically significant improvement on CAPS-2, IES, or Davidson for the reexperiencing/intrusion cluster, there were statistically significant differences on all three clusters across both studies and in the pooled study results. The differences in placebo responses were similar in 640 and 671 across all instruments except for the reexperiencing/intrusion cluster.

Comparison between LOCF and Observed Cases Analyses

The sponsor performed analyses on both the observed cases (OC) data set and the last observation carried forward (LOCF) data set for each of the four clinical studies (studies 640, 641, 671, 682). The results of the OC analyses for Study 640 and 671 appear in Figures 1 through 8. The results of the OC analyses at week 12 and the primary endpoint analyses are in agreement for the two neutral studies (641 and 682).

In the positive study 640, the mean differences between sertraline and placebo are consistent between the OC analyses at week 12 and the primary endpoint analyses. However, due to smaller sample sizes in the OC analyses only the Davidson Total remains significant. The p-values for CAPS-2 Total and the CGI Improvement were 0.066 and 0.065, respectively. In the second positive study 671, again the mean differences between sertraline and placebo are consistent between the OC analyses at week 12 and the primary endpoint analyses. In this study all endpoints in the OC analyses were significant except CGI Improvement which had a p-value of 0.062.

The general trend when comparing the OC analyses with the LOCF analyses was that there was close agreement between both until later visits (visits 8, 10, or 12). As expected, the LOCF analyses showed less of a difference from baseline than the OC analyses in the later visits, due to missing values. Overall, however, the differences between the OC and LOCF analyses are in general agreement.

Potential Interaction between Gender and Treatment Efficacy

In the two pivotal studies, there was evidence that the efficacy results of sertraline were gender dependent. Note that in Study 640, statistically significantly fewer males were enrolled at baseline in the sertraline group when compared to enrollment in the placebo group (p = 0.041). The sponsor analyzed the data to quantify any gender effect and we summarize these results here.

Table 4.8. Summary of treatment by gender interaction in Studies 640 and 671 (pooled). This table contains differences from baseline to endpoint, the p-values for the treatment effect in men and women and the p-value for the treatment-by gender interaction effect.

	Women			Men			Interaction
	Sert	Pbo	p-val.	Sert	Pbo	p-val.	p-val.
Sample Size	152	139		39	55		
CAPS-2 Total	-34	-23	0.0001	-29	-29	0.99	0.041
Reexp./Intrusion	-8	-6	0.005	-6	-7	0.39	0.033
Avoidance/Numbing	-15	-9	0.0001	-13	-12	0.76	0.052
Hyperarousal	-11	-8	0.0007	-10	-11	0.95	0.088
Assoc. Features	-10	-7	0.002	-12	-8	0.12	0.89
Davidson Total	-32	-16	0.0001	-24	-25	0.97	0.009
Reexp./Intrusion	-6	-4	0.0009	-5	-5	0.74	0.056
Avoidance/Numbing	-13	-6	0.0001	-10	-10	0.93	0.011
Hyperarousal	-12	-6	0.0001	-9	-10	0.62	0.004
IES Total	-18	-13	0.001	-16	-15	0.80	0.16
Intrusion	-9	-6	0.003	-7	-8	0.62	0.059
Avoidance	-10	-7	0.003	-9	-8	0.51	0.38
CGI-Improvement	2	3	0.0001	2	3	0.34	0.22
HAM-D Total	-8	-5	0.005	-6	-7	0.69	0.088

Although this table considers the change from baseline in endpoints when pooling studies 640 and 671, similar tables would result for studies 640 and 671 individually.

Table 4.9. The least-square differences in women from baseline to endpoint and the p-values for the treatment effect in each stratum. These strata were defined as women with baseline HAM-D totals above and below the median. These analyses pooled studies 640 and 671.

	HAM-D Total ≤ 21			HAM-D Total > 21		
	Sert	Pbo	p-val.	Sert	Pbo	p-val.
Variable	N=77	N=69		N=75	N=70	
CAPS-2 Total	-33	-24	0.015	-36	-21.71	0.001
Reexp./Intrusion	-7	-5	0.056	-8	-6	0.046
Avoidance/Numbing	-15	-10	0.018	-17	-9	0.0002
Hyperarousal	-11	-8	0.037	-11	-7	0.0081
Assoc. Features	-9	-6	0.039	-12	-8	0.023
Davidson Total	-27	-13	0.0005	-37	-20	0.0004
Reexp./Intrusion	-5	-2	0.002	-7	-5	0.11
Avoidance/Numbing	-10	-6	0.027	-16	-7	0.0001
Hyperarousal	-11	-6	0.0003	-14	-8	0.0009
IES Total	-17	-12	0.013	-20	-15	0.046
Intrusion	-8	-5	0.014	-10	-8	0.16
Avoidance	-9	-7	0.066	-10	-7	0.019
CGI-Improvement	2	3	0.012	2	3	0.001

Table 4.10. The least-square differences in women from baseline to endpoint and the p-values for the treatment effect in each stratum. These strata were defined as women with and without diagnosis of comorbid depression. These analyses pooled studies 640 and 671.

	No Comorbid Depression			Comorbid Depression		
	Sert	Pbo	p-val.	Sert	Pbo	p-val.
Variable	N=85	N=80		N=67	N=59	
CAPS-2 Total	-33	-22	0.0049	-39	-25	0.0024
Reexp./Intrusion	-7	-5	0.046	-9	-7	0.035
Avoidance/Numbing	-15	-9	0.0022	-17	-10	0.0014
Hyperarousal	-12	-8	0.024	-12	-8	0.011
Assoc. Features	-10	-7	0.028	-12	-8	0.035
Davidson Total	-30	-15	0.0004	-37	-20	0.0006
Reexp./Intrusion	-5	-3	0.024	-8	-4	0.015
Avoidance/Numbing	-12	-6	0.0016	-15	-7	0.0004
Hyperarousal	-12	-6	0.0001	-13	-8	0.0047
IES Total	-17	-13	0.031	-21	-14	0.010
Intrusion	-8	-6	0.039	-10	-7	0.033
Avoidance	-9	-7	0.087	-11	-6	0.0055
CGI-Improvement	2.3	3.0	0.0007	2.4	3.0	0.018

From the previous three tables, we can conclude that there are statistically significant differences in specific PTSD endpoints when we compare sertraline and placebo. In Table 4.10, the sponsor considers whether sertraline's PTSD-specific effect is consistent across clinical depression diagnoses, and the p-values in Table 4.10 confirm that there is improvement in PTSD-specific endpoints as measured by various PTSD instruments.

A reasonable follow-up question to ask is whether there are differences in PTSD response between patients with no improvement in depression symptoms and those who did improve in depression symptoms over the course of the trials. A further question is whether those who did not show

improvement in depression symptoms had differing responses in PTSD with respect to treatment (sertraline vs. placebo). We explore these questions as secondary analyses in the following sections. Note that these analyses are *post hoc* and the study was not powered to test formally these questions.

The medical reviewer defined depression non-improvers as follows:

In patients with HAM-D baseline totals greater than 19, a depression non-improver was categorized as those with a HAM-D Total difference of -9 or greater between total from baseline to last visit. In patients with HAM-D baseline totals of 19 or less, a depression non-improver was categorized as those with a HAM-D Total difference of -5 or greater between total from baseline to last visit. Therefore, patients whose depression worsened or remained the essentially the same (as measured by HAM-D Total) were considered to be depression non-improvers. All other patients were classified as depression improvers.

All statistical tests that we performed were two-sided and at the 0.05 level of significance. Analysis of covariance models, which included terms for treatment and HAM-D at baseline (as a covariate), were used to analyze the change from baseline PTSD on all three instruments.

The first analysis that we present considers differences in PTSD scores between the depression non-improver and depression improver subgroups. Note that the subgroups below ignore treatment. Table 4.11 shows that there were statistically significant differences between depression improvers and depression non-improvers with respect to PTSD symptoms across both genders, in the combination of genders, and across all PTSD instruments. One conclusion that may be drawn from this analysis is that there is a tendency for depression non-improvers not to improve with respect to PTSD symptoms as well (regardless of treatment).

Table 4.11. Means and p-values for comparing depression improvers vs. depression non-improvers, regardless of treatment, with respect to PTSD instruments.

Mean Changes from Baseline		CAPS-2			IES			CGI-S		
		Imprvrs	Non-Imprvrs	p-value	Imprvrs	Non-Imprvrs	p-value	Imprvrs	Non-Imprvrs	p-value
640/671	Males	-46	-15	0.0001	-20	-11	0.0053	-2.0	-0.5	0.0001
	Females	-46	-16	0.0001	-22	-12	0.0001	-1.8	-0.5	0.0001
	Combin.	-46	-16	0.0001	-22	-12	0.0001	-1.8	-0.5	0.0001
All 4	Males	-38	-11	0.0001	-19	-7	0.0001	-1.5	-0.3	0.0001
	Females	-46	-16	0.0001	-23	-12	0.0001	-1.7	-0.5	0.0001
	Combin.	-43	-14	0.0001	-22	-10	0.0001	-1.7	-0.5	0.0001
		Males		Females		Combin				
N		640/671	All 4	640/671	All 4	640/671	All 4			
Improvers		33	91	119	184	152	275			
Non-Improvers		41	137	113	185	154	322			

We performed an analysis that considered treatment effects among depression non-improvers and depression improvers subgroups, and these results appear in Table 4.12a. Analysis of covariance models which included terms for improvement group (depression improvers or non-improvers) and baseline HAM-D, which was treated as a covariate, were used to analyze the change from baseline PTSD on all three instruments. From Table 4.12a, we see that there are no statistically significant differences in PTSD between those male depression non-improvers treated with sertraline versus those treated with placebo. Female depression non-improvers showed a statistically significant difference on CAPS-2 in favor of sertraline when combining the two pivotal studies and a nearly statistically difference in CAPS-2 when combining the four Phase III studies (0.057). For the combined genders, there were no statistically significant differences in PTSD symptoms in either the combination of

pivotal studies or the combination of all four studies. This suggests that there is no sertraline advantage over placebo in men in these subgroups, and minimal sertraline advantage over placebo in women in these subgroups. Table 4.12a does not support the hypothesis that those sertraline-treated patients who did not show improvement in depression symptoms had differing responses in PTSD than those patients on placebo. Note that the studies were not powered to detect specifically these differences and that subgroup analyses such as this one and those below should be interpreted as merely exploratory, and not definitive, results.

Table 4.12a. P-values for comparing between sertraline and placebo with respect to PTSD instruments. Depression improvement here is measured by total HAM-D score.

Depression Non-improvers Only						
	Men		Women		Combined	
	640/671	All 4	640/671	All 4	640/671	All 4
CAPS-2	0.4770	0.2991	0.0356	0.0570	0.1107	0.4584
IES	0.1860	0.6071	0.1725	0.8234	0.0609	0.7873
CGI-S	0.3037	0.2637	0.1197	0.0803	0.0606	0.6086
N (sert/pbo)	16 / 25	68 / 69	51 / 62	85 / 100	67 / 87	153 / 169
Depression Improvers Only						
	Men		Women		Combined	
	640/671	All 4	640/671	All 4	640/671	All 4
CAPS-2	0.0623	0.5412	0.1868	0.3556	0.0682	0.1709
IES	0.4537	0.4095	0.8135	0.2550	0.6435	0.7514
CGI-S	0.5165	0.9313	0.1733	0.2319	0.2011	0.2308
N (sert/pbo)	12 / 21	38 / 53	70 / 49	101 / 83	82 / 70	139 / 136

In another secondary analysis, we tested the aforementioned hypothesis by considering a particular item on the HAM-D depression instrument regarding depressed mood. We defined depressed mood non-improvers as those patients with a difference between baseline depressed mood score to last visit depressed mood score of 0 or less. Depressed mood improvers were defined similarly with a difference of 1 or more. Therefore, patients whose depressed mood worsened or remained the essentially the same from the beginning of the study were considered to be depressed mood non-improvers. All other patients were classified as depressed mood improvers. Table 4.12b shows the same analysis as Table 4.12a, except that the subgroups are based on depressed mood improvement.

Table 4.12b. P-values for comparing between sertraline and placebo with respect to PTSD instruments. Depression improvement here is measured by change from baseline "depressed mood" score (Question #1 on the HAM-D).

Depressed Mood Non-improvers Only						
	Men		Women		Combined	
	640/671	All 4	640/671	All 4	640/671	All 4
CAPS-2	0.8598	0.9319	**0.0014**	**0.0416**	**0.0048**	0.1058
IES	0.2383	0.6841	**0.0460**	0.6855	**0.0248**	0.9734
CGI-S	0.4402	0.8600	**0.0101**	0.0504	**0.0123**	0.1577
N (sert/pbo)	16 / 25	68 / 69	51 / 62	85 / 100	67 / 87	153 / 169

Depressed Mood Improvers Only						
	Men		Women		Combined	
	640/671	All 4	640/671	All 4	640/671	All 4
CAPS-2	0.8130	0.5671	0.3428	0.4116	0.2384	0.5197
IES	0.7154	0.9018	0.8288	0.1896	0.7849	0.3972
CGI-S	0.9481	0.5552	0.3356	0.3434	0.3070	0.5412
N (sert/pbo)	12 / 21	38 / 53	70 / 49	101 / 83	82 / 70	139 / 136

Table 4.12b confirms that there are no statistically significant differences between sertraline and placebo among men in either subgroup. There are statistically significant differences between sertraline and placebo among women whose depressed mood does not improve. When one combines across gender, the statistically significant differences remain among the depressed mood non-improvers.

Table 4.13 shows analysis of covariance models which included terms for improvement group (depressed mood improvers or non-improvers) and baseline HAM-D, which was treated as a covariate, and which were used to analyze the change from baseline PTSD on all three instruments. With the exception of men in Studies 640 and 671, Table 4.13 shows that there were statistically significant differences between depressed mood improvers and depressed mood non-improvers with respect to PTSD symptoms across both genders, in the combination of genders, and across all PTSD instruments. There is also a statistically significant sertraline effect in women and combined men and women in Studies 640 and 671. One conclusion that may be drawn from this analysis is that PTSD symptoms in women improve even when one adjusts for depression effects. However, the sertraline advantage in men remains statistically non-significant after adjusting for depressed mood improvement.

Table 4.13. P-values for comparing depressed mood improvers vs. depressed mood non-improvers and sertraline vs. placebo with respect to PTSD instruments.

		Men		Women		Combined	
PTSD Instr.	Factor	640/671	All 4	640/671	All 4	640/671	All 4
CAPS-2	Dp. Mood	0.0997	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**
	Sertraline	0.7615	0.6698	**0.0045**	0.0534	**0.0058**	0.1227
CGI-S	Dp. Mood	**0.0093**	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**
	Sertraline	0.6472	0.5236	**0.0176**	**0.0445**	**0.0182**	0.1744
IES	Dp. Mood	0.1734	**0.0001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**
	Sertraline	0.7026	0.6243	0.1472	0.2436	0.1053	0.4973

We compared subgroups after pooling Studies 640 and 671. The combinations of subgroups that we considered were treatment (placebo vs. sertraline) and improvement in depressed mood (depressed mood improvers vs. depressed mood non-improvers). Tables 4.14 through 4.16 show the least-square means of each subgroup on the three PTSD instruments among the three PTSD instruments. This

exploratory analysis was performed to examine the hypothesis that men have little PTSD symptom improvement while on sertraline, whereas women tend to improve in sertraline regardless of whether they improve on depression.

Table 4.14. P-values for comparing subgroups among males in Studies 640 and 671 only. The subgroups under consideration are combinations of depressed mood improvers vs. depressed mood non-improvers and sertraline vs. placebo with respect to PTSD instruments. A large negative mean difference from baseline implies patient benefit.

Males in Studies 640 and 671 (Pooled)					
CAPS-2					
	Mean Diff. From BL	Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-24.0	—			
Pbo. / Dep. Imp.	-32.5	0.188	—		
Sert. / No Dep. Imp.	-25.4	0.828	0.344	—	
Sert. / Dep. Imp.	-34.1	0.143	0.831	0.268	—
CGI-S					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-0.7	—			
Pbo. / Dep. Imp.	-1.5	0.014	—		
Sert. / No Dep. Imp.	-0.9	0.490	0.099	—	
Sert. / Dep. Imp.	-1.5	0.021	0.988	0.119	—
IES					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-11.0	—			
Pbo. / Dep. Imp.	-18.7	0.058	—		
Sert. / No Dep. Imp.	-15.6	0.243	0.492	—	
Sert. / Dep. Imp.	-16.4	0.211	0.628	0.873	—

Table 4.14 shows the subgroup analysis for men in Studies 640 and 671. There were no statistically significant differences among any of the four subgroups for PTSD measured by CAPS-2 or IES.

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Table 4.15. P-values for comparing subgroups among females in Studies 640 and 671 only. The subgroups under consideration are combinations of depressed mood improvers vs. depressed mood non-improvers and sertraline vs. placebo with respect to PTSD instruments. A large negative mean difference from baseline implies patient benefit.

Females in Studies 640 and 671 (Pooled)					
CAPS-2					
	Mean Diff. From BL	Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-14.3	—			
Pbo. / Dep. Imp.	-39.8	0.001	—		
Sert. / No Dep. Imp.	-25.3	0.002	0.001	—	
Sert. / Dep. Imp.	-44.6	0.001	0.255	0.001	—
CGI-S					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-0.4	—			
Pbo. / Dep. Imp.	-1.6	0.001	—		
Sert. / No Dep. Imp.	-0.8	0.015	0.001	—	
Sert. / Dep. Imp.	-1.8	0.001	0.282	0.001	—
IES					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-8.8	—			
Pbo. / Dep. Imp.	-22.9	0.001	—		
Sert. / No Dep. Imp.	-13.3	0.057	0.001	—	
Sert. / Dep. Imp.	-23.8	0.001	0.758	0.001	—

Table 4.15 shows the subgroup analysis for women in Studies 640 and 671. In contrast to men (Table 4.14), there are statistically significant PTSD differences between subgroups across the three instruments. The sertraline + depressed mood improvers had the most PTSD benefit compared to the other three subgroups across all three instruments. However, the placebo + depressed mood improvers had consistently greater PTSD improvement over the sertraline + non-improver patients (as measured by the least-square means).

Table 4.16. P-values for comparing subgroups among all patients combined in Studies 640 and 671. The subgroups under consideration are combinations of depressed mood improvers vs. depressed mood non-improvers and sertraline vs. placebo with respect to PTSD instruments. A large negative mean difference from baseline implies patient benefit.

All patients in Studies 640 and 671 (Pooled)					
CAPS-2					
	Mean Diff. From BL	Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-17.0	—			
Pbo. / Dep. Imp.	-37.5	0.001	—		
Sert. / No Dep. Imp.	-25.3	0.008	0.001	—	
Sert. / Dep. Imp.	-42.5	0.001	0.173	0.001	—
CGI-S					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-0.5	—			
Pbo. / Dep. Imp.	-1.5	0.001	—		
Sert. / No Dep. Imp.	-0.8	0.017	0.001	—	
Sert. / Dep. Imp.	-1.7	0.001	0.276	0.001	—
IES					
		Pbo. / No Dep. Imp.	Pbo. / Dep. Imp.	Sert. / No Dep. Imp.	Sert. / Dep. Imp.
Pbo. / No Dep. Imp.	-9.4	—			
Pbo. / Dep. Imp.	-21.6	0.001	—		
Sert. / No Dep. Imp.	-13.8	0.031	0.001	—	
Sert. / Dep. Imp.	-22.4	0.001	0.763	0.001	—

Table 4.16 shows the subgroup analysis for all patients combined in Studies 640 and 671. The conclusions of this table are consistent with those of Table 4.15 (women only).

From Table 4.8, we see that there is evidence that there is improvement in PTSD-specific symptoms in women treated with sertraline. There is little evidence, however, that a similar improvement in PTSD symptoms is seen in men treated with sertraline, particularly in light of the subgroup analysis presented in Table 4.14. Based on the analyses of depression improvers vs. depression non-improvers and depressed mood improvers vs. depressed mood non-improvers, there is some question as to whether PTSD improvement is confounded with depression improvement. When one adjusts for depression improvement as we have done in Tables 4.11 through 4.16, women on sertraline consistently show a treatment effect with respect to PTSD symptoms. However, this exploratory analyses suggest that improvement in depression confounds the effect of sertraline with improvement in PTSD; this makes it difficult to isolate the impact of sertraline on PTSD symptoms considering that it has been shown to be effective in treating depression symptoms.

5. Summary and Conclusions

Out of the four similarly-designed studies (640, 641, 671, and 682) submitted in support of approval of sertraline as a safe and effective treatment of PTSD, Studies 640 and 671 showed a statistically significant improvement in PTSD in favor of sertraline over placebo. The primary endpoints used to measure PTSD improvement were differences from baseline on the CAPS-2, IES, and CGI instruments. Studies 640 and 671 were both statistically significant across nearly all primary endpoints and Study 671 was significant on numerous secondary endpoints.

There is evidence that sertraline has a differential PTSD effect in women than in men. There were statistically significant interactions between gender and treatment on several endpoints. Further examination shows that the statistically significant effect of sertraline in women is reproducible among

analyses of various subgroups. Conversely, we cannot detect any differences in PTSD symptoms among men treated with sertraline compared with men treated with placebo.

In analyses that were to determine the effect of sertraline on PTSD apart from its antidepressive effect, some statistically significant differences are less apparent between sertraline and placebo on the PTSD instruments in depression improvement subgroups based on the total HAM-D score. However, when one defines depression improvement based on the depressed mood item (Question #1 on the HAM-D), sertraline-treated women who did not improve depression-wise show improvement in PTSD symptoms. In addition, when we compared the strata of depression non-improvers with depression improvers on PTSD scales, we find that there were statistically significant differences. This suggests that the depression improvement may confound PTSD improvement and it is difficult to isolate sertraline's PTSD efficacy from its depression efficacy.

6. Overall Recommendations and Conclusions

In the two pivotal trials included in this submission, differences from baseline of the CAPS-2, IES, and CGI scales were the primary endpoints. The results of Study 640 and 671 show that the sertraline arm is statistically significantly superior than placebo in women. However, this conclusion does not extend to men in these same studies. The combined results (men + women) of Study 640 and 671 show that the sertraline arm is statistically significantly superior than placebo on all scales, although one must note that women were enrolled in a 3:1 ratio in these studies.

This reviewer has concerns as to the specific effect of sertraline on PTSD as a separate indication from depression. Our exploratory analyses suggest that improvement in depression may be confounded with improvement with PTSD symptoms. Sertraline's efficacy in women is consistent and statistically significant when one adjusts for sertraline's depression effect. In addition, sertraline provides evidence of a treatment effect relative to PTSD-specific endpoints such as reexperiencing and intrusive thoughts (Table 4.8). Sertraline has demonstrated efficacy in women for the proposed indication based on the pivotal trials that were submitted.

In light of the differences in efficacy between genders and the question of whether PTSD may be considered a distinct indication from depression, one must exercise care in the interpretation of these well-designed and well-analyzed studies, although there is evidence that sertraline is effective in treating PTSD in women.

/S/

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Mathematical Statistician

References

[1] Friedman, M. J., Drug treatment for PTSD: Answers and questions. In R. Yehuda and A. C. McFarlane (Eds.), Psychobiology of Posttraumatic Stress Disorder, Vol. 821, The New York Academy of Sciences, New York, 1997, pp. 359-371.

Concur:

Dr. Jin

/S/

Dr. Chi

cc: Archival NDA 19-839

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Smith / 27 September 1999 / Word / c:\data\wordfiles\19839.doc

This review consists of 25 pages of text and one appendix.

APPEARS THIS WAY
ON ORIGINAL

Appendix 1: Questions from PTSD instruments

DAVIDSON SELF-RATING PTSD SCALE:

IN THE PAST WEEK, HOW MUCH TROUBLE HAVE YOU HAD WITH THE FOLLOWING SYMPTOMS?

ANSWER QUESTIONS BASED ON THE FOLLOWING SCALE:

FREQUENCY:	SEVERITY:
0 = Not at all	0 = Not at all Distressing
1 = Once only	1 = Minimally Distressing
2 = 2-3 times	2 = Moderately Distressing
3 = 4-6 times	3 = Markedly Distressing
4 = Everyday	4 = Extremely Distressing

DAVIDSON SELF-RATING PTSD SCALE:

1. Have you had painful images, memories or thoughts of the event?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

2. Have you had distressing dreams of the event?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

3. Have you felt as though the event was reoccurring? Was it as if you were reliving it?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

4. Have you been upset by something which reminded you of the event?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

5. Have you been avoiding any thoughts or feelings about the event?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

6. Have you been avoiding doing things or going into situations which remind you of the event?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

7. Have you found yourself unable to recall important parts of the event?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

8. Have you had difficulty enjoying things?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

9. Have you felt distant or cut-off from other people?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

10. Have you been unable to have sad or loving feelings or have you generally felt numb?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

11. Have you found it hard to imagine having a long life span fulfilling your goals?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

12. Have you had trouble falling asleep or staying asleep?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

13. Have you been irritable or had outbursts of anger?

FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

DAVIDSON SELF-RATING PTSD SCALE:

14. Have you had difficulty concentrating?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

15. Have you felt on edge, been easily distracted, or had to stay "on guard"?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

16. Have you been jumpy or easily startled?
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

17. Have you been physically upset by reminders of the event? (this includes sweating, trembling, racing heart, shortness of breath, nausea, diarrhea)
FREQUENCY: _ (0-4) SEVERITY: _ (0-4)

IMPACT OF EVENT SCALE FOR PTSD:

THE SUBJECT SHOULD BE INSTRUCTED TO RATE HIS/HER EXPERIENCE OF THE FOLLOWING ITEMS ON A FOUR POINT SCALE OF INTENSITY:

0=Not At All
1=Mild
3=Moderate
5=Severe

Event :

IMPACT OF EVENT SCALE FOR PTSD

INTRUSION ITEMS:
1. I had waves of strong feelings about it. (0,1,3,5)

2. Things I saw or heard suddenly reminded me of it. (0,1,3,5)

3. I thought about it when I didn't mean to. (0,1,3,5)

4. Images related to it popped into my mind. (0,1,3,5)

5. Any reminder brought back emotions related to it. (0,1,3,5)

6. I have difficulty falling asleep because of images or thoughts related to the event. (0,1,3,5)

7. I have bad dreams related to the event. (0,1,3,5)

KEY: 0=Not At All, 1=Mild, 3=Moderate, 5=Severe

AVOIDANCE ITEMS:
1. I knew that a lot of unresolved feelings were still there, but I kept them under wraps. (0,1,3,5)

2. I avoided letting myself get emotional when I thought about it or was reminded of it. (0,1,3,5)

3. I wished to banish it from my store of memories. (0,1,3,5)

4. I made an effort to avoid talking about it. (0,1,3,5)

IMPACT OF EVENT SCALE FOR PTSD

AVOIDANCE ITEMS:

5. I felt unrealistic about it, as if it hadn't happened or as if it wasn't real. (0,1,3,5)

6. I stayed away from things or situations that might remind me of it. (0,1,3,5)

7. My emotions related to it were kind of numb. (0,1,3,5)

8. I didn't let myself have thoughts related to it. (0,1,3,5)

KEY: 0=Not At All, 1=Mild, 3=Moderate, 5=Severe

CLINICIAN-ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:

A. THE TRAUMATIC EVENT:

REMINDER: A FREQUENCY RATING OF 0 INDICATES THAT THE INTENSITY IS 0 ALSO.

CLINICIAN-ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:
B. THE TRAUMATIC EVENT IS PERSISTENTLY REEXPERIENCED:

(1) RECURRENT AND INTRUSIVE RECOLLECTIONS

Frequency: _ (0-4) Intensity: _ (0-4)

(2) DISTRESS WHEN EXPOSED TO EVENTS

Frequency: _ (0-4) Intensity: _ (0-4)

(3) ACTING OR FEELING AS IF EVENT RECURRING

Frequency: _ (0-4) Intensity: _ (0-4)

(4) RECURRENT DISTRESSING DREAMS OF EVENT

Frequency: _ (0-4) Intensity: _ (0-4)

CLINICIAN-ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:

REEXPERIENCING INTENSITY AND FREQUENCY SUMS

Frequency: _ (0-16) Intensity: _ (0-16)

REEXPERIENCING INTENSITY AND FREQUENCY MEANS

Frequency: (0-4) Intensity: (0-4)

CLINICIAN ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:

C. PERSISTENT AVOIDANCE OF STIMULI/NUMBING-OF RESPONSIVENESS:

(5) EFFORTS TO AVOID THOUGHTS OR FEELINGS

Frequency: _ (0-4) Intensity: _ (0-4)

(6) EFFORTS TO AVOID ACTIVITIES OR SITUATIONS

Frequency: _ (0-4) Intensity: _ (0-4)

(7) INABILITY TO RECALL TRAUMA ASPECTS

Frequency: _ (0-4) Intensity: _ (0-4)

(8) MARKEDLY DIMINISHED INTEREST IN ACTIVITIES

Frequency: _ (0-4) Intensity: _ (0-4)

(9) FEELINGS OF DETACHMENT OR ESTRANGEMENT

Frequency: _ (0-4) Intensity: _ (0-4)

(10) RESTRICTED RANGE OF AFFECT

Frequency: _ (0-4) Intensity: _ (0-4)

(11) SENSE OF A FORESHORTENED FUTURE

Frequency: _ (0-4) Intensity: _ (0-4)

AVOIDANCE/NUMBING INTENSITY AND FREQUENCY SUMS

Frequency: _ (0-28) Intensity: _ (0-28)

AVOIDANCE/NUMBING INTENSITY AND FREQUENCY MEANS

Frequency: _ (0-4) Intensity: _ (0-4)

CLINICIAN ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:

D. PERSISTENT SYMPTOMS OF INCREASED AROUSAL:

(12) DIFFICULTY FALLING OR STAYING ASLEEP

Frequency: _ (0-4) Intensity: _ (0-4)

(13) IRRITABILITY OR OUTBURSTS OF ANGER:

Frequency: _ (0-4) Intensity: _ (0-4)

(14) DIFFICULTY CONCENTRATING

Frequency: _ (0-4) Intensity: _ (0-4)

(15) HYPERVIGILANCE

Frequency: _ (0-4) Intensity: _ (0-4)

CLINICIAN ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:

D. PERSISTENT SYMPTOMS OF INCREASED AROUSAL:

(16) EXAGGERATED STARTLE RESPONSE

Frequency: _ (0-4) Intensity: _ (0-4)

(17) PHYSIOLOGIC REACTIVITY

Frequency: _ (0-4) Intensity: _ (0-4)

CLINICIAN ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:

INCREASED AROUSAL INTENSITY AND FREQUENCY SUMS

Frequency: _ (0-24) Intensity: _ (0-24)

INCREASED AROUSAL INTENSITY AND FREQUENCY MEANS

Frequency: (0-4) Intensity: (0-4)

OVERALL SYMPTOM INTENSITY AND FREQUENCY SCALES

Frequency: _ (0-68) Intensity: (0-68) _

OVERALL SYMPTOM INTENSITY AND FREQUENCY MEANS

Frequency: (0-4) Intensity: (0-4)

CLINICIAN ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:
CAPS INTERVIEWER RATINGS:

(18) IMPACT ON SOCIAL FUNCTIONING _ (0-4)

(19) IMPACT ON OCCUPATIONAL FUNCTIONING _ (0-4)

(20) GLOBAL IMPROVEMENT _ (0-4)

(21) RATING VALIDITY _ (0-4)

(22) GLOBAL SEVERITY _ (0-4)

HYPOTHESIZED OR ASSOCIATED FEATURES:
(23) GUILT OVER ACTS OF COMMISSION OR OMISSION

Frequency: _ (0-4) Intensity: _ (0-4)

(24) SURVIVOR GUILT

Frequency: _ (0-4) Intensity: _ (0-4)

(25) HOMICIDALITY

Frequency: _ (0-4) Intensity: _ (0-4)

(26) DISILLUSIONMENT WITH AUTHORITY

Frequency: _ (0-4) Intensity: _ (0-4)
CLINICIAN ADMINISTERED PTSD SCALE (CAPS-2) SUMMARY:
HYPOTHESIZED OR ASSOCIATED FEATURES:
(27) FEELINGS OF HOPELESSNESS

Frequency: _ (0-4) Intensity: _ (0-4)

(28) MEMORY IMPAIRMENT, FORGETFULNESS

Frequency: _ (0-4) Intensity: _ (0-4)

(29) SADNESS AND DEPRESSION

Frequency: _ (0-4) Intensity: _ (0-4)

(30) FEELINGS OF BEING OVERWHELMED
Frequency: _ (0-4) Intensity: _ (0-4)

CLINICAL GLOBAL IMPRESSIONS:

Severity of Illness: (1-7)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

1=Normal, not at all ill.
2=Borderline mentally ill.
3=Mildly ill.
4=Moderately ill.
5=Markedly ill.
6=Severely ill.
7=Among the most extremely ill patients.

CLINICAL GLOBAL IMPRESSIONS:

Global Improvement: (1-7)

Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment. Compared to his/her condition at baseline, how much has he/she changed?

1=Very much improved.
2=Much improved.
3=Minimally improved.
4=No change.
5=Minimally worse.
6=Much worse.
7=Very much worse.