19-839/S-026

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION for: 019839/S026

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-839/S-026

Pfizer Inc.
Attention: Margaret Longshore
Director, Regulatory Affairs
235 E. 42nd Street
New York, New York 10017

DEC - 7 1999

Dear Ms. Longshore:

Please refer to your supplemental new drug application dated October 7, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft[R] (sertraline hydrochloride) Tablets.

This supplement provides for the use of Zoloft[R] Tablets for the treatment of post-traumatic stress disorder as a new indication.

We also refer to your resubmission dated September 10, 1999.

We acknowledge receipt of your correspondence dated November 1, 19, and 30, 1999; and December 2 and 3, 1999.

We have completed the review of this supplemental application, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The labeling accompanying this letter should be used for marketing this drug product. This final labeling is based upon your labeling proposal for the PTSD indication agreed upon on October 29, 1999, and additional statements related to safety involved with NDA 20-990, agreed upon on November 30, 1999, with the Agency. It is identical to your final labeling proposal dated December 3, 1999, with minor changes to Table 3 and Table 4, agreed to on December 6, 1999, by the Agency.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-031/S-023." Approval of this submission by FDA is not required before the labeling is used.

Phase 4 Commitment:

Since post-traumatic stress disorder is regarded as a chronic disease and continued treatment of patients is expected beyond several months, we are interested in reviewing the results of a study which addresses the issue of long-term efficacy. In this regard, we note your November 1, 1999, commitment to submit the results of a long-term relapse prevention trial for our review.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

In addition, since we believe that post-traumatic stress disorder is also found in the pediatric population and, once approved for this indication, Zoloft[R] will likely be used in pediatric patients, we recommend that you conduct adequate and well-controlled trials for this disorder in this population.

In this regard, please be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Anna Marie Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

/S/

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Attachment

APPEARS THIS WAY
ON ORIGINAL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA: 19-839
Sponsor: Pfizer
Clock Date: 10/7/98

Drug Name

Generic Name sertraline
Trade Name Zoloft

Drug Characterization

Pharmacological Category: Antidepressant
Proposed Indication: Post Traumatic Stress Disorder (PTSD)
NDA Classification: 1S
Dosage Forms, Strengths, and Routes of Administration:
Oral Tablets 25mg, 50mg, 100mg

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 6/8/99

1.0 Material Reviewed

This NDA supplement received on 10/7/98 contains 45 volumes and includes a CDROM disk containing case report form tabulations. In addition there is a CANDA available through the Internet and on a lap-top provided to me by the sponsor along with word tables on flopy disks. There are also SAS and Jump files in the FDA electronic document room.

I have reviewed all narratives for patients meeting the criteria for adverse events leading to discontinuation and serious adverse events including vital signs and weight, laboratory analytes, and ECG intervals and heart rate. I have also reviewed case report forms for all subjects who discontinued due to an adverse event. The case report forms are consistent with the narratives and clinical summaries provided by the sponsor.

I requested the sponsor to provided me with information on the nature of the traumatic event and the time symptoms began in relationship to this event. This information was provided and reviewed.

There is no additional information in INDs (see section 2.2) directly relevant to this review.

The sponsor recently indicated they are reanalyzing the data because an investigator was thrown out due to misconduct. I have not yet seen these changes but the sponsor indicates that they effect less than 10% of the patients and do not influence the conclusions.

2.0 Background

2.1 Indication

The sponsor proposes using sertraline in the treatment of PTSD.

2.2 Related INDs and NDAs

The data contained in this application have been obtained from studies carried out under the following Applications:

IND#	Filing Date	Drug

2.3 Administrative History

NDA 19-839 for Zoloft® in the treatment of depression was approved on December 30, 1991. Supplemental NDAs for the use of sertraline in the treatment of obsessive-compulsive disorder and panic disorder were approved on October 25, 1996 and July 8, 1997, respectively. Sertraline use in pediatric OCD was approved on October 10, 1997.

Selection of rating scales to evaluate PTSD treatment was endorsed by a Protocol Design Advisory Panel held in July 1993.

On October 9, 1997, a pre-sNDA Meeting was held with the Division to discuss the proposed PTSD submission. As a follow-up to the pre-sNDA Meeting, a statistical analysis plan was provided to the Division on November 15, 1997 and discussed on January 20, 1998. Gender analysis was submitted to the Agency on August 21, 1998. The sNDA efficacy supplement for treatment of Posttraumatic Stress Disorder was submitted to the FDA on October 7, 1998.

Protocols 640 and 641 for sertraline in the treatment of PTSD were filed to IND [redacted] on February 23, 1994 and February 24, 1994, respectively. On November 21, 1995, Pfizer conducted interim analyses for administrative purposes which had been planned prospectively in each protocol (640 and 641). Forty-three sertraline subjects and forty-nine placebo subjects were included in the interim analysis of Protocol 640 and thirty-nine sertraline subjects and thirty-three placebo subjects in Protocol 641. The purpose of the interim analysis was to verify the assumptions in the sample size calculation for Protocol 671 and to determine if a fourth study should be added to the development program. The third protocol (671) of sertraline in the treatment of PTSD was filed to IND [redacted] on February 16, 1996. The first subject entered the study on May 1, 1996. The fourth protocol (682) of sertraline in the treatment of PTSD was filed to IND [redacted] on May 20, 1996.

2.4 Directions for Use

The sponsor's directions are listed below:

Panic Disorder and Posttraumatic Stress Disorder-ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily.

Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week. ZOLOFT should be administered once daily, either in the morning or evening.

2.5 Foreign Marketing

No registration applications requesting approval of sertraline in the treatment of post-traumatic stress disorder have been filed with any regulatory authorities anywhere in the world other than in the U.S.

3.0 Chemistry

The dosage form formulations approved December 30, 1991 in NDA 19-839 and March 6, 1996 in a supplement to NDA 19-839 will be used for the new indication.

4.0 Preclinical Pharmacology

No nonclinical pharmacology, toxicology, or pharmacokinetic studies in animal models of post-traumatic stress disorder were conducted for the present submission.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

The current submission for the use of sertraline in PTSD is based on data from four adequate and well-controlled clinical studies that completed as of the February 26, 1998 cut-off date. The studies are Protocols 93CE21-0640, 95CE21-0671, 93CE21-0641, and 96CE21-0682).

In addition, there are four ongoing protocols as of the February 26, 1998 cut-off date. Protocol 95CE21-0672 is a 24-week, open-label, flexible-dose extension study for subjects who have completed Protocol 671 or 682. Subjects who have completed and

responded to open-label treatment in Protocol 672 are eligible to enter Protocol 96CE21-703, which is a 28-week, double-blind, placebo-controlled study assessing relapse. The other two ongoing protocols (STL-NY-93-005 and STL-AUS-94-001) are double-blind, placebo-controlled trials of sertraline in the treatment of PTSD conducted outside of the United States and are non-IND studies.

Tables of all studies are presented below.

Table V.A.1 Table of Completed Controlled Studies (Primary Database)

Protocol #	Study Design	Sertraline Dosage (qd)	Total Randomized Sertraline/Placebo	Comments
93CE21-0640 Multicenter 12 sites	Double-blind Placebo-controlled Parallel Flexible dosing 12 weeks d.b. treatment 1 week placebo run-in	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	100/108	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Identical to Protocol 93CE21-0641
93CE21-0641 Multicenter 10 sites	Double-blind Placebo-controlled Parallel Flexible dosing 12 weeks d.b. treatment 1 week placebo run-in	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	86/83	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Identical to Protocol 93CE21-0640
95CE21-0671 Multicenter 14 sites	Double-blind Placebo-controlled Parallel Flexible dosing 12 weeks d.b. treatment 2 weeks placebo run-in	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	94/93	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Identical to Protocol 96CE21-0682 Completers may enter 24-wk open-label extension study (95CE21-0672; see Section 8.7.1)
96CE21-0682 Multicenter 16 sites	Double-blind Placebo-controlled Parallel Flexible dosing 12 weeks d.b. treatment 2 weeks placebo run-in	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	96/97	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Identical to Protocol 95CE21-0671 Completers may enter 24-wk open-label extension study (95CE21-0672; see Section 8.7.1)

Studies were completed before the cut-off date of February 26, 1998.

Table V.A.2 Table of Ongoing Studies (Secondary Database)

Protocol # *Investigator*	Study Design	Sertraline Dosage (qd)	# Subjects Planned	Comments
95CE21-0672 Multicenter U.S.	Open-label Flexible dosing 24 weeks treatment	25 mg for first week 50-200 mg thereafter PM dosing (may switch to AM dosing)	320 maximum	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Open-label extension study for subjects who completed double-blind treatment in Protocols 95CE21-0671 or 96CE21-0682 (see Section 8.5.1) Responders may enter 28-wk double-blind continuation study (96CE21-0703)
96CE21-0703 Multicenter U.S.	Double-blind Placebo-controlled Parallel Flexible dosing 28 weeks treatment	25-200 mg PM dosing (may switch to AM dosing)	320 maximum	Primary efficacy measures: CAPS-2, IES, CGI Severity and Improvement Double-blind continuation study for subjects who responded to open-label treatment in Protocol 95CE21-0672. Subjects are randomized to sertraline or placebo, and time to relapse is assessed. Subjects begin at their last dose from Protocol 95CE21-0672.
STL-NY-93-005 Israel *Zohar J*	Double-blind Placebo-controlled Parallel Flexible dosing 10 weeks d.b. treatment 1-2 weeks placebo run-in	50-200 mg AM dosing	60 efficacy evaluable	Primary efficacy measures: CAPS-2, CGI Severity and Improvement
STL-AUS-94-001 Australia *Crompton DR* *McFarlane A*	Double-blind Placebo-controlled Parallel Flexible dosing 25 weeks d.b. treatment 1 week placebo run-in	25 mg for first week 50-200 mg thereafter AM or PM dosing	150 efficacy evaluable	Primary efficacy measures: CAPS-2, CGI Ten sessions of cognitive behavior therapy given in conjunction with double-blind treatment

Studies ongoing as of February 26, 1998 cut-off date

. The U.S. clinical development program investigating the safety and efficacy of sertraline in the treatment of PTSD includes four completed, 12-week, flexible-dose, double-blind, placebo-controlled studies which form the basis for the current submission.

5.1.2 Demographics

As shown in the table below, 65% (246/376) of the sertraline group and 60% (231/381) of the placebo group were female. The subject sample was predominantly white, with approximately 20% of sertraline subjects and 15% of placebo subjects identified as non-white. Both treatment groups had a mean age of 40 years. Most subjects were between 18 and 44 years of age. Only 6 sertraline subjects and 7 placebo subjects were >65 years old.

Table V.C.1. Demographic Profile for Completed Controlled Studies Combined*

	Sertraline (N=376)		Placebo (N=381)	
Measure	**No.**	**(%)**	**No.**	**(%)**
Sex: No. (%)				
Female	246	(65.4)	231	(60.6)
Male	130	(34.6)	150	(39.4)
Race: No. (%)				
Asian	5	(1.3)	7	(1.8)
Black	52	(13.8)	43	(11.3)
White	301	(80.1)	323	(84.8)
Other	18	(4.8)	8	(2.1)
Age: (yrs)				
Mean ± S.D.	39.7 ± 11.0		39.7 ± 11.1	
18 - 44	236		233	
45 - 64	130		141	
>= 65	6		7	
Weight (lb.)				
Mean ± S.D.	174.8 ± 47.8		174.8 ± 45.7	

* all randomized subjects(includes 2 sertraline and 5 placebo patients who never received study drug)

Differences between groups were tested using the Pearson chi-squared statistic for race and sex, and F-test from two-way ANOVA for mean age and weight. There were no statistical differences between groups on any of these parameters.

5.1.3 Extent of Exposure (dose/duration)

The total patient-years of exposure for all sertraline-treated subjects (n=374) in the primary database was 73.5 years. The mean was 0.20 + .07 yr.

Table VIII.A.2: Sertraline Exposure According to Maximum Daily Dose and Duration of Therapy - Completed Controlled Studies

Duration of Therapy	25 mg	50 mg	75 mg	100 mg	150 mg	200 mg	>200 mg*	Total	(%)
01 - 07	9	0	0	0	0	0	1	10	2.67
08 - 14	6	10	0	0	0	0	0	16	4.28
15 - 21	2	7	1	4	0	0	0	14	3.74
22 - 28	1	3	0	4	3	0	0	11	2.94
29 - 42	0	3	0	6	6	2	0	17	4.55
43 - 56	0	1	0	5	8	2	0	16	4.28
57 - 70	0	2	0	1	4	4	0	11	2.94
71 - 84	2	2	0	25	29	76	1	135	36.10
>= 85	0	4	0	25	31	83	1	144	38.50
Total	20	32	1	70	81	167	3	374	100.00
(%)	5.35	8.56	0.27	18.72	21.66	44.65	0.80	100.00	

* Includes Subject 94N0177-176, who ingested 425 mg sertraline (see SAE narratives for more information).

Sertraline was administered to a total of 374 safety analyzable subjects in the four completed PTSD studies. In addition, 376 safety analyzable subjects received placebo. The mean duration of exposure for sertraline subjects was 72 days (range of 2-114 days). The mean duration of exposure for placebo subjects was 74 days (range of 1-109 days). The majority of patients received 100-200mg of sertraline for greater than 71 days, as seen in the table above.

Table VIII.A.3 Mean Daily Dose By Visit Week - All Safety Analyzable Subjects

Week	Sertraline (mg)			Placebo (mg equivalent)		
	N	Mean	SD	N	Mean	SD
Week 1	374	24.8	5.6	375	24.6	2.5
Week 2	358	44.5	10.0	364	45.7	8.9
Week 3	337	78.4	28.1	354	83.6	25.9
Week 4	325	106.2	39.0	337	115.4	38.8
Weeks 6	312	131.4	52.0	327	144.5	51.7
Weeks 8	297	142.6	52.0	308	156.5	49.2
Weeks 10	286	149.0	51.1	293	161.2	50.7
Weeks 12	272	152.2	49.1	286	162.9	50.1

Mean daily dose was 24.8 mg during week 1 in sertraline subjects, increasing to 106.2 mg during week 4 and 142.6 mg during weeks 7

and 8. During weeks 11 and 12, mean sertraline dose was 152.2 mg/day. Mean placebo dose increased in a similar fashion to 163 mg/day during weeks 11 and 12. The average sertraline dosage during weeks 11 and 12 of therapy was 152.2 mg/day.

5.1.4 Disposition

Premature discontinuation of therapy occurred in 28% (104/374) of sertraline subjects and 25% (95/376) of placebo subjects. 8.6% of all sertraline-treated subjects and 4.8% of all placebo-treated subjects discontinued due to adverse events. Five sertraline subjects (1%) and no placebo subjects discontinued due to laboratory abnormalities. Four sertraline subjects (1%) and 9 placebo subjects (2%) discontinued due to insufficient clinical response. Discontinuation due to treatment emergent adverse events during the first week of treatment occurred in 1% of sertraline and 1% of placebo subjects.

Table VIII.B Rates of Discontinuation by Treatment Group and Reason - All Safety Analyzable Subjects

Reason for Discontinuation	% Discontinued Sertraline (n=374)	% Discontinued Placebo (n=376)
Withdrawn Consent	5.9	8.8
Adverse Event	8.6	4.8
Lost To Follow Up	6.7	4.5
Protocol Violation	2.4	2.1
Other	1.6	2.7
Insufficient Clinical Response	1.1	2.4
Laboratory Abnormality	1.3	0.0
Does Not Meet Entrance Criteria	0.3	0.0
Total % Discontinued	27.8%	25.3%

Includes subject 93N0179/598 (Protocol 641, Treatment=placebo; male) who discontinued due to adverse events which had onset prior to randomization and thus are not considered treatment emergent.

5.2 Secondary Sources

5.2.1 Non-IND Studies

There are two Non-IND studies with which the sponsor has been associated.

STL-NY-93-005 Title: A ten week single center parallel group, double-blind, comparative, placebo controlled, dose titration study of the safety, efficacy and toleration of sertraline (50mg to 200mg) in the treatment of outpatients with post-traumatic stress disorder.

STL-AUS-94-001 Title: A 25 week, multicenter, parallel group, double blind, randomized, placebo controlled dose titration study of the efficacy, toleration and safety of sertraline (25mg-200mg) in combination with cognitive behavior therapy in the treatment of post traumatic stress disorder in a non-veteran outpatient population.

Both studies were terminated early and there are no final reports. Serious adverse events were captured and are in the database. See table of ongoing studies in section 5.1.1.

5.2.2 Post-Marketing Experience

Zoloft used in PSTD is not marketed anywhere is the world. The sponsor had provided an analysis of postmarketing use of sertraline for PTSD which I summarize in the safety section.

5.2.3 Literature

The sposnsor has provided a literature review described below.

A review of the worldwide literature on the use of sertraline in post-traumatic stress disorder (PTSD) was conducted using five commercial databases:

The search included the terms of PTSD, post-traumatic stress disorder, post traumatic stress disorder, posttraumatic stress disorder, PTSS, post-traumatic stress syndrome, post traumatic stress syndrome, posttraumatic stress syndrome and traumatic neurosis and included all clinical and preclinical studies in publication (including original articles, review articles, letters and editorials) by the cut-off date of 26 February 1998. Ms. Karen Erani, Manager, Information Retrieval of the corporate Information Center conducted the search, and the literature was reviewed by Kathleen S. Ice, Ph.D., Associate Director, Clinical and Scientific Affairs, both of Pfizer, Inc. There were no preclinical studies

identified in the search, and foreign language publications consisted of review articles. The complete list of references is provided.

The sponsor states that there were no reports of any WHO-coded adverse event not already included in the product labeling, nor was any adverse event reported with unexpected frequency. The conclusion of the Pfizer reviewer is that no findings were noted which adversely affect the conclusions of this submission with regard to the safety of sertraline in patients with PTSD.

I have reviewed the sponsor's synopses of relevant articles and agree that there are no new safety or efficacy issues identified.

5.3 Adequacy of Clinical Experience

The exposure to sertraline appears to be of an adequate duration and dosage and the clinical experience is otherwise satisfactory.

5.4 Data Quality and Completeness

The data quality appears to be adequate and complete in that the specified scales and tests were appropriate, performed, with results collected and analyzed. The sponsor provided data to show treatment response in patients with low and high scores on the HAM-D but did not analyze PTSD response independently from response to depression.

6.0 Summary of Human Pharmacokinetics

No human pharmacokinetics or bioavailability studies were conducted in subjects with post-traumatic stress disorder for the present submission.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

This section summarizes the four placebo-controlled studies (640, 671, 641 and 682) in the treatment of outpatients with PTSD. 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 sample included all randomized subjects who had at least one dose of study medication and one post baseline efficacy evaluation.

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.

Each study had a 12-week, multicenter, double-blind, placebo-controlled, parallel-group, flexible dose (50 mg, 100 mg, 150 mg, 200mg) design using a 25 mg starting dose and a single-blind placebo run-in period (one week in Protocols 640 and 641; two weeks in Protocols 671 and 682). The sponsor states that a dose-titration design was utilized in the PTSD program because fixed dose studies conducted in depression, obsessive-compulsive disorder and panic disorder failed to yield evidence of a dose-response relationship.

Dosing.

In all four studies, subjects were started on a dose of 25 mg per day sertraline or matching placebo for one week. At the End of Week 1 visit, in the absence of any dose-limiting adverse events, subjects were titrated up to 50 mg per day. Thereafter, dosage was flexibly titrated in accordance with the subject's clinical response, in 50 mg weekly increments or decrements, to a maximum daily dose of 200 mg.

Primary Efficacy Variables.

The prospectively defined primary efficacy variables in all four studies were the Clinician-Administered PTSD Scale Part 2 (CAPS-2) total severity score, the Impact of Event Scale (IES) total score, and the Clinical Global Impressions ratings of Severity of Illness (CGI-S) and Improvement (CGI-I). Selection of these types of ratings to evaluate PTSD treatment was endorsed by a panel of U.S. experts at a meeting held in New York (March 1998) and a panel of experts from Europe, Israel, South Africa and the U.S. held in France (May 1998), as well as a pre-study Advisory Panel held prior to the start of Protocol 640. The Davidson Self-Rating PTSD scale

also known in the literature as the Davidson Trauma Scale; DTS) was denoted as a secondary efficacy measure at the time these trials were run as it was relatively new and validation was not complete.

Secondary Efficacy Variables. One secondary efficacy measure, the Hamilton Depression Scale (HAM-D), was administered in all four protocols. In addition, the Hamilton Anxiety Scale (HAM-A), the Civilian Mississippi Scale for PTSD (Mississippi), the Disorders of Extreme Stress - Not Otherwise Specified scale (DES-NOS), and the Pittsburgh Sleep Quality Index (PSQI) were administered in Protocols 640 and 641. In Protocols 671 and 682, additional secondary efficacy ratings were the Quality of Life scale and the Health and Work Questionnaire, the latter being a pharmacoeconomic evaluation.

Statistical Analysis:

In all studies, subject evaluations were conducted at one-week or two-week intervals, but secondary rating scales were administered only at Baseline and the final or termination visit. The Davidson scale was administered at every visit. The endpoint was 12 weeks or the last evaluation visit for all four studies.

The primary efficacy analyses were intent-to-treat analyses performed on the efficacy measures from every subject who received at least one dose of double-blind medication and had a baseline plus one on-treatment efficacy evaluation. Primary efficacy analyses assessed change from baseline to endpoint, where endpoint was defined as the last observation.

All statistical tests were two-sided and were performed in SAS at the 0.05 level of significance. Analysis of covariance models which included terms for treatment, site, treatment-by-site, and baseline (the covariate) effects were used to analyze the change from baseline on all efficacy variables except CGI Improvement. Type III sums of squares were used to assess statistical significance. The actual endpoint score was used for analysis of CGI Improvement since the change from baseline is implicit in this rating. The post-hoc responder analysis assessed subjects with at least a 30% decrease in the CAPS-2 total severity score and/or a CGI Improvement score of 1 or 2. The responder analysis used a Mantel-Haenszel chi-square statistic stratifying on site.

STUDY RESULTS:

0641

In study 641 done in a VA setting the sertraline-treated group did not differ from the placebo group at endpoint on any of the primary

efficacy variables. The secondary rating scales (Davidson, DES-NOS, Mississippi, HAM-A, HAM-D, and PSQI) did not show any differences between the two treatment groups at endpoint, as well.

0682

In study 682 the sertraline-treated group did not improve significantly compared to the placebo group at endpoint on any of the primary efficacy variables. On the IES, the placebo group was significantly improved compared to the sertraline group (-13.6 v. -19.7; p=0.017).

The sponsor considers two of the four completed studies to be supportive of their indication and I will describe these two studies in detail.

Protocol 93CE21-0640

Investigators/Sites

Please see complete list of investigators in the appendix.

Objectives

The objective of this study was to show the efficacy and safety of Zoloft in PTSD.

Study Design

Protocol 640 was a double-blind, 12-week comparison of flexible doses of sertraline and matching placebo conducted at 12 study sites.

Rating Scales

See general study discussion above.

Analysis

See general study discussion above.

Study Outcome

Patient Disposition

Please see appendix table of completer rates by week. 74.5% of sertraline and 71.2% of placebo patients completed week 12. At my request the sponsor provided tables showing weekly improvement in patients at time of drop out. In general the Zoloft patients had improved about the same or slightly more than placebo patients at time of drop out.

Demographics

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). Subjects were approximately 37 years old with a mean duration of illness of approximately 12 years. 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. Please see appendix table.

Dosing Information

The mean final dose of sertraline was 125 mg/day at endpoint and 146 mg/day for weeks 11 and 12. The mean duration of treatment was 73 days in the sertraline group and 72 days in the placebo group.

Concomitant Medications

The appendix table presents the concomitant medication taken by subjects during the studies. 76% of sertraline-treated subjects and 81% of placebo-treated subjects took concomitant medication during double-blind treatment. Ibuprofen, acetaminophen, aspirin, and chloral hydrate were the medications most commonly taken in both treatment groups.

RESULTS:

My analysis indicated the following results.

In the CAPS-2, Sertraline does not win at weeks 1,2,3,4,6,8,10,12 for OC. The LOCF wins at week 12 P=.043 but at no other time.

In the IES, Sertraline does not win at weeks 1,2,3,4,6,8,10,12 for OC. The LOCF wins at week 12 P=.018 but at no other time.

In the CGI-S, Sertraline not win at weeks 1,2,3,4,6,8,10,12 for OC. The LOCF wins at week 12 P=.037 but at no other time.

In the CGI-I, Sertraline does not win at weeks 1,2,3,4,6,8,10,12 for OC. The LOCF wins at week 8 P=.041, week 10 P=.031, week 12 P=.001 but at no other time.

EFFICACY CONCLUSION STUDY I

No efficacy is seen in this study until week 12 and then it is only seen in females. This efficacy does not appear to be independent of the patient's mood (see predictors of response 7.3.1).

Protocol 95CE21-0671

Investigators/Sites

Please see complete list of investigators in the appendix.

Objectives

The objective of this study was to show the efficacy and safety of Zoloft in PTSD.

Study Design

Protocol 671 was a double-blind, 12-week comparison of flexible doses of sertraline and matching placebo conducted at 14 study sites.

Patient Disposition

Please see appendix table of completer rates by week. Sixty-nine percent of sertraline subjects and 73% of placebo subjects of the safety-analyzable population completed 12 weeks of treatment. At my request the sponsor provided tables showing weekly improvement in patients at time of drop out. In general the Zoloft patients had improved about the same or slightly more than placebo patients at time of drop out.

Demographics

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. Please see appendix table.

Dosing

The mean final dose of sertraline was 133 mg/day at endpoint and 151mg/day for weeks 11 and 12. The mean duration of treatment was 73 days in the sertraline group and 72 days in the placebo group.

Concomitant Medication

The appendix table presents the concomitant medication taken by subjects during the studies. 76% of sertraline-treated subjects and 81% of placebo-treated subjects took concomitant medication during double-blind treatment. Ibuprofen, acetaminophen, aspirin, and chloral hydrate were the medications most commonly taken in both treatment groups.

Rating Scales

See general study discussion above.

Analysis

See general study discussion above.

Efficacy Results

In the CAPS-2, Sertraline beats placebo at endpoint (OC) p=.016 and at week 2, P=.041, week 4 P=.00020, week 6 P=.011, week 8 P=.006, week 10 P=.004 and week 12 P=.023. The LOCF wins at weeks 2,4,6,8 and 10.. See appendix tables.

In the IES (OC), Sertraline beats placebo at week 10, P=.041, week 12 P=.049. The LOCF does not win at any time. See appendix tables.

In the CGI-S, Sertraline beats placebo at endpoint (OC) p=.012 and at week 4, P=.012, week 10 P=.030, week 12 P=.011,but does not win at weeks 1,2,3,6,8. The LOCF wins at week 4 P=.025, week 6 P=.024, week 10 P=.048, week 12 P=.012 but at no other time. See appendix tables.

In the CGI-I, Sertraline beats placebo at endpoint (OC) p=.016 and at week 1 P=.000, week 4 P=.000, week 6 P=.032, week 10 P=.008. The LOCF wins at weeks 1,4,6,8,10 and 12. See appendix tables.

EFFICACY CONCLUSION-STUDY 2

This study shows more consistent efficacy throughout the study period. Once again there is only a case for efficacy in females and this is influenced by mood improvement (see 7.3.1).

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

DOSE:

In each of the four completed studies, the starting dose of sertraline was 25 mg daily for one week, after which the dose was to be increased to 50 mg daily in the absence of dose-limiting adverse events. Thereafter, the daily dose could be titrated between 50 mg and 200 mg in weekly 50 mg increments or decrements based on clinical response and adverse events.

Mean daily dose was 24.8 mg during week 1 in sertraline subjects, increasing to 106.2 mg during week 4 and 142.6 mg during weeks 7 and 8. During weeks 11 and 12, mean sertraline dose was 152.2 mg/day. Mean placebo dose increased in a similar fashion to 163 mg/day during weeks 11 and 12. There is no evidence of a dose-response relationship.

AGE:

The majority of subjects in these studies were under 65 years of age (n = 13 for the four protocols), so no conclusions can be reached regarding the efficacy of sertraline in the treatment of PTSD in the elderly. There were no intrastudy differences in age distribution between sertraline and placebo groups

RACE:

The study population was predominately white (82%; 624/757 subjects), and no analysis was conducted stratified by race.

GENDER:

The sponsor concedes that the efficacy of sertraline in the treatment of PTSD may be different in men and women. A combined

analysis of the two positive studies was conducted to assess the difference in the efficacy of sertraline in men and women. See appendix table.

Seventy-six percent (76%) of the subjects were women. In women there was a significant difference between the sertraline and placebo groups in all efficacy measures. There were no significant differences in the efficacy measures between sertraline-treated men and placebo-treated men.

TRAUMATIC EVENT

Subjects were stratified by whether their traumatic event was one of physical/sexual assault or of another type. For the three PTSD rating scale totals, the change from baseline to the last observation was analyzed within men and women separately by analysis of covariance with the following effects included in the model: change= baseline, study, treatment, event, event by treatment. The clinical global improvement score was analyzed by the same model without a baseline covariate. Site effects were not used in this analysis because some sites had zero subjects in some strata.

The traumatic event in women was predominately physical/sexual assault (71.5%) while physical/sexual assault was the traumatic event in only 30.9% of the men. The sponsor states that sertraline is significantly efficacious in both strata of women. When men are stratified according to type of traumatic event the numbers of subjects in each stratum are small and no conclusions can be drawn
from this analysis.

IMPROVEMENT IN DEPRESSION AS PREDICTOR OF PTSD IMPROVEMENT

Dave Smith, Ph.D., FDA statistician and I attempted to see if there is improvement in PSTD scales independent from depression improvement. We tested the depression item on the HAM-D depression instrument regarding mood improvement. 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.

All statistical tests were two-sided and were performed in SAS at the 0.05 level of significance. 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, were used to analyze the change from baseline PTSD on all three instruments.

The table below compares the response to PTSD scales for mood item improvers vs. non-improvers and contrasts that against the sertraline vs. placebo response on PTSD scales. This table shows that patients had a more consistent response on PTSD scales based on mood item improvement rather than whether they took sertraline or placebo.

MOOD ITEM CHANGES

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

The next set of tables show various combinations of the variables mood item improved/mood item unchanged and sertraline/placebo

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 4.15. 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 4.16. 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	—

These tables help to indicate the extent to which both sertraline and placebo patients improve depending on whether their mood improves or not.

7.3.2 Size of Treatment Effect

The sponsor has provided the table below indicating the size of the treatment effect.

Table VII.G Treatment Effect Sizes - Protocols 640 and 671

	Protocol 640		Protocol 671	
	SERT Effect Size	Pbo-Subtracted Effect Size	SERT Effect Size	Pbo-Subtracted Effect Size
CAPS-2	-1.49	-0.31	-1.26	-0.37
Impact of Event	-1.56	-0.26	-1.35	-0.41
Davidson	-1.26	-0.48	-1.10	-0.47
CGI Severity	-1.18	-0.32	-1.04	-0.39

The effect size within each treatment group is the change from baseline divided by its standard deviation.

7.3.3 Choice of Dose

The following table indicates that the mean dosing for these patients is in the range recommended by the sponsor in their proposed labeling.

Table VIII.A.3 Mean Daily Dose By Visit Week - All Safety Analyzable Subjects

Week	Sertraline (mg)			Placebo (mg equivalent)		
	N	Mean	SD	N	Mean	SD
Week 1	374	24.8	5.6	375	24.6	2.5
Week 2	358	44.5	10.0	364	45.7	8.9
Week 3	337	78.4	28.1	354	83.6	25.9
Week 4	325	106.2	39.0	337	115.4	38.8
Weeks 6	312	131.4	52.0	327	144.5	51.7
Weeks 8	297	142.6	52.0	308	156.5	49.2
Weeks 10	286	149.0	51.1	293	161.2	50.7
Weeks 12	272	152.2	49.1	286	162.9	50.1

7.3.4 Duration of Treatment

There is insufficient data to support any efficacy claim beyond three weeks of treatment.

7.4 Conclusions Regarding Efficacy Data

Some things are easier than others to conclude from the efficacy data. It is clear that there is no data for efficacy in males in any of the four studies individually or combined. There is data for symptom reduction in study 640 seen only in females at week 12 (LOCF) but not week 12 (OC). There is more data seen at several weeks in study 671 indicating that females only have symptom reduction.

It is more difficult to characterize the nature of the symptom reduction seen only in females. Quite a bit of the effect on PTSD scales seems to be correlated with an improvement in the HAM-D. Whether Zoloft independently treats PTSD or simply treats associated comorbidity is difficult to determine.

8.0 Safety Findings

8.1 Methods

A total of 757 subjects (376 sertraline, 381 placebo) were randomized to double-blind medication in the completed PTSD studies as of the February 26, 1998 cut-off date of the present submission.

Of these, 750 subjects (374 sertraline, 376 placebo) received at least one dose of study medication and had at least one further contact with the study site. These 750 subjects comprise the "safety analyzable" population that forms the basis of the analyses in this summary.

The safety data from these four completed PTSD studies form the basis of this integrated summary of safety. Information is included on premature discontinuations of therapy, treatment emergent adverse events, serious adverse events, laboratory abnormalities, vital signs, body weight, and electrocardiography findings. In addition, as of the February 26, 1998 cut-off date, there are four ongoing PTSD studies including a total of 457 subjects receiving sertraline or placebo. Any serious adverse events from these ongoing studies that were entered into Pfizer's early alert system as of the cut-off date are discussed in this summary.

Serious adverse events were defined as events which: a) were fatal, b) were life-threatening or potentially life-threatening, c) resulted in permanent disability, d) required hospitalization or prolongation of a hospital stay, e) involved cancer, a congenital anomaly, or were the result of a drug overdose, or f) were deemed serious by the investigator.

All volunteered or observed treatment emergent adverse events were to be recorded and assessed by the investigator for relationship to study drug and severity. "Treatment emergent" was defined as beginning or worsening in severity after the subject was randomized, if the subject took at least one dose of study medication. Any objective test finding (e.g., an abnormal laboratory test result) which resulted in a change in study drug dosage or discontinuation of study drug was to be reported as an adverse event. Adverse event tables are organized according to body system and the preferred adverse event terms are used as listed in the Pfizer World Health Organization (WHO) Adverse Event Coding Glossary. In computing incidence of adverse events for a given table, a subject reporting more than one episode of the same adverse event, even of differing severity, was counted once and the highest level of severity was used. The incidence rates of subjects with any adverse event and of individual adverse events were compared between treatment groups using Fisher's exact test (2-tail). Adverse events occurring up to 7 days after the last dose of study drug are included in these analyses.

Laboratory safety evaluations were performed on all subjects receiving sertraline or placebo at baseline, at the end of week 6, and at end of week 12 (or when the subject discontinued the study). Clinical laboratory testing was performed at a central laboratory

At screening,

subjects with significant laboratory abnormalities in the investigator's opinion, as well as subjects with elevated liver function tests as specified in the protocols, were not to enter the studies. Laboratory evaluations made up to 7 days after the last dose of study drug are included in these analyses. Three methods were used to evaluate abnormal laboratory data that occurred during the studies, as listed below.

1. Premature discontinuations because of laboratory abnormalities.

2. Clinically significant laboratory test abnormalities using the threshold value criteria listed in Table 9.1.1 as adopted in sertraline Safety Update II for NDA #19-839, submitted to the U.S. Food and Drug Administration on 10/30/91.

3. Statistical comparison of the change from baseline in each laboratory parameter in the sertraline and placebo treatment groups. In addition, for hematology and serum chemistry parameters, the baseline and maximum (or minimum) laboratory values of each subject in each treatment group were graphically represented on scatterplots.

In all completed studies, blood pressure and heart rate were measured at every visit, after the subject had been sitting for 5 minutes.

In the completed studies, a 12-lead electrocardiogram was obtained at baseline and at the end of treatment (or when the subject discontinued from the study).

In all completed studies, body weight was measured at every visit.

The more commonly encountered adverse experiences were assessed using data from the placebo-controlled trials. Less frequent, but more grave adverse experiences were investigated by examining any death, reasons for premature discontinuation from clinical trials and the sponsor's safety reports of potentially serious adverse events from all studies.

8.2 Deaths

There were no deaths which occurred during or within 30 days of study discontinuation or poststudy (greater than 30 days following study discontinuation) for any study.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

The dropout rates for Sertraline and placebo due to adverse events were 8.6 vs 4,8. Please see table below.

Rates of Discontinuation by Treatment Group and Reason - All Safety Analyzable Subjects

Reason for Discontinuation	% Discontinued Sertraline (n=374)	% Discontinued Placebo (n=376)
Withdrawn Consent	5.9	8.8
Adverse Event	8.6	4.8
Lost To Follow Up	6.7	4.5
Protocol Violation	2.4	2.1
Other	1.6	2.7
Insufficient Clinical Response	1.1	2.4
Laboratory Abnormality	1.3	0.0
Does Not Meet Entrance Criteria	0.3	0.0
Total % Discontinued	27.8%	25.3%

Includes subject 93N0179/598 (Protocol 641, Treatment=placebo; male) who discontinued due to adverse events which had onset prior to randomization and thus are not considered treatment emergent.

8.3.2 Adverse Events Associated with Dropout

The discontinuation rate due to treatment-emergent adverse events/laboratory abnormalities at any time during the studies was 10% (37/374) in sertraline subjects and 5% (17/376) in placebo subjects. Sertraline was not associated with any statistically significant increased incidence of clinically significant abnormalities of laboratory parameters, vital signs, or body weight as compared to placebo.

Nausea and headache were the most common treatment-emergent adverse events leading to discontinuation in sertraline subjects.

Adverse Events Associated with Discontinuation - All Safety Analyzable Subjects
Protocols 640, 641, 671, 682

	Sertraline		Placebo	
Adverse Events	Subject N	Incidence (%)	Subject N	Incidence (%)
Nausea	7	(1.9)	1	(0.3)
Headache	5	(1.3)	2	(0.5)

The table above lists adverse events associated with discontinuation with an incidence > 1% in sertraline-treated subjects.

8.4 Search for Serious Adverse Events

Any serious adverse event occurring during the study or within 30 days after the last administration of study drug was to be reported regardless of causality. Any event that occurred greater than 30 days after the last administration of study drug was to be reported if the investigator felt that the event was causally related to study drug.

The serious adverse events which were entered into Pfizer's early alert safety database as of the February 26, 1998 cut-off date are presented for both completed and ongoing studies. Serious adverse events occurred in 2% (8/374) of sertraline subjects and 1% (5/376) of placebo subjects in the completed studies. As of the cut-off date, 5 sertraline subjects (with 7 events) and 5 subjects receiving blinded therapy experienced serious adverse events in the ongoing studies. None of these events were considered to be treatment-related by the investigator.

Serious adverse events among sertraline subjects were one of each of the following except where indicated: delirium (attributed to multiple sclerosis), suicide attempt, homicidal ideation, suicidal ideation (two subjects), head fracture, agitation, and cholecystitis.

Ten subjects out of a total of 457 subjects treated in studies ongoing as of February 26, 1998 (secondary database) experienced 12 serious adverse events. Among subjects treated with sertraline or blinded therapy, there was one of each of the following serious

adverse events, except where noted: fetal death, ovarian cyst (two subjects), basal cell carcinoma of the eyelid, bone graft, chest pain, pharyngeal constriction, breast reduction surgery, hernia, accidental hand laceration, paroxysmal atrial fibrillation, and suicidal ideation. None of the serious adverse events were considered by the investigator to be related to sertraline or blinded medication.

These events are listed in the safety appendix. I have reviewed this list and find no new or worrisome events that differ from the serious adverse events in the original submission.

Dropouts and deaths have been discussed in previous sections. Laboratory abnormalities, overdoses, withdrawal phenomena and pregnancy related events will be discussed in subsequent sections of this review.

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

8.5.1.1 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse event tables are organized according to body system and the preferred adverse event terms are used as listed in the Pfizer World Health Organization (WHO) Adverse Event Coding Glossary. I have reviewed this list and find the organization to be reasonable.

8.5.1.2 Incidence in Controlled Clinical Trials

At least one treatment emergent adverse event was reported by 88% (329/374) of sertraline-treated subjects and 80% (302/376) of placebo-treated subjects. The most frequent treatment emergent adverse events (10% incidence) in sertraline-treated subjects were diarrhea, headache, nausea, insomnia, somnolence, dry mouth, and malaise. The treatment emergent adverse events that occurred in at least 5% of sertraline subjects and with an incidence at least twice that of placebo were dry mouth, fatigue, anorexia, decreased libido, and tremor.

The adverse events reported in this submission are similar to those previously reported for the indications of depression, obsessive-compulsive disorder, and panic disorder, and reflected in the current labeling.

8.5.1.3 Post Marketing Spontaneous Reports

The sponsor had provided an analysis of postmarketing use of sertraline for PTSD. It is reproduced in truncated form in italics below.

Over 3,590,000,000 patient days of therapy with sertraline have been experienced worldwide through March 1998, since the drug was first launched in 1991. Sertraline has been approved for use in depression, obsessive-compulsive disorder, and panic disorder. Serious adverse events from spontaneous or literature reports of patients treated with sertraline for any indication (approved or unapproved) are entered into Pfizer's early alert safety database. This database was searched for spontaneous or literature reports of serious adverse events in patients treated for PTSD reported up to the data cut-off date of February 26, 1998. Thirteen such serious adverse events were found (Table 14). Only limited information is available for these events. Hypercholesterolemia in one patient and leukopenia in another patient were thought to be possibly related to sertraline by the reporters of the events; all other events were either not considered to be related to sertraline or were not assessed for relationship to sertraline by the reporters of the events. The most common event was intentional overdose, which was reported in five patients (see Section 8.10.12). All of the patients survived.

8.5.2 Laboratory Findings

5/374 of sertraline subjects and no placebo subjects prematurely discontinued study drug due to laboratory test abnormalities. Four of the five subjects had elevated SGOT and SGPT; maximum values for these subjects ranged from 50 to 172 U/L for SGOT and from 111 to 460 U/L for SGPT. The elevations were ascribed to hepatitis in one subject and to alcohol consumption in another subject. The last available follow-up values for these two subjects were 123 and 91 U/L, respectively, for SGOT and 111 and 121 U/L, respectively, for SGPT. In the other two subjects, the elevations were attributed to sertraline. In these subjects, values returned to normal after discontinuation of study drug. The fifth subject had decreases in hematocrit (from 30% to 27%) and hemoglobin (from 9.2 to 8.1 g/dL) attributed to a history of anemia. No follow-up values are available for this subject. None of these abnormalities were considered serious adverse events. No subjects discontinued due to vital sign abnormalities, electrocardiogram abnormalities, or weight changes.

The following sections will provide proportions of patients in the double-blind placebo-controlled trial who met arbitrarily defined criteria for changes in laboratory variables of possible clinical

significance. There will also be comparisons of sertraline versus placebo regarding mean changes in baseline parameters of laboratory values.

8.5.2.1 Clinical Chemistry Findings

There was no statistical difference in the incidence of laboratory test abnormalities in treated subjects (57 abnormalities in 46 subjects) as compared to placebo-treated subjects (66 abnormalities in 50 subjects). Mean changes from baseline in sertraline subjects which were significantly different from placebo included SGOT, SGPT, alkaline phosphatase, total protein, albumin, cholesterol, and uric acid. Sertraline treated subjects had higher mean change values for SGOT (3.11 vs -.13), SGPT (4.50 vs.67), Alk Phos (5.10 vs 1.43), total protein (7.33 vs4.16), cholesterol (13.31 s-2.90)

The chemistry criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined criteria for changes.

There were no significant changes in the proportions of patients exceeding defined criteria except for elevated SGPT where sertraline had 1.3% and Placebo .6%.

8.5.2.2 Hematology Findings

Mean changes from baseline in sertraline subjects which were significantly different from placebo included white blood count, red blood cells, neutrophils. These mean changes were small in magnitude and of minimal clinical importance.

The hematology criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the criteria for changes.

There were no significant changes in the proportions of patients exceeding defined criteria.

8.5.2.3 Urinalysis

The urinalysis criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined

criteria for changes.

There were no significant changes in the proportions of patients exceeding defined criteria.

There were no changes in urinary mean values reported.

8.5.3 Vital Signs

The sponsor provides the incidence of clinically significant abnormalities in vital signs in sertraline-treated subjects and placebo-treated subjects as determined by the following criteria: heart rate >120 bpm or <50 bpm; systolic blood pressure >180mmHg or <90mmHg; diastolic blood pressure >105 mmHg or <50 mmHg. In addition, in order to be classified as a clinically significant abnormality, the change from baseline was required to be greater than or equal to: 15 bpm for heart rate, 20 mmHg for systolic blood pressure and 15 mmHg for diastolic blood pressure. According to the above criteria there were 20 clinically significant abnormalities of vital signs among 19/370 (5%) sertraline-treated subjects compared with 17 such abnormalities among 17/368 (5%) placebo-treated subjects. None of the abnormalities were serious or warranted subject discontinuation. There were no statistically significant differences in the incidence of clinically significant vital sign abnormalities between the sertraline and placebo treatment groups.

The only statistically significant (p =.05) difference between the sertraline and placebo treatment groups in the mean change from baseline to final visit in any vital sign was heart rate. The mean decrease from baseline of 0.99 bpm (-1%) in sertraline-treated subjects compared with a mean increase of 1.31 bpm (+2%) in placebo-treated subjects is without clinical significance.

There were 12 sertraline subjects with low BP compared to 4 on placebo p=.07.

In all completed studies, body weight was measured at every visit. On the basis of a threshold criterion of a 7% change in weight from baseline during the study, 2/370 (1%) subjects in the sertraline group versus 7/367 (2%) subjects in the placebo group experienced a clinically significant weight gain, and 13/370 (4%) subjects in the

sertraline group versus 9/367 (2%) in the placebo group experienced a clinically significant weight loss. None of the weight changes led to discontinuation. The incidence of these body weight abnormalities was not significantly different in the sertraline and placebo treatment groups. The mean change in weight from baseline to final visit was -1.87 lbs for the sertraline group and +0.04 lbs for the placebo group. These changes are statistically significantly different (p=.05).

The vital sign criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the defined criteria for changes.

8.5.4 ECGs

Treatment-emergent clinically insignificant electrocardiogram abnormalities occurred in 9% of both sertraline (29/307) and placebo (28/306) subjects. No subjects had clinically significant electrocardiogram abnormalities. No subjects discontinued due to electrocardiogram abnormalities.

The ECG criteria used in this section appear in the safety appendix along with the tables of proportions of patients in the double-blind placebo-controlled trial who fell outside the arbitrarily defined criteria for changes.

There were no statistically significant changes in the proportions of patients exceeding defined criteria

There were no significant parameters among mean changes from baseline.

8.5.5 Special Studies

None done.

8.5.6 Withdrawal Phenomena/Abuse Potential

There was no new evidence of withdrawal signs or of indications of abuse potential in the four completed trials of sertraline for the treatment of Posttraumatic Stress Disorder. There is no significant change from previous data and recommendations in this section.

8.5.7 Human Reproduction Data

No human reproductive studies were included in this submission.

Of the 750 safety analyzable subjects in the completed controlled trials, two discontinued prematurely due to pregnancy, one in the sertraline group (93N0168/52) and one in the placebo group (94N0158/189). Of the 457 safety analyzable subjects in the ongoing trials as of the February 28, 1998 cut-off date, one subject (96N0192/1049) became pregnant after receiving 29 days of blinded therapy in Protocol 96CE21-0703. The patient had previously received 159 days of 100 mg/day open-label sertraline treatment. The patient discontinued treatment upon learning that she was pregnant. One month later her pregnancy terminated because of fetal death. The cause of the fetal death was unknown but not considered treatment related by the investigator. The subject was taking no concomitant medications. Previous pregnancy history is under investigation.

There is no significant change from previous data and recommendations in this section.

8.6 Overdose Experience

As of the February 26, 1998 data cut-off date, there was one reported case of sertraline overdosage in the completed and ongoing PTSD studies. Subject #94N0177-176 (Protocol 640) was a 39-year old white female who ingested 425 mg of sertraline in an attempt to obtain symptomatic relief following an encounter with a previous assailant. She suffered no sequelae of the overdose.

Five overdoses have been entered into Pfizer's early alert safety database as of February 26, 1998 from spontaneous or literature reports of patients treated with sertraline for PTSD. Only limited

information is available for these events. All of the patients survived. The amount of sertraline ingested by the five patients was 300 mg, 400 mg, 750 mg, 1500 mg, and an unknown amount. Three of the patients also overdosed on other medications at the same time. The patient that took 1500 mg was a 35-year old white female who also ingested 1000 mg of diphenhydramine at the same time. She was admitted to the hospital with decreased alertness, and electrocardiography revealed mild T wave changes. She also had a high blood alcohol level. The patient was treated with an orogastric lavage and a large number of pill fragments were returned. She was discharged from the hospital the next day.

8.7 Summary of Important Events Considered Drug Related

Weight:

On the basis of a threshold criterion of a 7% change in weight from baseline during the study, 2/370 (1%) subjects in the sertraline group versus 7/367 (2%) subjects in the placebo group experienced a clinically significant weight gain, and 13/370 (4%) subjects in the sertraline group versus 9/367 (2%) in the placebo group experienced a clinically significant weight loss. None of the weight changes led to discontinuation.

Liver Functions:

Four subjects had elevated SGOT and SGPT; maximum values for these subjects ranged from 50 to 172 U/L for SGOT and from 111 to 460 U/L for SGPT. The elevations were ascribed to hepatitis in one subject and to alcohol consumption in another subject. The last available follow-up values for these two subjects were 123 and 91 U/L, respectively, for SGOT and 111 and 121 U/L, respectively, for SGPT. In the other two subjects, the elevations were attributed to sertraline. In these subjects, values returned to normal after discontinuation of study drug.

EKG:

No subjects had clinically significant electrocardiogram abnormalities. No subjects discontinued due to electrocardiogram abnormalities.

8.8 Important Events Considered Not Drug Related

Certain events have been discussed elsewhere in this document and have been excluded from this list (i.e., deaths, overdoses, dropouts and changes in laboratory values).

The rest of the serious adverse events are considered not drug related and they are displayed in the Appendix of serious adverse events.

8.9 Summary of Drug Interactions

8.9.1 Drug-Demographic Interactions

GENDER:

89% (216/244) of females and 87% (113/130) of males in the sertraline group had treatment emergent adverse events, with 11% of females and 9% of males who received sertraline discontinuing due to treatment emergent adverse events. Headache, nausea, insomnia, and diarrhea were the most common (20%) treatment emergent adverse events in females. In males, diarrhea and headache were most common (20%).

AGE:

The sponsor presents the incidence of treatment emergent adverse events in 3 age groups: 18-44 years, 45-64 years, and 65 years. The percentage of sertraline subjects with treatment emergent adverse events was similar in the 18-44 year (90%; 213/238) and 45-64 year (85%; 111/130) age groups, as was the percentage of sertraline subjects discontinuing due to treatment emergent adverse events (10% for each age group). Incidences of individual adverse events were also comparable in these two groups. The number of sertraline subjects in the 65 year age group (n=6) was too small to allow meaningful interpretation.

RACE:

Among subjects receiving sertraline, 90% (271/300) of white subjects, 86% (44/51) of black subjects, and 61% (14/23) of subjects of other races reported treatment emergent adverse events. The incidence of discontinuation due to treatment emergent adverse events in sertraline subjects was 9% (28/300), 10% (5/51), and 17% (4/23) in these groups, respectively. The small sample size of

black and other non-white patients does not provide sufficient basis to draw meaningful conclusions about possible differences in sertraline tolerability with respect to race.

8.9.2 Drug-Disease Interactions

No potentially significant medical concern has been identified in subjects with PTSD that was not previously established in the safety profile of non-PTSD subjects as documented in previous submissions to NDA 19-839 and are reflected in the current labeling.

8.9.3 Drug-Drug Interactions

No new drug interactions have been reported with this submission. 76% of sertraline-treated subjects and 81% of placebo-treated subjects took concomitant medication during double-blind treatment. Ibuprofen, acetaminophen, aspirin, and chloral hydrate were the medications most commonly taken in both treatment groups.

9.0 Labeling Review

The labeling has been changed to include the larger data base now available. PTSD has been inserted in all areas where the indications are listed. The safety tables have been updated with PTSD columns. These listings appear to be correct. The significant changes are in the indications section where the sponsors add the indication and try to minimize the lack of effect in males.

10.0 Conclusions

There are no safety issues identified in subjects with PTSD that were not previously established in the safety profile of non-PTSD subjects as reflected in the current labeling.

There is little to no efficacy in males. There is some degree of efficacy in females who have a simultaneous improvement in mood (see 7.3.1).

11.0 Recommendations

The sponsor did not demonstrate efficacy in the full population that was intended. The efficacy they demonstrated was in a subpopulation (females) and then was highly associated with mood improvement.

This drug is currently available for use and I see no need to grant a new indication that is not fully proven for both men and women. My choice would be to describe these trials in the appropriate labeling section pointing out the gender differences and the high correlation with mood improvement.

/S/ 9/13/99

Earl D. Hearst, M.D.
Medical Reviewer

file/tlaughren/ehearst/ahomonnay

10-19-99

I disagree with Dr. Hearst's conclusion that Zoloft was not shown to be effective in PTSD overall. In fact, if the p-values had not been significant for the overall hypotheses, there would have been no basis for subgroup explorations. I agree that these explorations do suggest that the effects were derived predominantly from the women in those studies, however, as discussed at the PDAC meeting for this application, it might well be something other than gender that is driving the result. In any case, I agree with the majority of PDAC members who strongly urged FDA to approve Zoloft for PTSD in general, with a description of the exploratory analyses in the Clincical Trials section, as we ordinarily do in such situations. I also disagree with Dr. Hearst's suggestion that the correlations between the PTSD and the HAMD responses in some way diminish the evidence for effectiveness of Zoloft in PTSD. In fact, the exploratory analyses conducted by Drs. Smith and Hearst actually support the independence of the PTSD effect. Dr. Hearst's review is deficient in omitting what in my view are the most pertinent data, i.e., (1) the evidence that, with or without comorbid depression at baseline, there is evidence of a PTSD effect, and (2) the evidence for an effect on the cluster of items specific to PTSD. His suggestion, as an alternative to approving Zoloft for PTSD, to "describe these trials in the appropriate labeling section..." is without any clear meaning. See my 10-19-99 memo to the file for my more detailed comments on this application and my recommendation that Zoloft be approved for the treatment of PTSD.

/S/
TL, PDP

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APPENDIX

Table V.B List Of Investigators and Sites for Completed Controlled Studies

640 Principal Investigators	Study Sites
Jessy Colah, M.D., and Renuka Tank, M.D.	One Brookdale Plaza at Linden Boulevard Brooklyn, NY 11212
Kathleen Brady, Ph.D., M.D.	171 Ashley Avenue Charleston, SC 29425-0742
Paul Newhouse, M.D.	1 South Prospect Street Burlington, VT 05401
Barbara Rothbaum, Ph.D.[a]	Building B, Suite 6100 1365 Clifton Road NE Atlanta, GA 30322
Hisham Hafez, M.D., and Philip Santora, M.D.[a]	29 Northwest Blvd. Nashua, NH 03063
Peter Londborg, M.D.	901 Boren Avenue, Suite 940 Seattle, WA 98104
Teri Pearlstein, M.D.	345 Blackstone Blvd. Providence, RI 02906
Bessel van der Kolk, M.D., Ph.D.	227 Babcock Street Brookline, MA 02146
Wayne Phillips, M.D., Ph.D.	1650 38th Street Suite 105 W Boulder, CO 80301
Katherine Shear, M.D.[b]	3811 O'Hara Street Pittsburgh, PA 15213
Richard H. Weisler, M.D.	900 Ridgefield Drive Suite 320 Raleigh, NC 27609
William Patterson, M.D.	2120 Lyngate Drive Birmingham, AL 35216
Phebe Tucker, M.D.[d]	P.O. Box 26901 Oklahoma City, OK 73190-3048
641 Principal Investigators	**Study Sites**

Neal Kline, M.D.,and Mark Rapaport, M.D.[a]	3350 La Jolla Village Drive San Diego, CA 92161
June Corwin, Ph.D.	423 East 23rd Street New York, NY 10010
Israel Liberzon, M.D.	2215 Fuller Road Ann Arbor, MI 48105
Matthew J. Friedman, M.D., Ph.D.	White River Junction, VT 05009-0001
Joseph Westermeyer, M.D., Ph.D., M.P.H	One Veterans Drive Minneapolis, MN 55417
Jonathan Davidson, M.D.	508 Fulton Street Durham, NC 27705
Bruce Kagan, M.D.[b]	11301 Wilshire Blvd. Ward 207C Los Angeles, CA 90073
Dewleen G. Baker, M.D.	3200 Vine Street Cincinnati, OH 45220
Bruce Perry, M.D., Ph.D.	2002 Holcombe Blvd Houston, TX 77030
Mark H. Hamner, M.D.	109 Bee Street Charleston, SC 29401-5755
Thomas A. Mellan, M.D.	1201 N.W. 16th Street Miami, FL 33125
671 Principal Investigators	**Study Sites**
Gregory Asnis, M.D.	111 East 210 Street Bronx, NY 10467
Dewleen Baker, M.D.	3200 Vine Street Cincinnati, OH 45220

Robert Bielski, M.D.	26105 Orchard Lake Rd. Suite 301 Farmington Hills, MI 48334
Kathleen Brady, M.D., Ph.D.	171 Ashley Avenue Charleston, SC 29425-0742
Jonathan Davidson, M.D.[a]	3rd FLoor, Purple Zone, Room 3712 Trent Drive Durham, NC 27710
Edna Foa, Ph.D.and Richard J. Kavoussi, M.D.[b]	3200 Henry Avenue Philadelphia, PA 19129
Susanna Goldstein, M.D.	65 Central Park West #1-BR New York, NY 10023
Mark Hegel, Ph.D., and C. Lewis Ravaris, M.D., Ph.D.	One Medical Center Dr. Lebanon, N.H. 03756
Jonathan M Himmelhoch, M.D.[a]	3501 Forbes Avenue, Oxford Bldg., Room 738 Pittsburgh, PA 15213
Henry Lahmeyer, M.D.	310 Happ Road Suite 205 Northfield, IL 60093
Peter Londborg, M.D.	Cabrini Medical Tower 901 Boren Avenue, Suite 1800 Seattle, WA 98104
Teri Pearlstein, M.D.	345 Blackstone Boulevard Providence, RI 02906
Murray Rosenthal, D.O. and Andrew J. Ferber, R.N. MSN	9449 Balboa Avenue, Suite 205 San Diego, CA 92123
Barbara Rothbaum, Ph.D., and Philip T. Ninan, M.D.	1701 Uppergate Drive - Room 126 Atlanta, GA 30322
Ward Smith, M.D.[a]	1849 NW Kearney Portland, OR 97209

Phebe Tucker, M.D.	P.O. Box 26901 Oklahoma City, OK 73109-3048
682 Principal Investigators	**Study Sites**
Jon Bell, M.D.	4200 E. 9th Avenue Denver, CO 80262
Jessy Colah, M.D.[b] and Renuka Tank, M.D.	1335 Linden Blvd. Brooklyn, NY 11212
Lynn Cunningham, M.D.[a]	301 North Sixth Street Suite 330 Springfield, IL 62701-1098
Eugene A. DuBoff, M.D.	4704 Harlan Street, Suite 430 Denver, CO 80212
David Goldstein, M.D.	3750 Reservior Road Washington, DC 20007-2197
Wayne K. Goodman, M.D.[a]	1600 SW Archer Road Gainesville, FL 32608
Jon F. Heiser, M.D.[a]	1000 Dove Street Suite 200 Newport Beach, CA 92660-2814
Richard Maddock, M.D.	4430 V. Street Sacramento, CA 95817
Bharat Nakra, M.D.[a]	16216 Baxter Road, Suite 320 Chesterfield, MO 63017
William Patterson, M.D.	2120 Lynngate Drive Birmingham, AL 35216
Mark Pollack, M.D.[b]	WACC 815 15 Parkman Street Boston, MA 02114

Jeffrey Rausch, M.D.	1515 Pope Avenue Augusta, GA 30912-3800
Peter D. Londborg, M.D.	901 Boren Avenue, Suite 1800 Seattle, WA 98104
Teri Pearlstein, M.D.	345 Blackstone Boulevard Providence, RI 02906
Kathleen Brady, Ph.D., M.D.	171 Ashley Avenue Charleston, SC 29425-0742
Mark Hegel, Ph.D.	1 Medical Center Drive Lebanon, NH 03766
Henry Lahmeyer, M.D.	310 Happ Road Suite 205 Northfield, IL 60093
Barbara Rothbaum, Ph.D.	1701 Uppergate Drive - Room 126 Atlanta, GA 30322

Table VI. A. Inclusion/Exclusion Criteria for Completed Controlled Studies

Inclusion Criteria

1. Patients must be outpatients at least 18 years of age who are male, or if female, are practicing a medically acceptable method of contraception (e.g., oral contraceptive, barrier method, IUD, levonorgestrel implants), are surgically sterilized, or are at least 2 years post-menopausal.

2. Patients must fulfill DSM-III-R criteria for Post-traumatic Stress Disorder as determined by Part 1 of the Clinician Administered PTSD Scale (CAPS), with duration of symptoms > 6 months. The CAPS is to be administered by the investigator or a co-investigator who has been trained to administer the CAPS.

3. Patients must have a complete medical and psychiatric history and a physical examination at the time of entry into the study. The initial physical examination and laboratory values must be normal, or abnormalities must be clinically insignificant. These data will be recorded during the single-blind washout.

4. If the patient is a female of childbearing potential, she must have a negative serum beta-HCG pregnancy test at the time of study entry.

5. At baseline (end of washout), patients must continue to meet diagnostic criteria for current PTSD as determined by a score of 50 or above on Part 2 of the CAPS.

6. A urine drug screen on day 1 of washout must be negative. *(Studies 640 and 641 only)*

7. All other psychotropic medication (except chloral hydrate for sleep) must have been discontinued prior to entry into the study (see also Exclusion Criteria).

8. Patient must be literate in English and must be able to communicate intelligently with the investigative team.

9. Patients must be judged reliable for medication compliance and clearly motivated to obtain benefit from treatment. They must agree to keep appointments for study visits and all tests and examinations required by the protocol.

Exclusion Criteria

1. Pregnant women and women who are breast feeding. If a patient becomes pregnant during the study, she will be discontinued from the study immediately and followed appropriately.

2. Patients with Organic Mental Disorder (including post-concussion syndrome).

3. Patients who have a primary diagnosis meeting DSM-III-R criteria for:

   a. Major Depression, single episode or recurrent;

   b. Dysthymic Disorder;

   c. Personality Disorders from Clusters other than Cluster C (Avoidant, Dependent, Passive Aggressive *(640/641 only)*, and Obsessive-Compulsive Personality Disorders);

   d. Obsessive Compulsive Disorder, Generalized Anxiety Disorder, Panic Disorder, Simple Phobia, Social Phobia, Agoraphobia, or Anxiety Disorder NOS;

   e. Conversion Disorder *(671/682 only)*.

4. Patients who meet DSM-III-R criteria for Factitious Disorder or Malingering. *(671 and 682 only)*

5. Patients who meet DSM-III-R criteria for Bipolar Disorder (Depressed, Manic, Mixed or NOS), either currently or by history.

6. Patients with any current psychotic features or with a history of Schizophrenia, Delusional Disorder, Schizophreniform Disorder, or Psychotic Disorder NOS.

7. Patients with a Psychoactive Substance Abuse Disorder within the past 6 months.

8. Patients with medical contraindications to therapy with antidepressants as determined by past medical history, physical examination, or known allergy or hypersensitivity to antidepressants. *(671 and 682 only)*

9. Patients with a history or evidence of malignancy (other than excised basal cell carcinoma). Patients with significant hematological, endocrine, cardiovascular, renal, hepatic, neurological (including >1 childhood febrile seizure and all forms of epilepsy) or gastrointestinal disease. If there is a history of such disease, but the condition has been stable for more than 6 months *(671 and 682)* or 1 year *(640 and 641)* and is judged by the investigator not likely to interfere with the patient's participation in the study, the patient may be included if approved by the Pfizer Project Clinician.

10. Patients with any liver function test greater than twice the upper limit of the normal range at the screening visit (day 1 of washout); however *(for 671, 682 only)*, if any liver function test falls between 1.5 times and twice the upper limit of the normal range, the patient may be entered if approved by the Pfizer Project Clinician.

11. Patients on concomitant therapy with another investigational drug, or patients who have been in an investigational drug study within one month prior to entering this study, or who have ever been in a previous investigational study of sertraline.

12. Patients requiring concomitant psychotropic therapy of any type (with the exception of chloral hydrate) or drugs with a psychotropic component (Donnatal, metoclopramide HCl, sedating antihistamines, etc.). If there is any doubt regarding the choice of an acceptable concomitant medication (as noted in the concomitant medication table), the sponsor should be contacted.

13. Patients who have taken a monoamine oxidase inhibitor (MAOI) within two weeks prior to the first administration of double-blind study medication. (Patients will be instructed not to take MAOIs for 2 weeks after completing the study.)

14. Patients who have had therapy with any daily neuroleptic, antidepressant [(including lithium), anticonvulsant *(671/682 only)*], hypnotic or anxiolytic medication in the 2 weeks prior to the first administration of double-blind study medication; or any depot neuroleptic within 6 months of the first administration of double-blind study medication; or patients who have had regular therapy with fluoxetine (Prozac) in the 5 weeks prior to the first administration of double-blind study medication.

15. Patients with a history of non-response to adequate treatment (adequate dosage and duration) with sertraline or with at least two different classes of antidepressants (e.g., heterocyclics, MAOIs, atypicals/SSRIs).

16. Patients who will be receiving behavior therapy during the study. Psychotherapy is permitted but cannot be initiated or terminated during the study. If psychotherapy is ongoing, it must have been initiated at least 3 months prior to the screening visit. (Patients may attend support groups during the study.)

17. Patients who would pose a serious suicide risk during the course of the study.

18. Patients with current impulse control problems (i.e., who have committed an act of violence within the past 12 months) or who are judged to be potentially violent.

19. Patients who test positive for psychotropic drugs or drugs of abuse on the urine drug screen at the Screening visit.

20. Patients currently involved in criminal proceedings or in litigation for disability benefits or for damages related to their disorder.

21. Patients who, in the investigator's opinion, might not be suitable for the study.

TABLE VI. B. SCHEDULE OF ASSESSMENTS FOR COMPLETED CONTROLLED STUDIES

Assessment	Day 1 of Washout	Day 8[c] of Washout	Baseline	Double-Blind Treatment: End of Week*							
				1	2	3	4	6	8	10	12**
SCID-P	x										
Clinician Administered PTSD Scale (CAPS) - Part I	x										
CAPS - Part 2			x	a	x	a	x	x	x	x	x
Impact of Event Scale	a		x	x	x	x	x	x	x	x	x
Clinical Global Impressions (CGI)		b	x	x	x	x	x	x	x	x	x
Davidson Self-Rating PTSD Scale	a		x	x	x	x	x	x	x	x	x
Hamilton Depression Scale			x								x
Hamilton Anxiety Scale			a								a
Civilian Mississippi Scale			a								a
Pittsburgh Sleep Quality Index			a								a
Disorders of Extreme Stress			a								a
Quality of Life Scale			b								b
Health & Work Questionnaire		b									b
Physical Exam	x										x
BP/Pulse/Body Weight	x	b	x	x	x	x	x	x	x	x	x
Clinical Laboratory Work	x							x			x
Pregnancy Test	x							x			x
Thyroid Function Tests	x										a
Urine Drug Screen	x							a			
Electrocardiogram	x										x

* "End of Week" refers to "after 7 days of treatment."

** or if a patient is discontinued prior to End of Week 12

a Protocols 640 and 641 only

b Protocols 671 and 682 only

c Protocols 640/641 had 1 week washout; 671/682 had 2 weeks washout

Table V.C.2. Demographic Characteristics by Study for All Randomized Subjects

	Protocol 640			Protocol 641			Protocol 671			Protocol 682		
	Sert n=100	Pbo n=108	P value	Sert n=86	Pbo n=83	P value	Sert n=94	Pbo n=93	P value	Sert n=96	Pbo n=97	P value
Sex												
Female	84	78		18	16		71	66		73	71	
Male	16	30	0.041	68	67	0.789	23	27	0.481	23	26	0.650
Race												
Asian	0	2		0	1		2	3		3	1	
Black	13	12		18	16		14	8		7	7	
White	83	91		58	62		76	82		84	88	
Other	4	3	0.523	10	4	0.287	2	0	0.255	2	1	0.701
Age (yrs)												
Mean ± SD	37.6±11.1	36.6±10.1	0.564	44.8±10.9	45.9±9.7	0.386	40.2±9.6	39.5±10.6	0.536	36.8±10.8	38.2±11.7	0.487
18 - 44	75	80		31	25		60	61		73	67	
45 - 64	23	28		51	54		34	31		23	28	
>= 65	2	0		4	4		0	1		0	2	
Weight (lb)												
Mean ± SD	167.2±49.1	169.1±39.3	0.751	190.0±45.8	191.6±47.5	0.789	181.2±52.4	168.5±45.6	0.088	162.8±38.5	172.8±48.0	0.128
Duration of Illness (yrs)												
Mean ± SD	11.7±11.1	12.8±12.4	0.505	17.4±12.3	19.2±12.1	0.245	13.1±11.8	11.2±12.7	0.295	11.0±11.1	10.2±10.8	0.504
Time from Traumatic Event (yrs)												
Mean ± SD	18.3±12.8	18.5±15.5	0.969	22.2±12.3	24.2±11.3	0.181	19.9±13.5	17.4±15.5	0.283	15.0±13.3	14.9±13.4	0.878
Comorbid Axis I Diagnoses												
Anxiety	23	16		17	10		17	11		25	29	
Depression	50	51	0.778	43	35	0.307	37	31	0.392	45	42	0.618
OCD	0	1		1	1		2	1		0	1	
Other	7	9		5	5		3	2		1	1	
None	40	46		40	45		50	55		43	41	

Differences between groups are based on the Pearson chi squared statistic for race and sex, and F test from two way ANOVA for mean age, weight, duration of illness, time from traumatic event, and Comorbid Axis I Diagnoses respectively.

a enrolled subjects at more than one location
b did not enroll any subjects in the trial

Table VII.A **Subject Completion Rates by Week for Completed Controlled Studies, and Combined**

Study Treatment Group	No. Rand	ITT Sample	Number (%) Patients Completing							
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12
640 Sert	100	98	98 (100)	93 (94.9)	91 (92.9)	88 (89.8)	82 (83.7)	77 (78.6)	75 (76.5)	73 (74.5)
640 Pbo	105	104	104 (100)	102 (98.1)	99 (95.2)	95 (91.3)	88 (84.6)	81 (77.9)	77 (74.0)	74 (71.2)
641 Sert	86	84	84 (100)	81 (96.4)	75 (89.3)	71 (84.5)	68 (81.0)	65 (77.4)	63 (75.0)	62 (73.8)
641 Pbo	83	82	82 (100)	81 (98.8)	80 (97.6)	78 (95.1)	75 (91.5)	73 (89.0)	70 (85.4)	69 (84.1)
671 Sert	94	93	93 (100)	90 (96.8)	87 (93.5)	83 (89.2)	77 (82.8)	72 (77.4)	69 (74.2)	64 (68.8)
671 Pbo	93	90	90 (100)	87 (96.7)	83 (92.2)	81 (90.0)	74 (82.2)	70 (77.8)	69 (76.7)	67 (74.4)
682 Sert	96	94	94 (100)	89 (94.7)	83 (88.3)	81 (86.2)	79 (84.0)	75 (79.8)	72 (76.6)	72 (76.6)
682 Pbo	97	94	94 (100)	90 (95.7)	86 (91.5)	85 (90.4)	81 (86.2)	79 (84.0)	75 (79.8)	71 (75.5)
Total Sert	376	369	369 (100)	353 (95.7)	336 (91.1)	323 (87.5)	306 (82.9)	289 (78.3)	279 (75.6)	271 (73.4)
Total Pbo	381	370	370 (100)	360 (97.3)	348 (94.1)	339 (91.6)	318 (85.9)	303 (81.9)	291 (78.6)	281 (75.9)

a enrolled subjects at more than one location
b did not enroll any subjects in the trial

Efficacy Tables

Table VII.C.1.a Protocol 640: CAPS-2 Change from Baseline by Visit - Observed Cases

Adjusted Mean Change From Baseline
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE	98	73.9	+/-	16.2	104	73.5	+/-	16.1	0.853
WEEK 1	95	-11.8	+/-	1.54	104	-7.6	+/-	1.48	0.052
WEEK 2	92	-15.9	+/-	1.65	100	-13.1	+/-	1.55	0.222
WEEK 3	90	-21.6	+/-	2.34	95	-21.2	+/-	2.24	0.882
WEEK 4	87	-23.7	+/-	2.29	95	-24.6	+/-	2.24	0.773
WEEK 6	82	-31.4	+/-	2.57	87	-28.0	+/-	2.69	0.357
WEEK 8	76	-31.5	+/-	2.79	81	-29.5	+/-	2.98	0.613
WEEK 10	74	-34.3	+/-	2.83	77	-30.2	+/-	2.99	0.323
WEEK 12	73	-38.2	+/-	2.86	74	-30.5	+/-	3.03	0.066
ENDPOINT	98	-33.0	+/-	2.41	104	-26.2	+/-	2.33	0.043

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

Table VII.C.1.b: Protocol 640: CAPS-2 Change from Baseline by Visit - LOCF

Adjusted Mean Change From Baseline (1)
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE (2)	98	73.9	+/-	16.2	104	73.5	+/-	16.1	0.853
WEEK 1	98	-11.6	+/-	1.53	104	-7.6	+/-	1.48	0.062
WEEK 2	98	-15.7	+/-	1.58	104	-13.1	+/-	1.53	0.248
WEEK 3	98	-22.1	+/-	2.14	104	-20.6	+/-	2.07	0.621
WEEK 4	98	-23.2	+/-	2.09	104	-23.1	+/-	2.02	0.975
WEEK 6	98	-30.0	+/-	2.28	104	-25.3	+/-	2.20	0.137
WEEK 8	98	-30.1	+/-	2.38	104	-25.9	+/-	2.30	0.204
WEEK 10	98	-30.3	+/-	2.39	104	-26.7	+/-	2.31	0.272
WEEK 12	98	-33.0	+/-	2.41	104	-26.2	+/-	2.33	0.043

(1) Means are adjusted for treatment, site, treatment-by-site, and baseline values.
(2) Mean and standard deviation at baseline.

Table VII.C.1.c Protocol 640: IES Change from Baseline by Visit - Observed Cases

Adjusted Mean Change From Baseline
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE	98	38.5	+/-	15.6	104	40.1	+/-	14.5	0.471
WEEK 1	94	-4.8	+/-	1.24	102	-4.1	+/-	1.20	0.685
WEEK 2	92	-6.9	+/-	1.34	100	-6.5	+/-	1.27	0.845
WEEK 3	90	-11.0	+/-	1.57	95	-11.4	+/-	1.50	0.854
WEEK 4	88	-13.8	+/-	1.54	95	-12.2	+/-	1.51	0.439
WEEK 6	82	-16.2	+/-	1.58	87	-14.9	+/-	1.64	0.568
WEEK 8	76	-17.2	+/-	1.81	80	-14.8	+/-	1.94	0.378
WEEK 10	73	-18.6	+/-	1.90	77	-17.9	+/-	1.97	0.796
WEEK 12	72	-21.1	+/-	1.77	74	-17.6	+/-	1.86	0.174
ENDPOINT	98	-19.2	+/-	1.53	104	-14.1	+/-	1.48	0.018

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

Table VII.C.1.d Protocol 640: IES Change from Baseline by Visit - LOCF

Adjusted Mean Change From Baseline (1)
+/- Standard Error

		Sertraline				Placebo				
		N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE (2)		98	38.5	+/-	15.6	104	40.1	+/-	14.5	0.471
WEEK	1	98	-4.6	+/-	1.20	104	-4.1	+/-	1.16	0.749
WEEK	2	98	-7.0	+/-	1.28	104	-6.5	+/-	1.24	0.762
WEEK	3	98	-11.3	+/-	1.45	104	-10.6	+/-	1.40	0.736
WEEK	4	98	-13.6	+/-	1.43	104	-11.9	+/-	1.38	0.402
WEEK	6	98	-16.1	+/-	1.46	104	-13.5	+/-	1.41	0.195
WEEK	8	98	-17.0	+/-	1.58	104	-13.2	+/-	1.53	0.090
WEEK	10	98	-18.2	+/-	1.58	104	-15.3	+/-	1.53	0.194
WEEK	12	98	-19.2	+/-	1.53	104	-14.1	+/-	1.48	0.018

(1) Means are adjusted for treatment, site, treatment-by-site, and baseline values.
(2) Mean and standard deviation at baseline.

Table VII.C.1.e Protocol 640: CGI-S Change from Baseline by Visit - Observed Cases

Adjusted Mean Change From Baseline
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE	98	4.6	+/-	0.96	104	4.6	+/-	0.93	0.429
WEEK 1	94	-0.2	+/-	0.06	104	-0.2	+/-	0.06	0.782
WEEK 2	92	-0.3	+/-	0.07	100	-0.3	+/-	0.06	0.479
WEEK 3	90	-0.7	+/-	0.09	95	-0.6	+/-	0.09	0.489
WEEK 4	88	-0.9	+/-	0.10	95	-0.8	+/-	0.10	0.571
WEEK 6	81	-1.1	+/-	0.12	88	-0.8	+/-	0.12	0.101
WEEK 8	76	-1.2	+/-	0.12	81	-1.0	+/-	0.13	0.246
WEEK 10	74	-1.4	+/-	0.13	77	-1.2	+/-	0.13	0.201
WEEK 12	73	-1.6	+/-	0.14	74	-1.2	+/-	0.15	0.123
ENDPOINT	98	-1.3	+/-	0.12	104	-1.0	+/-	0.12	0.037

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

Adjusted Mean Change From Baseline (1)
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE (2)	98	4.6	+/-	0.96	104	4.6	+/-	0.93	0.429
WEEK 1	98	-0.2	+/-	0.06	104	-0.2	+/-	0.06	0.843
WEEK 2	98	-0.3	+/-	0.06	104	-0.3	+/-	0.06	0.692
WEEK 3	98	-0.7	+/-	0.08	104	-0.6	+/-	0.08	0.361
WEEK 4	98	-0.8	+/-	0.09	104	-0.7	+/-	0.09	0.454
WEEK 6	98	-1.0	+/-	0.10	104	-0.8	+/-	0.10	0.078
WEEK 8	98	-1.1	+/-	0.10	104	-0.9	+/-	0.10	0.055
WEEK 10	98	-1.2	+/-	0.11	104	-0.9	+/-	0.11	0.066
WEEK 12	98	-1.3	+/-	0.12	104	-1.0	+/-	0.12	0.037

(1) Means are adjusted for treatment, site, treatment-by-site, and baseline values.
(2) Mean and standard deviation at baseline.

Table VII.C.1.g Protocol 640: CGI-I Score by Visit - Observed Cases

Adjusted Mean +/- Standard Error

		Sertraline				Placebo				
		N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
WEEK	1	94	3.6	+/-	0.08	104	3.6	+/-	0.08	0.771
WEEK	2	92	3.2	+/-	0.10	100	3.4	+/-	0.09	0.218
WEEK	3	90	2.8	+/-	0.11	95	3.0	+/-	0.11	0.209
WEEK	4	88	2.7	+/-	0.12	95	2.9	+/-	0.12	0.177
WEEK	6	81	2.4	+/-	0.12	88	2.5	+/-	0.12	0.536
WEEK	8	76	2.4	+/-	0.15	81	2.6	+/-	0.16	0.349
WEEK	10	74	2.3	+/-	0.14	77	2.6	+/-	0.15	0.191
WEEK	12	73	2.0	+/-	0.14	74	2.4	+/-	0.14	0.065
ENDPOINT		98	2.3	+/-	0.13	104	2.8	+/-	0.12	0.014

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

Table VII.C.1.h Protocol 640: CGI-I Score by Visit - LOCF

Adjusted Mean +/- Standard Deviation

		Sertraline				Placebo				
		N	Mean	+/-	SD	N	Mean	+/-	SD	p-value
WEEK	1	98	3.5	+/-	0.84	104	3.6	+/-	0.80	0.815
WEEK	2	98	3.2	+/-	0.93	104	3.4	+/-	0.87	0.372
WEEK	3	98	2.9	+/-	0.86	104	3.1	+/-	1.07	0.094
WEEK	4	98	2.8	+/-	0.99	104	3.1	+/-	1.06	0.075
WEEK	6	98	2.6	+/-	1.00	104	2.8	+/-	1.13	0.182
WEEK	8	98	2.5	+/-	1.17	104	2.9	+/-	1.20	0.041
WEEK	10	98	2.4	+/-	1.09	104	2.8	+/-	1.25	0.031
WEEK	12	98	2.2	+/-	1.16	104	2.8	+/-	1.21	0.001

Means are adjusted for treatment, site, treatment-by-site.

Table VII.C.2.a Protocol 671: CAPS-2 Change from Baseline by Visit - Observed Cases

Adjusted Mean Change From Baseline
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE	93	76.6	+/-	17.5	90	75.1	+/-	17.7	0.684
WEEK 1									
WEEK 2	87	-19.5	+/-	1.94	86	-13.9	+/-	1.94	0.041
WEEK 3									
WEEK 4	81	-27.6	+/-	2.39	81	-17.1	+/-	2.24	0.002
WEEK 6	77	-31.3	+/-	2.61	74	-21.8	+/-	2.61	0.011
WEEK 8	72	-37.2	+/-	3.12	70	-25.4	+/-	2.84	0.006
WEEK 10	68	-40.3	+/-	3.50	69	-26.5	+/-	3.06	0.004
WEEK 12	64	-39.3	+/-	3.89	67	-27.3	+/-	3.42	0.023
ENDPOINT	93	-33.0	+/-	2.82	90	-23.2	+/-	2.86	0.016

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

CAPS-2 was not administered during visits at the end of weeks 1 and 3 in Protocol 671.

APPEARS THIS WAY
ON ORIGINAL

Table VII.C.2.b Protocol 671: CAPS-2 Change from Baseline by Visit - LOCF

Adjusted Mean Change From Baseline (1)
+/- Standard Error

		Sertraline				Placebo				
		N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE (2)		93	76.6	+/-	17.5	90	75.1	+/-	17.7	0.684
WEEK	2	93	-18.2	+/-	1.86	90	-13.4	+/-	1.89	0.072
WEEK	4	93	-24.3	+/-	2.16	90	-15.9	+/-	2.20	0.007
WEEK	6	93	-28.8	+/-	2.42	90	-20.1	+/-	2.45	0.012
WEEK	8	93	-30.9	+/-	2.49	90	-22.6	+/-	2.53	0.021
WEEK	10	93	-32.8	+/-	2.65	90	-23.1	+/-	2.69	0.012
WEEK	12	93	-33.0	+/-	2.82	90	-23.2	+/-	2.86	0.016

(1) Means are adjusted for treatment, site, treatment-by-site, and baseline values.
Mean and standard deviation at baseline.

Table VII.C.2.c Protocol 671: IES Change from Baseline by Visit - Observed Cases

Adjusted Mean Change From Baseline
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE	93	37.7	+/-	15.7	90	36.7	+/-	15.4	0.687
WEEK 1	90	-4.3	+/-	1.18	90	-3.5	+/-	1.18	0.642
WEEK 2	87	-7.8	+/-	1.37	87	-7.9	+/-	1.36	0.981
WEEK 3	83	-11.7	+/-	1.42	79	-11.1	+/-	1.43	0.746
WEEK 4	81	-14.1	+/-	1.52	81	-10.0	+/-	1.43	0.053
WEEK 6	77	-15.5	+/-	1.58	74	-13.8	+/-	1.58	0.438
WEEK 8	72	-19.4	+/-	1.86	70	-14.5	+/-	1.68	0.052
WEEK 10	68	-20.4	+/-	2.11	69	-14.6	+/-	1.83	0.041
WEEK 12	64	-19.9	+/-	2.19	67	-14.0	+/-	1.90	0.049
ENDPOINT	93	-16.2	+/-	1.60	90	-12.1	+/-	1.63	0.071

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

Table VII.C.2.g Protocol 671: CGI-I Score by Visit - Observed Cases

Adjusted Mean +/- Standard Error

		Sertraline				Placebo				
		N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
WEEK	1	91	3.6	+/-	0.06	90	3.9	+/-	0.06	0.000
WEEK	2	87	3.1	+/-	0.09	87	3.3	+/-	0.09	0.081
WEEK	3	83	3.1	+/-	0.10	78	3.3	+/-	0.10	0.181
WEEK	4	81	2.7	+/-	0.10	81	3.3	+/-	0.10	0.000
WEEK	6	77	2.7	+/-	0.12	74	3.0	+/-	0.11	0.032
WEEK	8	72	2.3	+/-	0.13	70	2.7	+/-	0.12	0.066
WEEK	10	67	2.2	+/-	0.17	68	2.8	+/-	0.15	0.008
WEEK	12	64	2.3	+/-	0.18	67	2.7	+/-	0.16	0.062
ENDPOINT		93	2.5	+/-	0.13	90	3.0	+/-	0.14	0.016

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

Table VII.C.2.h Protocol 671: CGI-I Score by Visit - LOCF

Adjusted Mean +/- Standard Deviation

	Sertraline				Placebo				
	N	Mean	+/-	SD	N	Mean	+/-	SD	p-value
WEEK 1	93	3.6	+/-	0.61	90	3.9	+/-	0.63	0.001
WEEK 2	93	3.2	+/-	0.94	90	3.4	+/-	0.77	0.142
WEEK 3	93	3.2	+/-	0.87	90	3.3	+/-	0.83	0.180
WEEK 4	93	2.9	+/-	0.92	90	3.3	+/-	0.92	0.004
WEEK 6	93	2.8	+/-	0.98	90	3.1	+/-	0.97	0.026
WEEK 8	93	2.6	+/-	1.00	90	2.9	+/-	1.01	0.030
WEEK 10	93	2.5	+/-	1.10	90	3.0	+/-	1.20	0.004
WEEK 12	93	2.5	+/-	1.22	90	3.0	+/-	1.20	0.017

Means are adjusted for treatment, site, treatment-by-site.

able VII.D.1 Protocol 640: Davidson Change from Baseline by Visit - Observed Cases

Adjusted Mean Change From Baseline
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE	97	74.5	+/-	26.9	104	73.8	+/-	26.2	0.789
WEEK 1	94	-10.1	+/-	2.08	102	-4.4	+/-	2.02	0.054
WEEK 2	92	-16.0	+/-	2.13	100	-9.2	+/-	2.01	0.021
WEEK 3	90	-20.6	+/-	2.89	95	-16.0	+/-	2.77	0.249
WEEK 4	88	-22.4	+/-	2.81	95	-18.3	+/-	2.76	0.295
WEEK 6	83	-28.9	+/-	2.92	87	-23.3	+/-	3.08	0.195
WEEK 8	76	-30.2	+/-	3.46	80	-22.6	+/-	3.72	0.137
WEEK 10	74	-32.9	+/-	3.33	77	-26.2	+/-	3.51	0.168
WEEK 12	73	-35.8	+/-	3.29	74	-25.3	+/-	3.47	0.029
ENDPOINT	97	-32.3	+/-	2.81	104	-20.0	+/-	2.70	0.002

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

Table VII.D.2 Protocol 671: Davidson Change from Baseline by Visit - Observed Cases

Adjusted Mean Change From Baseline
+/- Standard Error

	Sertraline				Placebo				
	N	Mean	+/-	SE	N	Mean	+/-	SE	p-value
BASELINE	90	71.9	+/-	24.1	88	68.5	+/-	27.8	0.481
WEEK 1	88	-8.0	+/-	1.81	88	-2.8	+/-	1.85	0.048
WEEK 2	84	-15.2	+/-	2.31	85	-12.6	+/-	2.32	0.431
WEEK 3	82	-20.5	+/-	2.60	77	-15.4	+/-	2.68	0.177
WEEK 4	79	-23.8	+/-	2.87	79	-13.1	+/-	2.75	0.008
WEEK 6	76	-25.3	+/-	2.87	72	-18.0	+/-	2.93	0.077
WEEK 8	70	-32.1	+/-	3.33	68	-18.4	+/-	3.09	0.003
WEEK 10	66	-36.2	+/-	3.63	67	-17.3	+/-	3.21	0.000
WEEK 12	63	-35.6	+/-	3.63	65	-19.2	+/-	3.24	0.001
ENDPOINT	90	-28.1	+/-	2.77	88	-16.1	+/-	2.85	0.003

Individual study means are adjusted for treatment, site, treatment-by-site, and baseline values.

Table VIII.L.1 Concomitant Medications Allowed and Not Allowed in Completed Controlled Studies

	P.R.N.	Chronic
Allopurinol (specified in 640/641 only)	Y	Y
Analgesics (non-narcotic); (chronic use not permitted in 640/641)	Y	Y
Anesthetics (specified in 671/682 only)		
General	N	N
Local	Y	N
Anorexics	N	N
Antacids (except cisapride in 671/682); (chronic use not permitted in 640/641)	Y	Y
Anti-inflammatory drugs (except Indocin and systemic corticosteroids); (sulindac not permitted in 640/641)	Y	Y*
Antianginal agents (permitted in 640/641 if taken for 6 mos at stable dose)	N	N
Antiarrhythmics	N	N
Antiasthma agents	Y	Y
Antibiotics	Y	Y[a]
Anticoagulants (only aspirin max. 5 gr/day for chronic use)	Y	Y
Anxiolytics	N	N
Anticonvulsants	N	N
Antidepressants	N	N
Antidiarrheal agents (only loperamide HCl, Kaolin preparations and Pepto-Bismol in 671/682)	Y	N
Antifungal Agents (only specified in 671/682)		
Systemic	N	N
Topical	Y	Y
Antihistamines (only cetirizine and loratidine in 671/682); (only terfenadine and astemizole in 640/641, and no chronic dosing)	Y	Y[a]
Antihypertensives	N	Y[b]**
Antinauseants	Y[c]	N
Antipsychotics	N	N
Antiviral agents (only acyclovir; specified in 671/682 only)	Y	Y*
Colchicine (specified in 640/641 only)	Y	Y
Cough/Cold preparations: 640/641: only products without pseudoephedrine, phenylpropanolamine, or narcotic decongestants were permitted, and for episodic use only. 671/682: cetirizine and loratidine were permitted for episodic use. Narcotic decongestants were not permitted. Other cough and cold preparations were restricted to use 3 days per week. The Pfizer clinician was to be called regarding chronic use.	see text	see text
Diuretics	Y[e]*	Y*
H2 Blockers (640/641: ranitidine only, and no episodic use; 671/682: cimetidine not permitted)	Y	Y**
Hormones	N	Y[f]**
Hormone Suppressants (specified in 671/682 only; only finasteride allowed)	N	Y**
Hypoglycemic agents (oral hypoglycemic agents only)	N	Y**
Hypolipidemics (specified in 671/682 only: only statins allowed)	N	Y**
Insulin	N	N
Laxatives (only fiber products and Colace)	Y	Y*
Muscle Relaxants (specified in 671/682 only)	N	N

Table VIII.L.1 (cont.)

Psychotropic drugs not otherwise specified	N	N
Sedatives/hypnotics	N[9]	N
Steroids (for 671/682 only; no steriods allowed in 640/641)		
Systemic	N	N
Topical	Y	Y
Inhalant	Y	N
Tryptophan (640/641 expressly not allowed)	N	N
Vaccines (specified in 671/682 only)	Y	N/A

Table VII.F.1 Summary of Analysis of Treatment by Sex Interaction Effect for Studies 640 and 671. The table contains the least-square changes from baseline to endpoint, the p-values for the treatment effect in men and women and the p value for the treatment x sex interaction effect.

Variable	Women			Men			
	Sertraline (N=152)	Placebo (N=139)	p[1]	Sertraline (N=39)	Placebo (N=55)	p[1]	p[2]
CAPS-2 Total	-34.34	-22.50	0.0001	-29.04	-29.13	0.99	0.041
CAPS-B	-7.67	-5.52	0.005	-5.92	-7.09	0.39	0.033
CAPS-C	-15.32	-9.13	0.0001	-12.81	-12.08	0.76	0.052
CAPS-D	-11.26	-7.69	0.0007	-10.38	-10.50	0.95	0.088
CAPS-AF	-10.45	-6.91	0.002	-11.58	-8.36	0.12	0.89
Davidson Total	-32.16	-16.40	0.0001	-24.45	-24.63	0.97	0.009
DAV-B	-6.27	-3.53	0.0009	-4.76	-5.26	0.74	0.056
DAV-C	-13.74	-6.33	0.0001	-10.72	-10.51	0.93	0.013
DAV-D	-12.24	-6.35	0.0001	-8.79	-9.82	0.62	0.004
IES Total	-18.46	-12.85	0.001	-16.05	-15.30	0.80	0.16
IES-B	-8.82	-6.05	0.003	-7.00	-7.81	0.62	0.059
IES-C	-9.65	-6.69	0.003	-8.98	-7.80	0.51	0.38
CGI Improvement	2.36	2.96	0.0001	2.49	2.73	0.34	0.22
HAM-D Total[3]	-8.24	-4.95	0.005	-6.49	-7.34	0.69	0.088
	(N=121)	(N=111)		(N=28)	(N=46)		

1. p value for treatment effect within men and women.
2. p value for treatment x sex interaction
3. N's = no. of subjects with baseline and endpoint HAM-D.

SAFETY TABLES

PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682

ALL SAFETY ANALYZABLE SUBJECTS

TABLE VIII.F INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES

Sertraline			Placebo					
ABN	%	ALL	ABN	%				ALL
GROUP	PARAMETER				UNITS	CRITERIA		
	HEMATOLOGY							
	HCT(HEMATOCRIT)				%	<=	32(F) 37(M)	
3	0.9	327	3	0.9				318
	HGB(HEMOGLOBIN)				g/dl	<=	9.5(F) 11.5(M)	
1	0.3	327	1	0.3				319
	WBC (WHITE BLOOD COUNT)				X 10 3	<=	2.8	
1	0.3	327	0	0.0				319
						>=	16	
2	0.6	327	0	0.0				319
	RBC (RED BLOOD CELLS)				X 10 6	<=	3	
0	0.0	327	0	0.0				319
						>=	6	
1	0.3	327	2	0.6				319
	NEUTROPHILS				%	<=	15	
0	0.0	327	0	0.0				319
	EOSINOPHILS				%	>=	10	
2	0.6	327	1	0.3				319
	PLATELETS				X 10 3	<=	75	
0	0.0	327	0	0.0				320
						>=	700	
0	0.0	327	0	0.0				320
	SERUM CHEMISTRY							
	SGOT UNITS				U/L	>=	3.0 X ULN	
2	0.6	328	1	0.3				320
	SGPT UNITS				U/L	>=	3.0 X ULN	
4	1.3	328	2	0.6				320
	ALK PHOSPHATASE				U/L	>=	3.0 X ULN	
0	0.0	328	0	0.0				321
	T/PROTEIN				g/dl	<=	4.5	
0	0.0	328	0	0.0				321

0	0.0	328	0	0.0				
			ALBUMIN		g/dl	<=	3.5	320
15	4.7	328	22	6.7				
						>=	6.5	320
0	0.0	328	0	0.0				
			RANDOM GLUCOSE		mg/dl	>=	140	320
16	5.0	328	21	6.4				
			T/BILIRUBIN		mg/dl	>=	2	320
1	0.3	328	2	0.6				
			BUN		mg/dl	>=	30	321
0	0.0	328	1	0.3				
			CREATININE		mg/dl	>=	2	321
0	0.0	328	0	0.0				
			CHOLESTEROL		mg/dl	>=	330	321
3	0.9	328	2	0.6				
			URIC ACID		mg/dl	>=	8.5(F) 10.5(M)	321
1	0.3	328	1	0.3				
			URINALYSIS					
			GLUCOSE:URINE			>=	2	320
1	0.3	328	3	0.9				
			PROTEIN:URINE			>=	2	319
4	1.3	328	4	1.2				

PROGRAM NAME: T90101 BY DEG

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PROTOCOL: PROTOCOLS 0640, 0641, 0671,_0682
ALL SAFETY ANALYZABLE SUBJECTS

TABLE VIII.G **INCIDENCE OF CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS**

NUMBER AND % OF SUBJECTS SPECIFIED CHANGE(2)

PARAMETER	CRITERION VALUE	CHANGE RELATIVE TO BASELINE	NUMBER TESTED(1) SERTRALINE	NUMBER TESTED(1) PLACEBO	WITH SERTRALINE	WITH PLACEBO	P-VALUE(3)
SITTING SYSTOLIC BP	>=180 MMHG	INCREASE >=20	370	368	2	0.5%	1.000
	<= 90 MMHG	DECREASE >=20	370	368	12	3.2%	0.074
SITTING DIASTOLIC BP	>=105 MMHG	INCREASE >=15	370	368	2	0.5%	0.450
	<= 50 MMHG	DECREASE >=15	370	368	2	0.5%	0.450
SITTING HEART RATE	>=120 BPM	INCREASE >=15	370	368	0	0.0%	0.499
	<= 50 BPM	DECREASE >=15	370	368	2	0.5%	1.000

(1) TOTAL NUMBER OF SUBJECTS FOR WHOM EACH VITAL SIGN ASSESSMENT WAS AVAILABLE AT BASELINE AND AT LEAST ONE FOLLOW-UP TIME.
(2) NUMBER AND % OF SUBJECTS FOR WHOM ONE OR MORE FOLLOW-UP VALUE MEETS THE CRITERION.
(3) COMPARISON OF INCIDENCE RATES USING THE FISHER'S EXACT TEST (TWO-TAILED).

NOTE: IN ORDER TO BE IDENTIFIED, A VALUE MUST MEET THE CRITERION VALUE AND ALSO REPRESENT A CHANGE OF AT LEAST
THE MAGNITUDE NOTED IN THE CHANGE COLUMN.

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PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682
ALL SAFETY ANALYZABLE SUBJECTS

TABLE VIII.H **INCIDENCE OF CLINICALLY SIGNIFICANT CHANGES IN BODY WEIGHT**

CHANGE	NUMBER AND % OF SUBJECTS WITH SPECIFIED CHANGE			
	SERTRALINE		PLACEBO	
P-VALUE**	N=(370)*		N=(367)*	
INCREASE (>=7% ABOVE BASELINE)	2	0.5%	7	1.9%
0.1060				
DECREASE (>=7% BELOW BASELINE)	13	3.5%	9	2.4%
0.5170				

* TOTAL NUMBER OF SUBJECTS FOR WHOM BODY WEIGHT DATA WAS AVAILABLE AT BASELINE AND AT LEAST ONE FOLLOW-UP TIME.

** COMPARISON OF INCIDENCE RATES USING THE FISHER'S EXACT TEST (TWO-TAILED).

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PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682
ALL SAFETY ANALYZABLE SUBJECTS

TABLE VIII.I INCIDENCE OF CHANGES FROM BASELINE IN ECG

BASELINE/FOLLOW-UP P-VALUE*	NUMBER OF SUBJECTS (%) SERTRALINE		PLACEBO	
	(N=307)		(N=306)	
NORMAL /NORMAL	202	(65.8%)	204	(66.7%)
NORMAL /ABNORMAL 0.888	29	(9.4%)	28	(9.2%)
ABNORMAL/NORMAL	21	(6.8%)	25	(8.2%)
ABNORMAL/ABNORMAL	55	(17.9%)	49	(16.0%)

NOTE: INCIDENCES FOR ALL VISITS WERE SUMMARIZED.
SUBJECT REQUIRED A BASELINE ECG AND AT LEAST ONE ADDITIONAL ECG IN ORDER TO BE INCLUDED IN THE SUMMARY.

* FISHER'S EXACT TEST (TWO-TAILED) WAS USED TO COMPARE THE PROPORTION OF SUBJECTS IN EACH GROUP WHO HAD A NORMAL BASELINE ECG AND AT LEAST ONE ABNORMAL FOLLOW-UP ECG.

TABLE 9.2: PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682
STUDY: ALL COMPLETED STUDIES

LABORATORY TEST CHANGES FROM BASELINE TO FINAL VALUE

LABORATORY TEST	SERTRALINE BASELINE N	SERTRALINE BASELINE MEAN	SERTRALINE CHANGE FROM BASELINE MEAN	SERTRALINE CHANGE FROM BASELINE S.E.	PLACEBO BASELINE N	PLACEBO BASELINE MEAN	PLACEBO CHANGE FROM BASELINE MEAN	PLACEBO CHANGE FROM BASELINE S.E.	GROUP COMPARISON P-VALUE
HEMATOLOGY									
HCT(HEMATOCRIT)	317	42.11	-0.15	0.15	323	42.85	-0.47	0.16	0.141
HGB(HEMOGLOBIN)	318	14.12	-0.06	0.04	324	14.34	-0.09	0.04	0.623
WBC (WHITE BLOOD COUNT)	318	7.37	0.14	0.09	324	7.29	-0.22	0.09	0.006
RBC (RED BLOOD CELLS)	318	4.67	-0.01	0.01	324	4.72	-0.05	0.01	0.043
NEUTROPHILS	318	60.22	1.72	0.47	323	60.22	-0.70	0.51	0.001
EOSINOPHILS	318	2.17	0.19	0.09	323	2.06	0.23	0.09	0.714
PLATELETS	319	262.31	-5.66	2.21	324	255.75	-1.84	1.97	0.197
SERUM CHEMISTRY									
SGOT UNITS	320	20.75	3.11	0.63	327	20.53	-0.13	0.37	0.000
SGPT UNITS	320	30.39	4.50	1.30	327	29.60	0.67	0.67	0.009
ALK PHOSPHATASE	321	72.68	5.10	0.79	327	75.29	-1.43	0.59	0.000
T/PROTEIN	321	7.33	-0.02	0.02	327	7.34	-0.10	0.02	0.026
ALBUMIN	320	4.14	-0.02	0.01	327	4.16	-0.08	0.01	0.002
RANDOM GLUCOSE	320	92.33	1.44	1.44	327	91.97	2.94	1.18	0.420
T/BILIRUBIN	315	0.52	-0.04	0.01	326	0.54	-0.02	0.01	0.150
BUN	321	12.38	0.22	0.19	327	12.58	0.20	0.17	0.920
CREATININE	321	0.81	-0.00	0.01	327	0.82	0.00	0.01	0.719
CHOLESTEROL	321	200.35	13.31	1.49	327	199.01	-2.90	1.43	0.000
URIC ACID	321	4.61	-0.42	0.04	327	4.82	-0.02	0.04	0.000

THE CHANGE FROM BASELINE MEAN WAS COMPUTED ON THE CHANGE FROM BASELINE TO FINAL VISIT VALUE FOR EACH SUBJECT.

PROGRAM: T0902 SAS by DEG
DATE : 12MAY98 TIME: 17:00

PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682
STUDY: ALL COMPLETED STUDIES

TABLE 11.1: INCIDENCE OF CHANGES FROM BASELINE IN ECG

BASELINE/FOLLOW-UP	NUMBER OF SUBJECTS (%) SERTRALINE (N=307)	PLACEBO (N=306)	P-VALUE*
NORMAL /NORMAL	202 (65.8%)	204 (66.7%)	
NORMAL /ABNORMAL	29 (9.4%)	28 (9.2%)	0.888
ABNORMAL/NORMAL	21 (6.8%)	25 (8.2%)	
ABNORMAL/ABNORMAL	55 (17.9%)	49 (16.0%)	

NOTE: INCIDENCES FOR ALL VISITS WERE SUMMARIZED.
SUBJECT REQUIRED A BASELINE ECG AND AT LEAST ONE ADDITIONAL ECG IN ORDER TO BE INCLUDED IN THE SUMMARY.

* FISHER'S EXACT TEST (TWO-TAILED) WAS USED TO COMPARE THE PROPORTION OF SUBJECTS IN EACH GROUP WHO HAD A NORMAL BASELINE ECG AND AT LEAST ONE ABNORMAL FOLLOW-UP ECG.

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PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682
STUDY: ALL COMPLETED STUDIES

TABLE 10.3: VITAL SIGNS AND BODY WEIGHT CHANGES FROM BASELINE TO FINAL VALUE

	SERTRALINE						PLACEBO							
VITAL SIGN	N*	MEAN BASELINE VALUE	CHANGE FROM BASELINE MEAN	S.D.	MIN	MAX	N*	MEAN BASELINE VALUE	CHANGE FROM BASELINE MEAN	S.D.	MIN	MAX	P-VALUE** OF MEAN BASELINE	P-VALUE** OF MEAN CHANGES
SITTING SYSTOLIC BP MMHG	370	118.47	-0.06	11.76	-48.0	40.0	368	118.72	-1.19	11.19	-40.0	34.0	0.7749	0.2875
SITTING DIASTOLIC BP MMHG	370	76.87	-0.94	8.96	-24.0	30.0	368	77.14	-0.86	7.88	-21.0	20.0	0.6385	0.8011
SITTING HEART RATE BPM	370	73.29	-0.99	10.72	-35.0	36.0	368	72.43	1.31	10.41	-30.0	40.0	0.3883	0.0083
BODY WEIGHT LB.(1)	370	175.92	-1.87	5.57	-27.0	18.5	367	176.23	0.04	5.52	-41.0	20.6	0.7430	0.0001

* TOTAL NUMBER OF SUBJECTS FOR WHOM EACH VITAL SIGN ASSESSMENT WAS AVAILABLE AT BASELINE AND AT LEAST ONE FOLLOW-UP TIME.
** COMPARISONS OF BASELINE VALUES AND CHANGE FROM BASELINE USING THE WILCOXON RANK SUM TEST.
(1) ALL BODY WEIGHT DATA ENTERED IN KG WAS CONVERTED TO LB.

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DATE : 29JUN98 TIME: 9:36

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PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682
STUDY: ALL COMPLETED STUDIES

TABLE 10.3: VITAL SIGNS AND BODY WEIGHT CHANGES FROM BASELINE TO FINAL VALUE

	SERTRALINE						PLACEBO							
		MEAN	CHANGE FROM BASELINE					MEAN	CHANGE FROM BASELINE				P-VALUE**	P-VALUE**
VITAL SIGN	N*	BASELINE VALUE	MEAN	S.D.	MIN	MAX	N*	BASELINE VALUE	MEAN	S.D.	MIN	MAX	OF MEAN BASELINE	OF MEAN CHANGES
SITTING SYSTOLIC BP MMHG	370	118.47	-0.06	11.76	-48.0	40.0	368	118.72	-1.19	11.19	-40.0	34.0	0.7749	0.2875
SITTING DIASTOLIC BP MMHG	370	76.87	-0.94	8.96	-24.0	30.0	368	77.14	-0.86	7.88	-21.0	20.0	0.6385	0.8011
SITTING HEART RATE BPM	370	73.29	-0.99	10.72	-35.0	36.0	368	72.43	1.31	10.41	-30.0	40.0	0.3883	0.0083
BODY WEIGHT LB.(1)	370	175.92	-1.87	5.57	-27.0	18.5	367	176.23	0.04	5.52	-41.0	20.6	0.7430	0.0001

* TOTAL NUMBER OF SUBJECTS FOR WHOM EACH VITAL SIGN ASSESSMENT WAS AVAILABLE AT BASELINE AND AT LEAST ONE FOLLOW-UP TIME.
** COMPARISONS OF BASELINE VALUES AND CHANGE FROM BASELINE USING THE WILCOXON RANK SUM TEST.
(1) ALL BODY WEIGHT DATA ENTERED IN KG WAS CONVERTED TO LB.

PROGRAM: T:\HOME\JEANMLAY\PC\SERT\PTSD\SPTSVITL.SAS
DATE : 29JUN98 TIME: 9:36

SERIOUS ADVERSE EVENTS

TABLE 6
SERTRALINE PTSD SUBMISSION
ALL CAUSALITIES
REPORTING PERIOD: CUMULATIVE THROUGH 26FEB98

AEM CASE NO./ (a) PATIENT IDENTIFIER	COUNTRY	SEX	AGE	RACE	WEIGHT (KG)	TOTAL DAILY DOSE (b)	EVENT ONSET DAY (c)	THER-APY STOP DAY	EVENT TERM	ACTION TAKEN	INVESTIGATOR CAUSALITY	OUTCOME(d)
TREATMENT: Sertraline Hydrochloride												
PHARMACEUTICALS												
9500811 N-0640 061 93-N-0169	US	F	39	W	77.0	50.00 MG	57	53	DELIRIUM; ATAXIC	DOSE PERMANENTLY STOPPED	OTHER ILLNESS (Multiple sclerosis.)	UNKNOWN HOSPITALI-ZATION
9511820 N-0640 176 94-N-0177	US	F	39	W	72.5	425.00 MG	4	4	AGITATION	DOSE PERMANENTLY STOPPED	DISEASE UNDER STUDY	RESOLVED HOSPITALI-ZATION
9407747 N-0641 510 93-N-0173	US	M	44	O	71.0	200.00 MG	58	78	HOMICIDAL IDEATION	NO ACTION TAKEN	OTHER (Social stressor)	RESOLVED HOSPITALI-ZATION
9410385 N-0641 565 93-N-0180	US	M	46	W	92.0	25.00 MG	6	5	SUICIDAL IDEATION	DOSE PERMANENTLY STOPPED	OTHER (Stressors in patient's life)	RESOLVED HOSPITALI-ZATION
9510882 N-0641 588 93-N-0177	US	M	51	W	84.8	25.00 MG	3	2	RIGHT RADIAL HEAD FRACTURE; LOSS OF CONSCIOUSNESS	DOSE PERMANENTLY STOPPED	OTHER ILLNESS (Probable vasovagal episode)	DISABILITY HOSPITALI-ZATION

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
(i) Inpatient hospitalization or (ii) Prolongation of hospital stay
ND = NOT DONE
N/A = NOT AVAILABLE
RACE KEY: W = WHITE A = ASIAN
B = BLACK O = OTHER

TABLE 6
SERTRALINE PTSD SUBMISSION
ALL CAUSALITIES
REPORTING PERIOD: CUMULATIVE THROUGH 26FEB98

AEM CASE NO./ (a) PATIENT IDENTIFIER	COUNTRY	SEX	AGE	RACE	WEIGHT (KG)	TOTAL DAILY DOSE (b)	EVENT ONSET DAY (c)	THER-APY STOP DAY	EVENT TERM	ACTION TAKEN	INVESTIGATOR CAUSALITY	OUTCOME(d)
TREATMENT: Sertraline Hydrochloride												
PHARMACEUTICALS												
9705197 N-0671 0183 95-N-0074	US	F	38	W	70.8	50.00 MG	32	13	SUICIDE ATTEMPT	POST THERAPY EVENT - DRUG PREVIOUSLY DISCONTINUED	OTHER ILLNESS (Alcohol abuse)	RESOLVED HOSPITALI-ZATION
9704544 N-0672 7025 95-N-0087	US	F	48	W	105.2	200.00 MG	174	N/A	INCISIONAL HERNIA	NO ACTION TAKEN	OTHER (HERNIA)	RESOLVED HOSPITALI-ZATION
9703602 N-0672 8012 96-N-0058	US	F	32	B	169.2	50.00 MG	7	N/A	SHORTNESS OF BREATH; CHEST PAIN	NO ACTION TAKEN	DISEASE UNDER STUDY	RESOLVED HOSPITALI-ZATION
9716299 N-0672 8012 96-N-0058	US	F	32	B	139.3	50.00 MG	166	165	NEW ONSET OF ASTHMA; ANGIOEDEMA; PHARYNGEAL CONSTRICTION	DOSE PERMANENTLY STOPPED	CONCOMITANT TREATMENT (LOTENSIN)	RESOLVED HOSPITALI-ZATION
9713924 N-0672 8020 96-N-0054	US	F	25	W	107.9	200.00 MG	44	N/A	RIGHT OVARIAN CYST	DOSE TEMPORARILY STOPPED	OTHER ILLNESS (RECURRENT OVARIAN CYST)	RESOLVED HOSPITALI-ZATION

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
(i) Inpatient hospitalization or (ii) Prolongation of hospital stay

ND = NOT DONE
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RACE KEY: W = WHITE A = ASIAN
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SERIOUS ADVERSE EVENTS

TABLE 6
SERTRALINE PTSD SUBMISSION
ALL CAUSALITIES
REPORTING PERIOD: CUMULATIVE THROUGH 26FEB98

AEM CASE NO./ (a) PATIENT IDENTIFIER	COUNTRY	SEX	AGE	RACE	WEIGHT (KG)	TOTAL DAILY DOSE (b)	EVENT ONSET DAY (c)	THERAPY STOP DAY	EVENT TERM	ACTION TAKEN	INVESTIGATOR CAUSALITY	OUTCOME(d)
TREATMENT: Sertraline Hydrochloride												
PHARMACEUTICALS												
9709099 N-0672 8041 96-N-0061	US	F	30	B	88.0	100.00 MG	115	N/A	BREAST REDUCTION SURGERY	NO ACTION TAKEN	OTHER (Large breast)	RESOLVED HOSPITALIZATION
9717764 N-0672 8123 96-N-0057	US	F	40	W	89.4	50.00 MG	7	N/A	BASAL CELL CARCINOMA OF THE RIGHT LOWER EYELID	NO ACTION TAKEN	OTHER ILLNESS (basal cell carcinoma)	EVENT STILL PRESENT, BETTER THAN ONSET
9728606 N-0672 8123 96-N-0057	US	F	41	W	90.7	100.00 MG	136	N/A	BONE GRAFT OF THE LEFT HUMERUS; REMOVAL AND REPLACEMENT INTRAMEDULLARY ROD	NO ACTION TAKEN	OTHER (MOTOR VEHICLE ACCIDENT)	RESOLVED HOSPITALIZATION
9718413 N-0682 151 96-N-0040	US	F	24	W	53.2	200.00 MG	95	84	SUICIDAL IDEATION	POST THERAPY EVENT - TREATMENT PERIOD COMPLETED	DISEASE UNDER STUDY	RESOLVED HOSPITALIZATION

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
(i) Inpatient hospitalization or (ii) Prolongation of hospital stay

ND = NOT DONE
N/A = NOT AVAILABLE
RACE KEY: W = WHITE A = ASIAN B = BLACK O = OTHER

SERIOUS ADVERSE EVENTS

TABLE 6
SERTRALINE PTSD SUBMISSION
ALL CAUSALITIES
REPORTING PERIOD: CUMULATIVE THROUGH 26FEB98

AEM CASE NO./ (a) PATIENT IDENTIFIER	COUNTRY	SEX	AGE	RACE	WEIGHT (KG)	TOTAL DAILY DOSE (b)	EVENT ONSET DAY (c)	THERAPY STOP DAY	EVENT TERM	ACTION TAKEN	INVESTIGATOR CAUSALITY	OUTCOME(d)
TREATMENT: Sertraline Hydrochloride												
PHARMACEUTICALS												
9724689 N-0682 207 97-N-0053	US	F	58	W	73.9	150.00 MG	62	88	CHOLECYSTITIS	NO ACTION TAKEN	OTHER ILLNESS (CHOLECYSTOLITHIASIS)	RESOLVED HOSPITALIZATION
TREATMENT: Blinded Therapy												
PHARMACEUTICALS												
9615371 STL-AUS-94-001 008 00127	AUSTRALIA	M	48	W	93.0	N/A	24	23	ATRIAL FIBRILLATION; PALPITATIONS	DOSE TEMPORARILY STOPPED	OTHER (unknown-possibly cardiac problem)	RESOLVED HOSPITALIZATION
9706158 STL-AUS-94-001 029 00545	AUSTRALIA	F	29	W	65.0	N/A	N/A	N/A	OVARIAN CYST	DOSE TEMPORARILY STOPPED	OTHER ILLNESS (Ovarian Cyst)	RESOLVED HOSPITALIZATION
9616277 STL-AUS-94-001 145 00128	AUSTRALIA	F	33	W	ND	N/A	6	7	SUICIDAL IDEATION, PROGRESSION OF; FEELINGS OF HOPELESSNESS; FEELINGS OF HELPLESSNESS	DOSE PERMANENTLY STOPPED	DISEASE UNDER STUDY	EVENT STILL PRESENT, BETTER THAN ONSET HOSPITALIZATION

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
(i) Inpatient hospitalization or (ii) Prolongation of hospital stay

ND = NOT DONE
N/A = NOT AVAILABLE
RACE KEY: W = WHITE A = ASIAN B = BLACK O = OTHER

SERIOUS ADVERSE EVENTS

TABLE 6
SERTRALINE PTSD SUBMISSION
ALL CAUSALITIES
REPORTING PERIOD: CUMULATIVE THROUGH 26FEB98

AEM CASE NO./ (a) PATIENT IDENTIFIER	COUNTRY	SEX	AGE	RACE	WEIGHT (KG)	TOTAL DAILY DOSE (b)	EVENT ONSET DAY (c)	THERAPY STOP DAY	EVENT TERM	ACTION TAKEN	INVESTIGATOR CAUSALITY	OUTCOME(d)
TREATMENT: Double Blind Study Drug												
PHARMACEUTICALS												
9716632 N-0703 1049 96-N-0192	US	F	32	W	60.8	N/A	60	29	FETAL DEATH	POST THERAPY EVENT - DRUG PREVIOUSLY DISCONTINUED	OTHER (Unknown, not study drug related.)	RESOLVED
9802075 N-0703 1054 96-N-0199	US	M	48	W	97.1	N/A	199	N/A	POWER SAW INJURY TO LEFT DORSAL HAND	NO ACTION TAKEN	OTHER (Accidental trauma)	RESOLVED HOSPITALIZATION
TREATMENT: Placebo												
PHARMACEUTICALS												
9405385 N-0641 557 93-N-0179	US	M	47	W	104.0	0.00 MG	43	84	SUICIDAL IDEATION	NO ACTION TAKEN	DISEASE UNDER STUDY	RESOLVED HOSPITALIZATION
9606407 N-0641 594 93-N-0175	US	M	25	W	73.5	0.00 MG	22	21	ADJUSTMENT REACTION	POST THERAPY EVENT - DRUG PREVIOUSLY DISCONTINUED	DISEASE UNDER STUDY	RESOLVED HOSPITALIZATION

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
(i)Inpatient hospitalization or (ii)Prolongation of hospital stay

ND = NOT DONE
N/A = NOT AVAILABLE
RACE KEY: W = WHITE A = ASIAN B = BLACK O = OTHER

TABLE 6
SERTRALINE PTSD SUBMISSION
ALL CAUSALITIES
REPORTING PERIOD: CUMULATIVE THROUGH 26FEB98

AEM CASE NO./ (a) PATIENT IDENTIFIER	COUNTRY	SEX	AGE	RACE	WEIGHT (KG)	TOTAL DAILY DOSE (b)	EVENT ONSET DAY (c)	THERAPY STOP DAY	EVENT TERM	ACTION TAKEN	INVESTIGATOR CAUSALITY	OUTCOME (d)
TREATMENT: Placebo												
PHARMACEUTICALS												
9607452 N-0641 698 93-N-0174	US	F	34	W	91.6	0.00 MG	45	50	EXACERBATION OF BRONCHIAL ASTHMA	DOSE PERMANENTLY STOPPED	OTHER ILLNESS (Pre-existing bronchial asthma)	RESOLVED HOSPITALIZATION
9617762 N-0671 014 95-N-0064	US	F	32	W	108.9	0.00 MG	35	32	HIVES	DOSE PERMANENTLY STOPPED	OTHER (Xylocaine)	RESOLVED HOSPITALIZATION
9701420 N-0682 0042 96-N-0047	US	F	39	W	101.6	0.00 MG	25	25	GANGRENE, LEFT HAND; HEMORRHAGE	DOSE PERMANENTLY STOPPED	OTHER (Impaired blood flow in left hand 2nd to smoking)	EVENT STILL PRESENT, BETTER THAN ONSET HOSPITALIZATION

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
(i) In-patient hospitalization or (ii) Prolongation of hospital stay

ND = NOT DONE
N/A = NOT AVAILABLE

RACE KEY: W = WHITE A = ASIAN
B = BLACK O = OTHER

PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682
STUDY: ALL COMPLETED STUDIES

TABLE 5.2.1 : LIST OF SERTRALINE SAFETY ANALYZABLE SUBJECTS WHO DISCONTINUED DUE TO MEDICAL REASONS*

TREATMENT GROUP: SERTRALINE

SITE	SUBJECT	SEX	AGE (YRS)	DOSE AT TIME OF WITHDRAWAL (MG/DAY)	DURATION OF THERAPY(DAYS)	REASON
PROTOCOL: 0640						
93N0165	29	F	26	100	46	ADVERSE EVENT
93N0168	122	F	52	25	5	ADVERSE EVENT
93N0169	61	F	39	50	53	ADVERSE EVENT
93N0170	118	F	34	25	8	ADVERSE EVENT
93N0171	77	F	42	50	27	ADVERSE EVENT
93N0185	11	F	43	25	13	ADVERSE EVENT
94N0157	100	M	62	50	41	ADVERSE EVENT
94N0158	109	F	40	50	29	ADVERSE EVENT
94N0177	176	F	39	425	4	ADVERSE EVENT
PROTOCOL: 0641						
93N0172	507	F	29	50	25	ADVERSE EVENT
93N0172	655	M	25	25	12	ADVERSE EVENT
93N0172	657	F	39	25	14	ADVERSE EVENT
93N0172	670	M	42	100	42	ADVERSE EVENT
93N0172	671	F	29	25	7	ADVERSE EVENT
93N0173	666	M	51	25	11	ADVERSE EVENT
93N0176	540	M	52	150	49	ADVERSE EVENT
93N0177	575	M	58	150	31	ADVERSE EVENT
93N0177	588	M	51	25	2	ADVERSE EVENT
93N0180	565	M	46	25	5	ADVERSE EVENT
94N0175	608	M	49	100	21	ADVERSE EVENT
PROTOCOL: 0671						
95N0061	78	F	49	50	20	ADVERSE EVENT
95N0065	125	F	51	150	57	ADVERSE EVENT
95N0074	48	F	40	50	43	ADVERSE EVENT
95N0075	51	F	53	25	8	ADVERSE EVENT

*MEDICAL REASONS: ADVERSE EVENT,LABORATORY ABNORMALITY,OTHER:PREGNANCY

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PROTOCOL: PROTOCOLS 0640, 0641, 0671, 0682
STUDY: ALL COMPLETED STUDIES

TABLE 5.2.1 : LIST OF SERTRALINE SAFETY ANALYZABLE SUBJECTS WHO DISCONTINUED DUE TO MEDICAL REASONS*

TREATMENT GROUP: SERTRALINE

SITE	SUBJECT	SEX	AGE (YRS)	DOSE AT TIME OF WITHDRAWAL (MG/DAY)	DURATION OF THERAPY(DAYS)	REASON
95N0053	53	F	30	150	31	ADVERSE EVENT
PROTOCOL: 0682						
96N0040	22	M	30	50	42	ADVERSE EVENT
96N0041	112	F	35	50	12	ADVERSE EVENT
96N0042	101	F	29	50	11	ADVERSE EVENT
96N0043	124	F	38	150	58	ADVERSE EVENT
96N0047	46	F	50	50	19	ADVERSE EVENT
96N0049	81	F	35	50	14	ADVERSE EVENT
97N0052	195	F	23	100	20	ADVERSE EVENT
PROTOCOL: 0640						
93N0165	27	F	36	150	47	LABORATORY ABNORMALITY
93N0184	230	M	48	200	47	LABORATORY ABNORMALITY
PROTOCOL: 0671						
95N0062	69	F	32	150	51	LABORATORY ABNORMALITY
95N0065	124	F	37	150	44	LABORATORY ABNORMALITY
95N0074	183	F	37	50	13	LABORATORY ABNORMALITY
PROTOCOL: 0640						
93N0168	52	F	20	25	2	OTHER:PREGNANCY

*MEDICAL REASONS: ADVERSE EVENT,LABORATORY ABNORMALITY,OTHER:PREGNANCY

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Statistical Review and Evaluation

SEP 27 1999

NDA Number:	19-839
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 atment 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

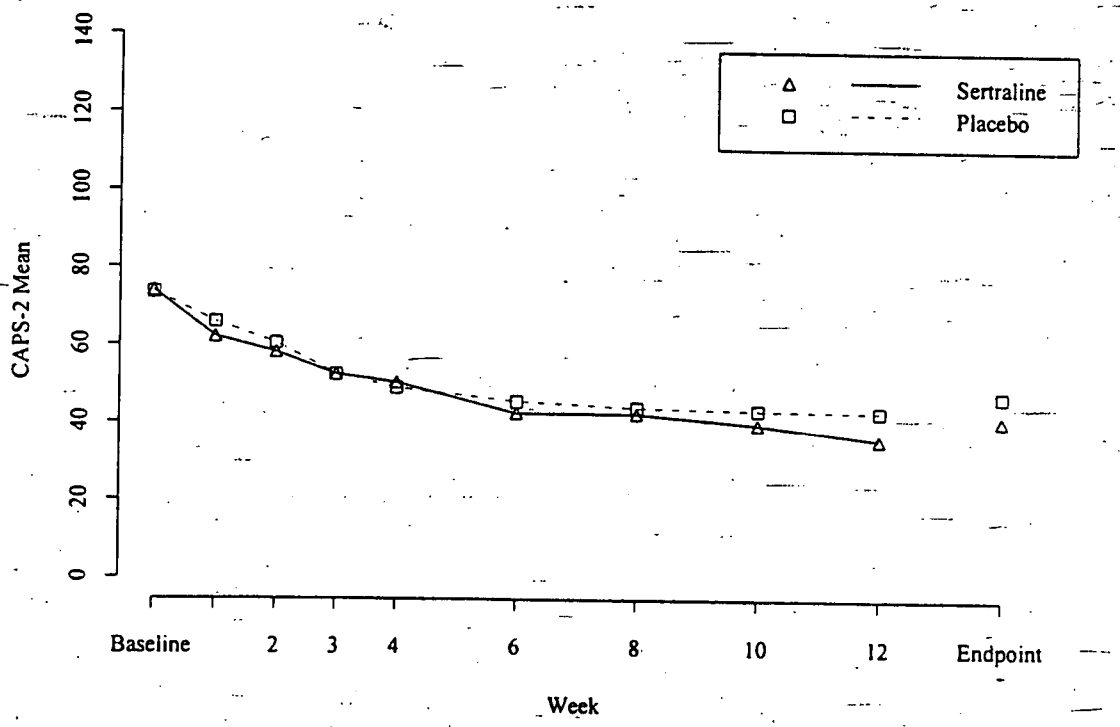

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Figure 2. IES graph for Study 640

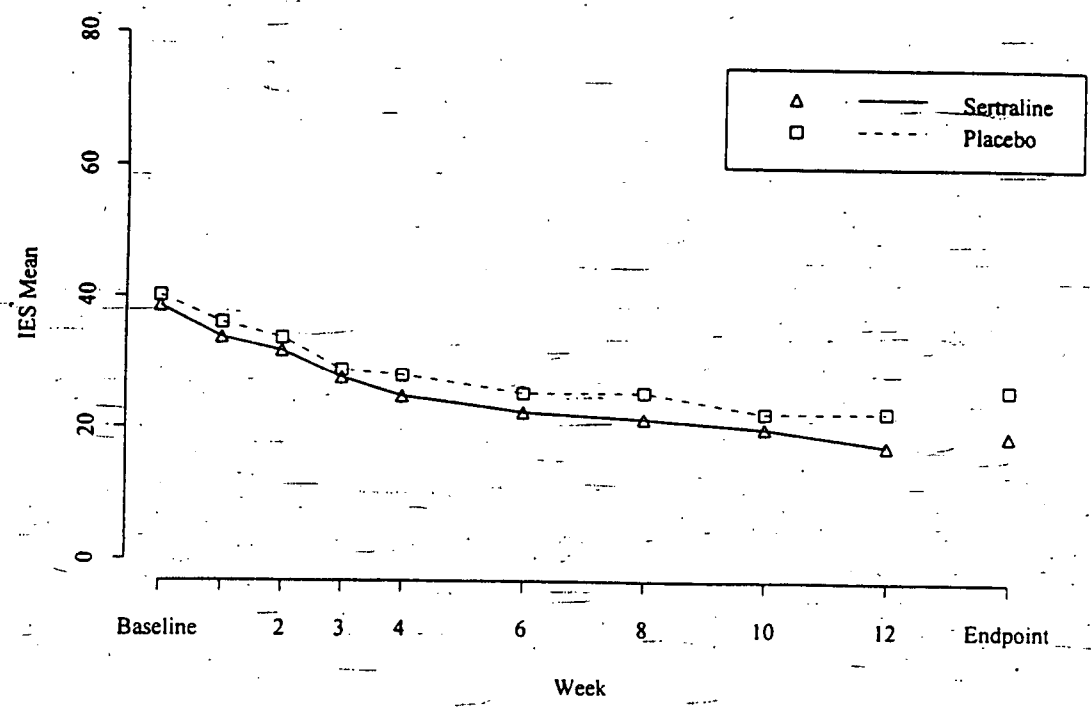


Figure 3. CGI-S graph for Study 640

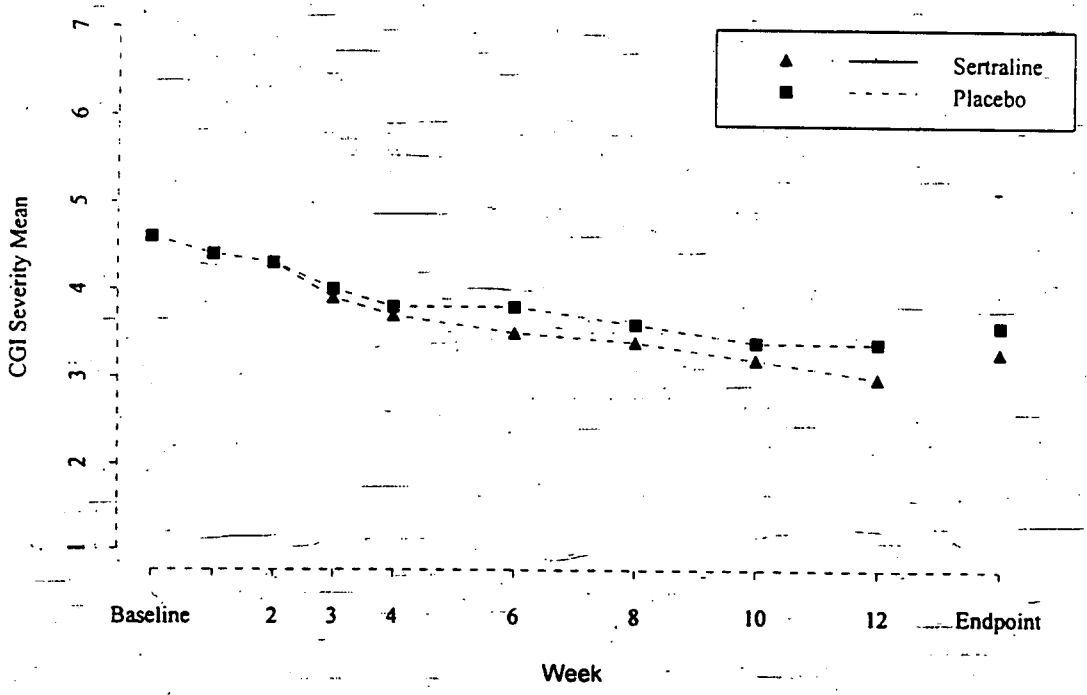
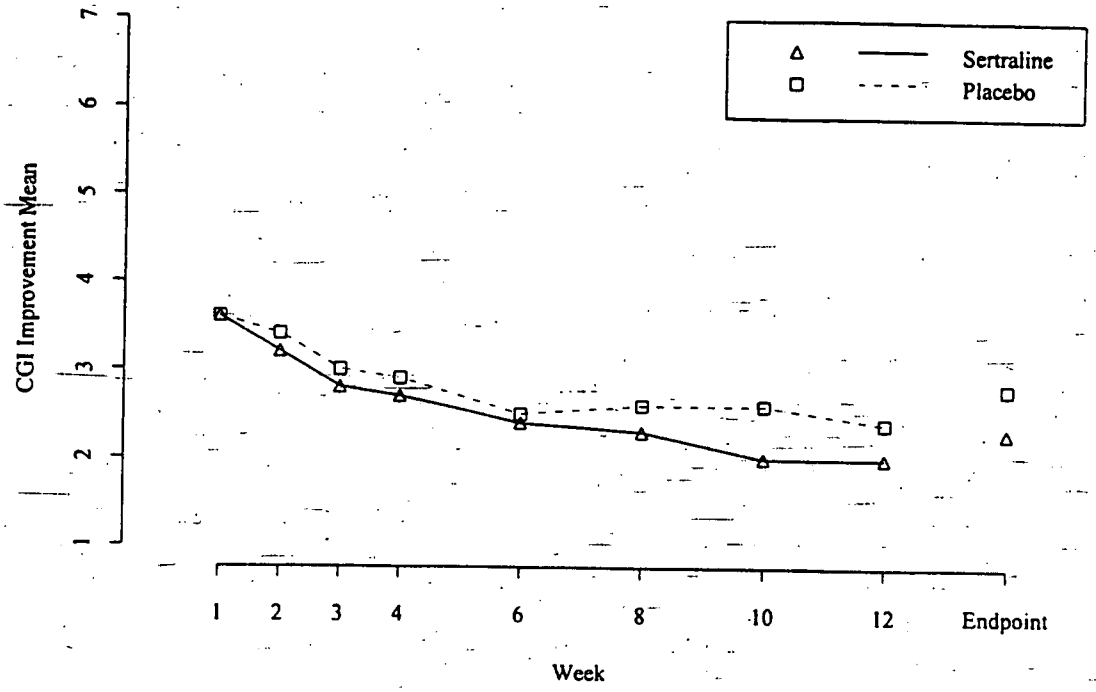


Figure 4. CGI-I graph for Study 640



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

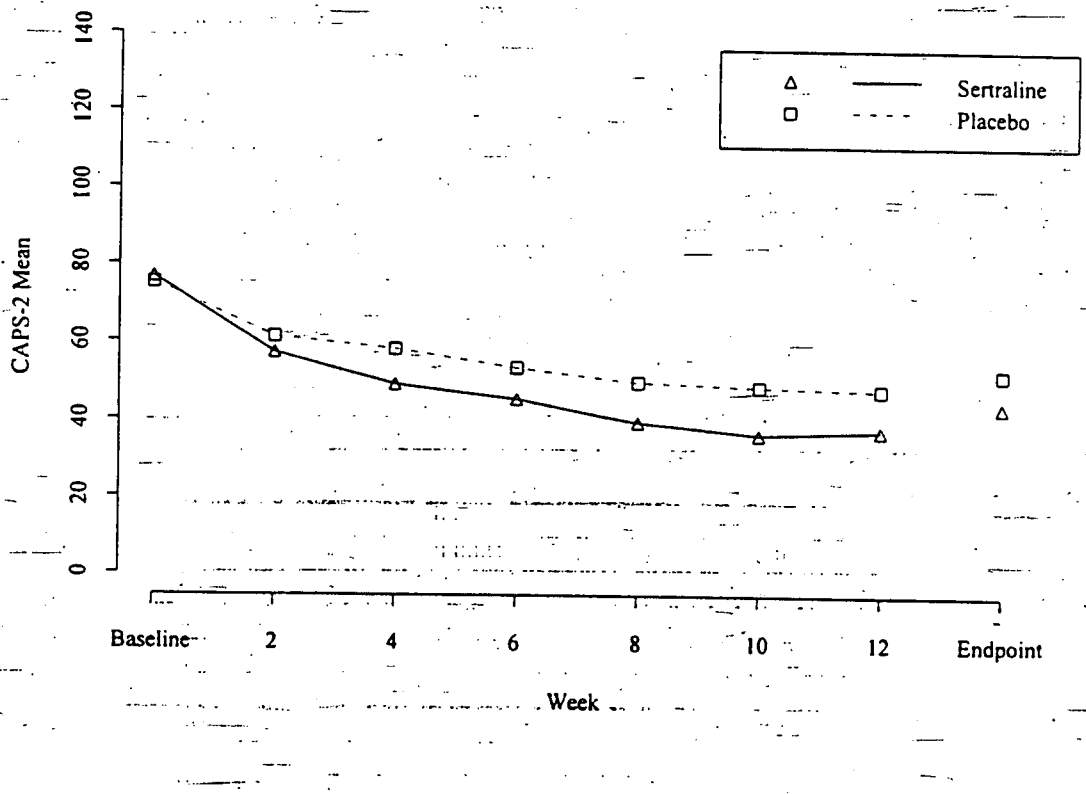


Figure 6. IES graph for Study 671

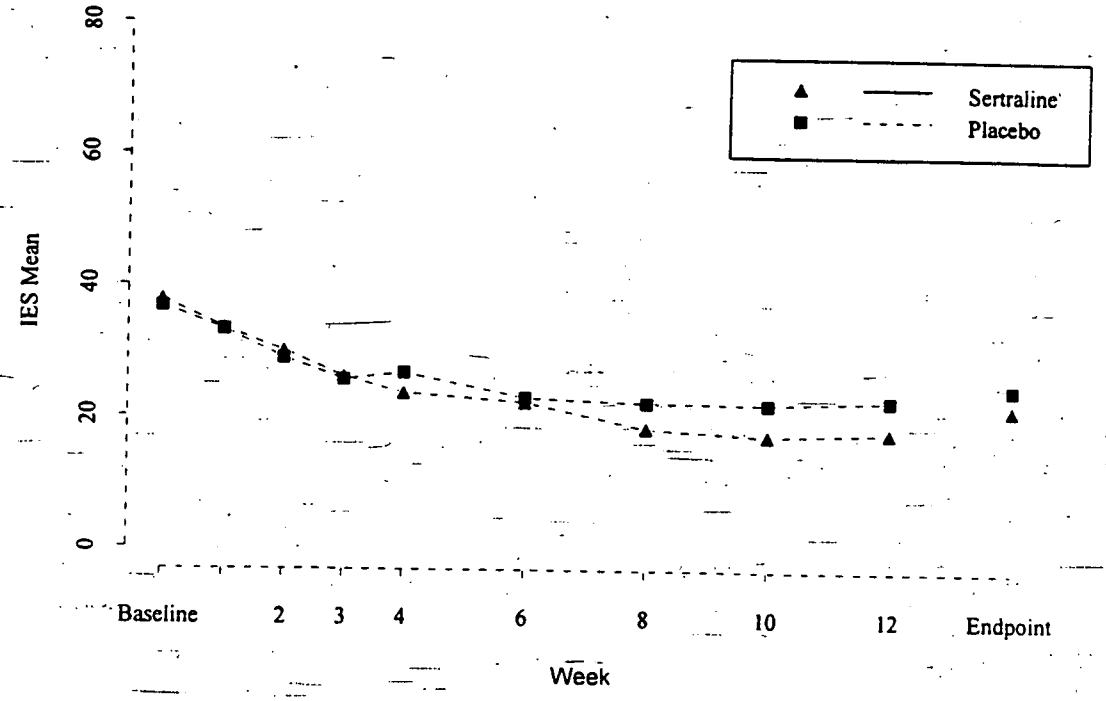


Figure 7. CGI-S graph for Study 671

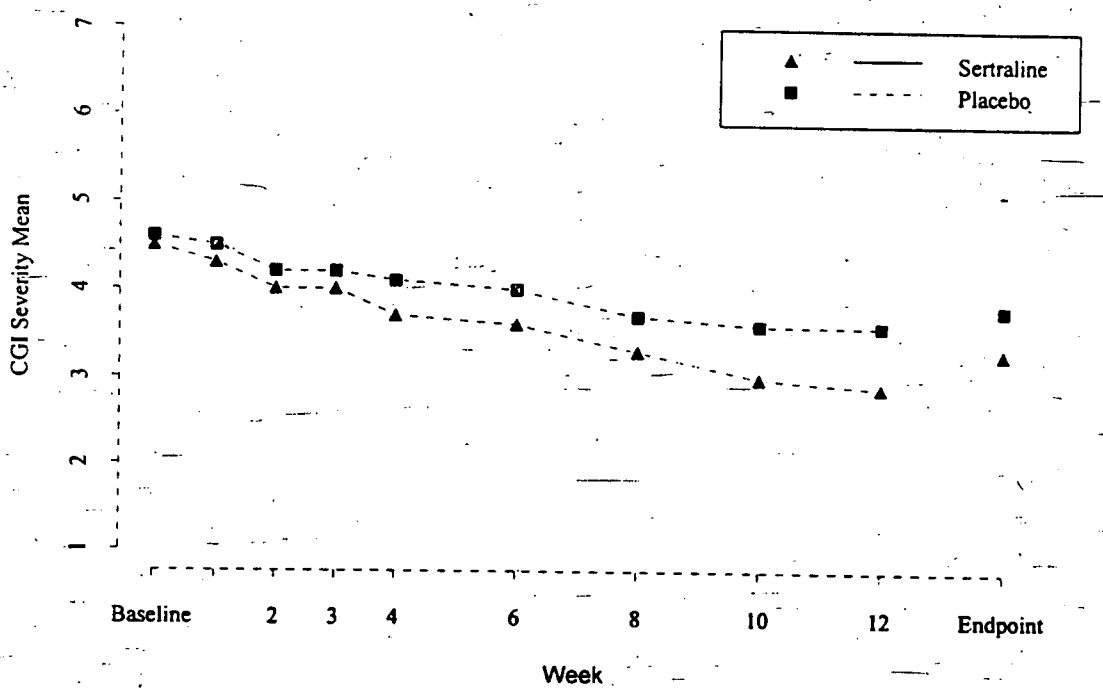
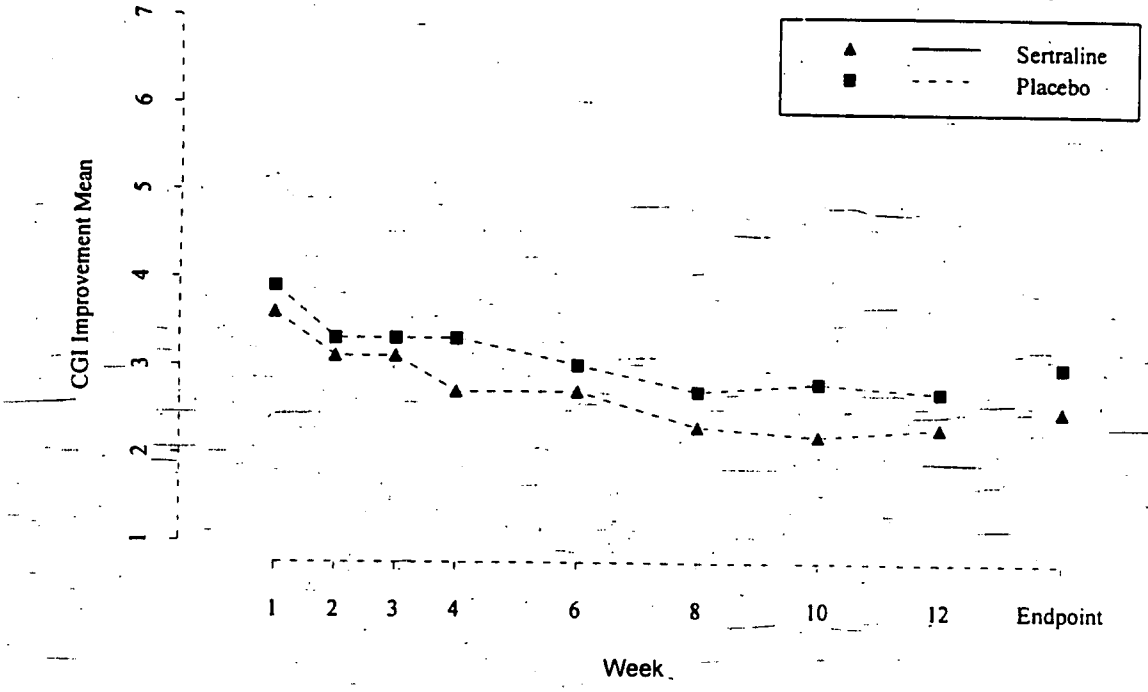


Figure 8. CGI-I graph for Study 671



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.

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/

David Smith, Ph.D.
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

HFD-120 / Ms. A. Homonnay-Weikel, Project Manager

HFD-120 / Dr. R. Katz

HFD-120 / Dr. E. Hearst

HFD-120 / Dr. T. Laughren

HFD-344 / Dr. B. Barton

HFD-710 / Dr. G. Chi

HFD-710 / Dr. K. Jin

HFD-710 / Dr. D. Smith

HFD-710 / Chron

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.

MEMORANDUM

DATE: December 6, 1999

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 19-839/S-026

SUBJECT: Action Memo for NDA 19-839/S-026, for the use of Zoloft (sertraline) in patients with Post Traumatic Stress Disorder (PTSD)

On 10/7/98, Pfizer Inc. submitted supplement 026 for the use of Zoloft (sertraline hydrochloride) in patients with post-traumatic stress disorder (PTSD). In support of this claim, the sponsor submitted the results of 4 placebo controlled trials adequate by design to address the question of Zoloft's effectiveness for this indication.

The safety and effectiveness data have been reviewed by Dr. Hearst of the Division (review dated 6/8/99) and the efficacy data have been reviewed by Dr. Smith of Biometrics (review dated 9/27/99).

Dr. Laughren, Team Leader of the Psychiatric Drugs Group, has written a memo (10/19/99) in which he reviews the relevant data and discusses the issues of potential concern in the application. Specifically, these issues were:

1) Only 2 of the trials yielded results that reached statistical significance for their primary outcomes. One of the 2 trials that did not yield a statistically significant result enrolled patients similar to those enrolled in the 2 "positive" trials (these trials enrolled patients from a general community population whose precipitating traumatic events were typically physical/sexual trauma); the fourth study enrolled VA patients exclusively, whose primary traumatic event was typically war related.
2) In the 2 "positive" trials, the effects seemed to arise only from the women enrolled in the trials.
3) There was concern that the results seen on the primary outcome measures (scales which purported to assess PTSD specific symptomatology but that did have items that assessed depressive symptoms) could have been accounted for by the known antidepressant effect of Zoloft, given that depression was a fairly common co-morbid diagnosis in these patients.

As noted by Dr. Laughren, the Psychopharmacological Drugs Advisory Committee discussed this application at a meeting on 10/8/99. They recommended, by a vote of 6-1, that the supplement should be approved. There was in-depth discussion of all of the points of concern described above.

I will briefly comment on each of these areas.

1) As noted by Dr. Laughren, it is not uncommon, in the development program of effective psychotropic drugs, that several adequate and well controlled trials may not yield results that are statistically significant. The reasons for this are usually not clear; that is the case here, in my view. In particular, however, the non-positive results in the VA study raise the question of the ability of patients whose primary traumatic event(s) were war-related to respond to this treatment. As Dr. Laughren points out, this outcome is apparently consistent with other studies reported in the literature which apparently also show that these patients do not respond to available therapies to which other patients (patients with other precipitating traumatic events) respond. This raises interesting questions about the disorder (for example, do the war-related trauma patients simply represent the most severe, and therefore treatment refractory, patients with PTSD, or do they suffer from a disorder that, although clinically similar to the disorder suffered by patients with other precipitating traumatic events, is fundamentally different from it). However, interesting though these questions are, there is nothing in the data in this supplement that addresses them definitively, and, more important, the evidence that the sponsor has submitted certainly meets the test for substantial evidence of effectiveness.
2) Again, as noted by Dr. Laughren, the effect of the treatment appears to come essentially completely from women (see the table on Page 7 of his memo). The reason for this is not well understood at this time. One could imagine that sex is confounded with specific traumatic event (in the VA study, most patients were men), but this was not true for the 2 studies that were "positive" (in these 2 studies, men did not seem to have systematically different types of traumatic events compared to the women in these studies, although there were relatively few men in these studies). The difference did also not seem to be related to any systematic differences in kinetics between the sexes.

I find the difference in outcomes between the sexes intriguing. An examination of this outcome reveals an almost complete lack of treatment effect in men; there are essentially no numerical trends in favor of the drug, suggesting that the lack of statistical significance in men was not related to inadequate power, but that men and women may respond fundamentally differently to this treatment. Again, the application does not provide definitive information on this point.

There was considerable discussion at the Advisory Committee meeting on this point. No definitive understanding of the phenomenon emerged from that discussion, but the committee did generally agree that the drug should not be specifically indicated for use in women (although there was not unanimity on this point). I agree that such a limitation should not be imposed at this time; as Dr. Laughren noted at the meeting, limiting the indication to a specific sub-group identified by post hoc analyses (even one as "natural" as sex) is treacherous business, and should not be done lightly. However, I do believe that this is an issue that warrants further exploration (apparently, the sponsor has at least one additional study on-going that may address this question, and we await its completion and the submission of the results).

3) Depression is common in patients with PTSD (about 57% of the patients in the 2 positive studies had a diagnosis of depression at baseline). This gave rise to concern that the effects seen on the presumed "PTSD specific" outcome measures were related to sertraline's know anti-depressant effect. As noted by Dr. Laughren, however, analyses which examined the strata of patients defined by presence or absence of pre-existing depression showed statistically significant between treatment differences in both strata. In addition, the analyses performed by Drs. Hearst and Smith, although somewhat arbitrary in its choice of depression "improvers" and "non-improvers", also seems to support an effect of sertraline on the symptoms of PTSD independent of its anti-depressant effects. Finally, an analysis of those items of the scales used that are expected to measure symptoms that are truly specific to PTSD (intrusions) and do not overlap with items that might also be expected to detect an antidepressant effect also show an effect of sertraline. As discussed by Dr. Laughren, though, (page 6 of his memo), the between treatment comparisons on the intrusion items on the 2 scales only reach nominal significance in one study when the results are pooled; in the second study, the results when pooled almost reach nominal significance. I agree with Dr. Laughren that the lack of nominal significance for the individual studies is most likely related to the inadequate power to find such a difference.

I have reviewed the labeling that accompanies this package; this labeling has been negotiated between the review team and the sponsor, and both have agreed to it. I agree that the labeling is acceptable. It contains not only PTSD specific changes in various sections, but also changes in other sections (Clinical Pharmacology, Adverse Reactions, Overdosage) that are the result of data submitted in various supplements in response to various Agency requests (the review of the studies in renal and hepatic impaired patients is in the file for NDA 20-990, for the use of sertraline concentrate).

ACTION

The sponsor has submitted substantial evidence of effectiveness for Zoloft as a treatment for patients with Post Traumatic Stress Disorder. Specifically, given that this is the first application to be submitted for this indication, all other relevant aspects of the protocol and development program are acceptable (e.g., the population enrolled, the outcome measures used in the trials, the duration of the studies). As such, I will issue the attached Approval letter.

APPEARS THIS WAY
ON ORIGINAL

/S/

Russell Katz, M.D.

Cc:
NDA 19-839/S-026
HFD-120
HFD-120/Katz/Laughren/Hearst/Homanny
HFD-710-Smith/Jin

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 19, 1999

/S/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Zoloft tablets (sertraline) for the treatment of Posttraumatic Stress Disorder (PTSD)

TO: File NDA 19-839/S-026
[**Note:** This overview should be filed with the 10-7-98 original submission.]

1.0 BACKGROUND

Sertraline is a selective serotonin reuptake inhibitor currently approved and marketed for depression, OCD, and panic disorder in an immediate release tablet, i.e., Zoloft (NDA 19-839, originally approved for depression 12-30-91; subsequent approvals for OCD on 10-25-96 and panic disorder 7-8-97). S-026 provides data in support of a new claim for this same Zoloft tablet in the treatment of Posttraumatic Stress Disorder (PTSD) in a dose range of 50-200 mg/day.

It should be noted that, at the current time, there are no drugs specifically approved in the US for the treatment of PTSD. However, PTSD has long been recognized by the psychiatric community as a legitimate psychiatric disorder and is listed in DSM-IV. Nevertheless, given the symptom overlap between patients with PTSD and those with various depressive disorders, one of the concerns identified early in the development of this new indication for Zoloft was how this overlap would be sorted out in making a judgement regarding the specific benefit of this product in PTSD.

While we did not have a formal end-of-phase 2 meeting with the sponsor during the development of this indication, we did communicate with them by letter regarding study design and overall development plans.

We met with the sponsor on 10-9-97 for a preNDA meeting, and again, one issue was our concern about the symptom overlap of PTSD with various depressive disorders. We also provided technical advice about the submission of the NDA.

Since the proposal is to use the currently approved Zoloft immediate release tablets for this expanded population, there was no need for chemistry, pharmacology, or biopharmaceutic reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Earl Hearst, M.D., from the clinical group. David Smith, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The studies supporting this supplement were conducted under IND [redacted]. The original supplement for this expanded indication (S-026) was submitted 10-7-98.

We took this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC) on 10-8-99. The committee voted 6 to 1 in favor of Zoloft being shown to be effective for PTSD, and 7 to 0 in favor of it being shown to be safe for treatment of this new indication.

2.0 CHEMISTRY

As Zoloft tablets are already marketed, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Zoloft tablets are already marketed, there were no pharm/tox issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Zoloft tablets are already marketed, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of 4 multicenter, double-blind, randomized, parallel group, 12-week, flexible dose, placebo-controlled trials (640, 641, 671, 682) in adult outpatients meeting DSM-III-R criteria for PTSD. These were all 2-arm trials, with patients assigned to sertraline receiving an initial dose of 25 mg/day (all dosing qd, PM or AM), with increase to 50 mg by the end of week 1. Thereafter, patients were titrated, on the basis of tolerability and efficacy, within a range of 50-200 mg/day. Dose changes were in increments of 50 mg per week.

Patients were screened using the SCID to establish the diagnosis of PTSD and exclude other axis I disorders as primary diagnoses. Protocols 640 & 641 were identical, as were 671 & 682. The only important difference between the 2 sets of studies was the length of placebo washout, with a 1-week washout for 640,641 and 2 weeks for 671,682. All studies were conducted at US sites. Subjects must have had a Clinician-Administered PTSD Scale Part 2 (CAPS-2) baseline score of at least 50 to be entered.

Primary efficacy assessments at each visit were: the CAPS-2, the Impact of Event (IES) scale, and the CGI. The identified primary outcome measures for these studies were change from baseline for three of these measures (CAPS-2 total score, IES total score, and CGI-S), and the raw score at endpoint for CGI-I. Importantly, patients were also assessed on the HAMD. The CAPS-2 has a total of 30 items (rated by clinicians), with each item being rated on a scale of 0 to 4 for both frequency and intensity. However, for the purpose of assessing change in treatment trials, the focus is on the first 17 items that map directly to the 17 items in the DSM-IV criteria for PTSD. That was the case for Pfizer's PTSD program as well, so the CAPS-2 total scores for these 17 items, again with frequency and intensity rated separately, ranges from 0 to 136. The IES total score (self rating) ranges from [redacted] (15 items with ratings on 0, 1,3, or 5 on each). The CGI ranges from 1-7 for both severity and improvement.

The statistical model was ANCOVA with terms for treatment, site, Rx-by-site, and baseline score was the covariate (except for CGI-I). Analyses were done on the datasets for all patients randomized and who also received at least 1 dose of assigned treatment and who were assessed for efficacy at baseline and at least 1 followup time.

Four additional trials were ongoing at the time of submission, including (1) 672, a 24-wk open extension for 671 & 682; (2) 703, a 28-wk relapse prevention trial for responders in 672; (3) 005, a nonUS RCT; and (4) 001, also a nonUS RCT.

5.1.2 Summary of Study Results

5.1.2.1 Demographic and Illness Characteristics

-Patients were predominantly female in 3 of the studies (640:78%; 671:73%; 682:75%), and predominantly male in the 4th study (641:20% female), which was conducted in VA hospitals.

-Patients were predominantly caucasian in all 4 studies.

-Mean ages ranged from 37 to 46 across the 4 studies.

-These patients were in general chronically ill with PTSD, with mean durations of illness ranging from 11 to 18 years.

-The predominant trauma for the patients in the 3 nonVA studies was physical or sexual assault.

-Mean total scores on the CAPS-2 (first 17 items) at baseline ranged from [redacted] across the groups in the 4 studies.

-Although patients with other axis I disorders as a primary diagnosis were excluded, axis I disorders were permitted as secondary diagnoses, and depression was a very common secondary diagnosis, occurring in proportions ranging from [redacted] of study-subjects across the 4 studies. Anxiety was the second most common comorbid psychiatric condition, occurring in proportions ranging from 14% to 27% of study subjects across the 4 studies.

5.1.2.2 Completion Rates

Proportions of the intent-to-treat samples (all patients randomized who received at least 1 dose of assigned treatment and at least 1 postbaseline efficacy assessment) who completed to the 12-week endpoint across the 4 studies were as follows:

Study	Sertraline	Placebo
640	73/98(75%)	74/104(71%)
641	62/84(74%)	69/82(84%)
671	64/93(69%)	67/90(74%)
682	72/94(77%)	71/94(76%)

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5.1.2.3 Sertraline Doses

The mean sertraline doses (for weeks 11 & 12) for completers were as follows:

Study	Dose
640	146 mg/day
641	156 mg/day
671	151 mg/day
682	156 mg/day

5.1.2.4 Efficacy Results

Summary results (LOCF at the 12 week endpoint) for the 4 primary endpoints for the 4 studies are provided in appendix Table 1. This table summarizes the outcomes for the study samples overall; results broken out according to gender and improvement on depression will be provided subsequently.

Table 1 reveals the following:

In the LOCF analyses for studies 640 and 671, sertraline is favored over placebo on essentially all primary endpoints; the only exception is IES for study 671, where the p-value just misses nominal significance at 0.07. For study 640, while none of the OC analyses at week 12 reach statistical significance for sertraline over placebo, the p-values are close for CAPS-2 and CGI-I (0.066 & 0.065, respectively), and the effects (drug/placebo differences) are about the same size as in the LOCF analyses; Dr. Smith attributes this loss of statistical significance to diminished power, and I agree. For study 671, all of the OC analyses at week 12 reach statistical significance for sertraline over placebo, except for CGI-I, for which the p-value is 0.062; and again, the effect sizes for all outcomes in the OC analyses are consistent with those seen in the LOCF analyses.

In the LOCF analyses for studies 641 and 682, there is not even a hint of a difference between sertraline and placebo, except for IES in study 682, where placebo is superior to sertraline (p=0.017). In study 641, there is dramatically less change from baseline for both sertraline and placebo than was seen in the other 3 studies, with no difference between these treatment groups. This was the VA study, and this result may reflect the very chronic and refractory PTSD found in that setting. In fact, this finding is consistent with published studies of drug treatment of PTSD in veteran populations. In study 682, the placebo effect was somewhat larger than that seen in the 2 positive studies, while the sertraline effect was somewhat less. In any case, there was no sertraline/placebo difference observed, except for that noted above, and this study is also negative.

5.1.3 Comment on Other Findings in the Efficacy Analyses for Sertraline in PTSD

Results for PTSD Clusters

The 17 items from the CAPS-2 comprising the total score for this primary outcome map directly to items in the DSM-IV criteria for PTSD, and these are divided into 3 clusters that define PTSD:

(1) re-experiencing/intrusion:
intrusive thoughts

psychological distress
flashbacks
distressing dreams

(2) avoidance/numbing:
avoiding thoughts of trauma
avoiding places
amnesia
diminished interest
feelings of detachment
restricted affect
foreshortened future

(3) hyperarousal.
difficulty falling/staying asleep
difficulty concentrating
irritability/anger
hypervigilance
exaggerated startle
physiological reactivity

While there is considerable overlap between items typically on depression rating scales and the items on both the avoidance/numbing and hyperarousal clusters, the re-experiencing/intrusion cluster appears to be reasonably specific to PTSD.

The sponsor presented the individual results for these 3 clusters for both positive studies (640 and 671) and also the pooled results for these clusters for these 2 studies. The p-values (sertraline vs placebo) for these clusters are as follows:

CAPS-2 Cluster	640	671	640/671
Re-experiencing/Intrusion	0.30	0.14	0.06
Avoidance/Numbing	0.02	0.02	<0.001
Hyperarousal	0.12	0.03	0.007

For the IES, there was also a sorting of items into clusters, i.e., re-experiencing/intrusion and avoidance/numbing, and the p-values for these 2 clusters were as follows:

IES Cluster	640	671	640/671
Re-experiencing/Intrusion	0.03	0.16	0.02
Avoidance/Numbing	0.05	0.09	0.004

While these results are not as strong for the one cluster of the CAPS-2 that appears to be relatively specific to PTSD as for the other 2 clusters, there is reasonable support for an effect of sertraline on the re-experiencing/intrusion item, at least for the pooled analysis. The studies were not individually powered to detect differences on clusters.

Interaction Between Gender and Effectiveness

In the 2 positive studies, there was evidence of an interaction for gender, as follows:

Gender Interaction for Pool of 2 Positive Studies (640 & 671)							
Outcome	Women			Men			
	Change from BL		p-value	Change from BL		p-value	Inter-action p-value
	Sert.	Placebo		Sert.	Placebo		
(N)	152	139		39	55		
CAPS-2	-34	-23	0.0001	-29	-29	0.99	0.04
IES	-18	-13	0.001	-16	-15	0.80	0.16
CGI-I	2	3	0.0001	2	3	0.34	0.22
HAMD	-8	-5	0.005	-6	-7	0.69	0.09

The male sample was roughly 1/3 the size of the female sample, and that may have accounted for some of the failure to find statistically significanct differences among the male patients, e.g., for the CGI-I. However, the effect sizes also revealed the differences between the 2 genders, especially for the CAPS-2 and IES totals, and also, importantly, for the HAMD; for all 3, there were essentially no drug/placebo differences in the males. An examination for the individual study data revealed that this gender interaction was apparent for both studies individually as well. While there is no clear explanation for this difference, one possible factor is the type trauma; physical and/or sexual assault was a more common trauma for women with PTSD than men with this disorder.

Depression as a Potential Confounder

As noted, even before receiving this supplement, we alerted the sponsor to our concerns about potential confounding by the presence of depression and the antidepressant effects of sertraline. In this section, I will summarize analyses done both by the sponsor and by Drs. Smith and Hearst to explore for such confounding.

The sponsor conducted several analyses to look for differences in PTSD responses based on presence or absence of depression at baseline.

In one of these analyses, women from a pool of the 2 positive studies were subgrouped based on those with and without a comorbid diagnosis of depression at baseline. The results were as follows:

Subgroup Analysis Based on Presence or Absence of Comorbid Depression for Pool of Women from 2 Positive Studies (640 & 671)						
Outcome	No Comorbid Depression			Comorbid Depression		
	Change from BL		p-value	Change from BL		p-value
	Sert.	Placebo		Sert.	Placebo	
(N)	85	80		67	59	
CAPS-2	-33	-22	0.005	-39	-25	0.002
IES	-17	-13	0.031	-21	-14	0.010
CGI-I	2.3	3.0	0.001	2.4	3.0	0.018

This analysis demonstrated that, whether or not comorbid depression was present at baseline, an approximately equal (and significant) effect was seen for sertraline on PTSD outcomes.

Given the overlap in symptoms on the HAMD and various instruments used to assess PTSD, the sponsor also looked at correlations between change from baseline in the HAMD and change from baseline in various total and cluster scores for PTSD measures. Not surprisingly, strong correlations were noted. However, they were strong for both sertraline and placebo patients, suggesting that the correlation is not related specifically to a sertraline effect. It is important to note that whether or not patients met criteria for clinical depression at baseline, they had higher than normal depression scores on the HAMD at baseline (about 24 for those designated as having comorbid depression and about 19 for those without). It is also important to note that a designation of clinical depression is based on a clinician's judgement, not on a quantitative rating on an instrument like the HAMD. The data showing a positive correlation between changes in the HAMD and changes in PTSD measures should not, in my view, be considered support for the hypothesis that it is the antidepressant effects of sertraline that are the basis for the apparent specific improvements on the PTSD measures. It would not be surprising that mood is improving in someone whose PTSD is improving, and that might be viewed more as a secondary effect than a primary effect. In fact, it would not be surprising to see a positive correlation between responses on the HAMD and responses on other disease specific measures, even for nonpsychiatric disorders, since it would be expected that mood would improve with improvement in whatever primary disease is being treated.

An alternative approach was used by Drs. Smith and Hearst to explore for confounding. They subgrouped patients on the basis of whether or not they had improved on a measure of depression and then looked at the PTSD responses in these different subgroups. They hypothesized that whether or not a patient improves on depressive symptoms should not influence the patient's responsiveness on PTSD measures, providing these outcomes are independent. They defined improvers and non-improvers in terms of how much their HAMDs changed from baseline to endpoint, taking into consideration what the HAMD was at baseline. Based on this subgrouping,

the p-values for the sertraline/placebo differences for key PTSD outcomes for the pooled data for the 2 positive studies (640 & 671) are as follows:

Outcome	Depression Non-Improvers	Depression Improvers
CAPS-2	0.11	0.07
IES	0.06	0.64
CGI-S	0.06	0.20

These data for the measures identified as primary outcomes in these trials suggest there is either no difference in the PTSD response on the basis of this subgrouping, or perhaps an advantage for depression non-improvers. One possible effect of this subgrouping is to separate out the placebo responders, i.e., those subjects with prominent changes on all measures (PTSD and HAMD), regardless of treatment assignment. In any case, these findings tend to provide support for the independence of the PTSD response from an antidepressant response, in my view.

Drs. Smith and Hearst also provided a series of similar analyses using a classification of patients as depression improvers or non-improvers based on the HAMD depressed mood item. These analyses yield similar results as for the subgroupings based in HAMD responses, and thus, again tend to support an independence of the PTSD response from the antidepressant response.

Evidence Bearing on the Question of Dose/Response for Efficacy

All 4 studies in the development program involved flexible dosing in a range of 50-200 mg/day, and thus, provided no evidence pertinent to the issue of dose response. The mean doses for completers to 12 weeks in the two positive studies were 146 and 151 mg/day, respectively, but these findings are not interpretable regarding dose response since patients in such trials are generally pushed to the higher end of the permitted dose range, regardless of need. Thus the most one can say about dosing for PTSD is that there was evidence of response for patients dosed within a range of 50-200 mg/day.

Size of Treatment Effect

It is difficult to clinically interpret the effect sizes on the measures observed for the 2 positive studies in terms of differences between drug and placebo in change from baseline. For the CAPS-2 total score, mean baseline scores ranged from [redacted] and sertraline patients had decreases to mean scores of roughly 42, compared to decreases to about 50 for placebo patients. As is the case for other psychiatric indications, the mean score after treatment was still within a range that would leave many patients considered clinically ill. Another way of looking at the treatment effect is to classify patients as responders/nonresponders. A definition of response as a rating on the CGI-I of 1 (very much improved) or 2 (much improved) yielded the following results for the 2 positive studies:

	% Responders	
Studies	Sertraline	Placebo
640	74%	54%
671	61%	42%

These results, while not striking, are consistent with what we often observe in psychotropic treatment trials and they suggest to me a clinically relevant treatment effect.

Duration of Treatment

The two positive studies provide evidence of effectiveness for patients dosed up to 12 weeks. The only study in the development program capable of addressing effectiveness beyond 12 weeks is study 703. However, the results from that study have not yet been submitted.

5.1.3 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of a beneficial effect of Zoloft in the treatment of PTSD. Two of the 3 studies in PTSD patients in the general population were able to distinguish sertraline from placebo, albeit only in women with this disorder. Nevertheless, studies 640 & 671 were positive overall, and the failure to find an effect in men with this disorder is something that can be noted in labeling. There was considerable discussion of this issue at the PDAC meeting, and it was clearly also the committee's view that the claim should be for PTSD overall, with the gender finding described in Clinical Trials. Regarding the number of positive trials, it is not uncommon for drug trials in psychiatric disorders to fail, and so the finding of 1 failure among 3 studies is not uncharacteristic. The failure of the VA study is apparently consistent with similar studies in this population, and can be discounted.

A major review concern was whether or not the effect of sertraline in this disorder can be considered a specific effect or is simply another demonstration of sertraline's antidepressant properties. While this question can be approached in several ways, I find 2 pieces of evidence supportive of a specific effect: (1) a benefit was demonstrated for the re-experiencing/intrusion cluster of both the CAPS-2 and IES, and I consider that cluster reasonably specific to PTSD; (2) whether or not patients were clinically depressed at baseline, it was possible to demonstrate an effect on PTSD measures. In my view, these results are perhaps the most persuasive in favor of a specific benefit, in the sense that patients not diagnosed with depression, and therefore not candidates for treatment with Zoloft according to FDA approved labeling, were, nevertheless, demonstrated to benefit from such treatment with improvement on measures of PTSD. I am less persuaded that the correlation of responses on the HAMD and PTSD measures is a reasonable basis for denying a specific claim for this disorder, and in fact, the analyses of Drs. Smith and Hearst subgrouping patients into depression improvers and nonimprovers actually provided support for the view that the PTSD effect is independent of the antidepressant effect. This issue also had considerable discussion at the PDAC meeting, and the committee's view was that an independent PTSD effect had been demonstrated.

The issue of longer-term efficacy cannot be addressed until we have received and reviewed the results of study 703. In addition, since PTSD is also a disorder found in the pediatric population and, once aproved for this indication, Zoloft will likely be used in pediatric patients, we will recommend adequate and well-controlled trials of Zoloft in this population as well. The PDAC strongly endorsed the need for pediatric studies in this disorder.

5.2 Safety Data

Dr. Hearst's safety review of S-026 was based on an integrated database consisting of a pooling of safety data for the four 12-week studies. In addition, any serious events reported in from 4 ongoing PTSD studies were included in this supplement. The cut-off date for safety data was 2-26-98. There was no safety update.

Overall, 374 patients were exposed to sertraline in the sponsor's development program for PTSD (i.e., in the 4 completed studies). The demographic charcteristics and the dosing information for these patients were previously described.

Given our prior knowledge of the risks associated with sertraline use in the same dose range utilized in this program, the focus in the safety review was on any differences between the recognized safety profile for this drug in its approved indications from that observed in the PTSD population.

5.2.2 Overview of Adverse Event Profile for Zoloft in PTSD

Overall, the adverse events profile for sertraline in these PTSD trials was comparable to that observed in patients with depression, OCD, and panic disorder receiving this drug.

5.2.3 Conclusions Regarding Safety of Zoloft in PTSD

There were no new safety findings to suggest a substantially different safety profile for Zoloft in PTSD compared to that observed for the other 3 approved indications, and no basis for substantial changes in the labeling for Zoloft from the standpoint of safety.

5.3 Clinical Sections of Labeling

Following the 10-8-99 PDAC meeting, we negotiated with the sponsor regarding labeling and were able to reach agreement on 10-18-99. The only points of disagreement were with the description of the clinical trials and the Indications and Usage statement.

6.0 WORLD LITERATURE

Dr. Hearst reviewed the sponsor's reports on the published literature for sertraline in PTSD included in the NDA and did not discover any previously unrecognized important safety concerns for this drug.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Zoloft is not approved for the treatment of PTSD anywhere at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we took this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC) on 10-8-99. The committee voted 6 to 1 in favor of Zoloft being shown to be effective for PTSD, and 7 to 0 in favor of it being shown to be safe for treatment of this new indication.

9.0 DSI INSPECTIONS

Although DSI does not routinely inspect investigative sites for supplements, and did not in this case, none of the listed investigators for these trials was recognized as having had compliance problems in the past.

10.0 LABELING AND APPROVAL LETTER

10.1 Final Labeling Attached to Approval Package

The mutually agreed upon final labeling is attached to the approval letter.

10.2 Foreign Labeling

Zoloft is not approved for PTSD anywhere at this time.

10.3 Approval Letter

The approval letter includes final labeling and requests for additional studies of Zoloft in PTSD, in particular, (1) a report on study 703, the completed relapse prevention trial, and (2) studies of PTSD in pediatric populations with this disorder.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Pfizer has submitted sufficient data to support the conclusion that Zoloft tablets are effective and acceptably safe in the treatment of PTSD. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling and the above noted requests.

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cc:
Orig NDA 19-839/S-026
HFD-120
HFD-120/TLaughren/RKatz/EHearst/AMHomonnay

DOC: MEMZPTSD.AP1

Table 1
Summary of Efficacy Results (LOCF) for 4 Studies of Sertraline in PTSD

Study	Variable	Baseline[1]	Sertraline[2]	Placebo[2]	P-Value[3]
640	CAPS-2	74	-33.0	-26.2	0.043
	IES	39	-19.2	-14.1	0.018
	CGI-S	4.6	- 1.3	- 1.0	0.037
	CGI-I	-	2.3	2.8	0.014
641	CAPS-2	73	-13.1	-15.4	0.587
	IES	42	- 8.7	- 8.1	0.799
	CGI-S	4.6	- 0.5	- 0.6	0.468
	CGI-I	-	3.0	3.0	0.879
671	CAPS-2	76	-33.0	-23.2	0.016
	IES	37	-16.2	-12.1	0.071
	CGI-S	4.6	- 1.2	- 0.8	0.012
	CGI-I	-	2.5	3.0	0.016
682	CAPS-2	72	-27.4	-27.9	0.896
	IES	39	-13.6	-19.7	0.017
	CGI-S	4.5	- 1.0	- 0.9	0.798
	CGI-I	-	2.6	2.6	0.891

1 Mean score at baseline (both groups combined) for CAPS-2, IES, and CGI-S.

2 Mean change from baseline to endpoint for CAPS-2, IES, and CGI-S; mean raw score at endpoint for CGI-I.

3 Sertraline vs Placebo, 2-sided.

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 (GAPS-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.

Sertraline (Zoloft)
NDA 19-839 (S-026)
Submission Date: October 1, 1998
Reviewer: Iftekhar Mahmood, Ph. D.

Pfizer, Inc.
New York, NY 10017
Received by OCPB: October 13, 1998.

Review of a Efficacy Supplement

This submission contains efficacy supplement with no pharmacokinetics or biopharmaceutics data. Therefore, no action is necessary on this submission from pharmacokinetics or biopharmaceutics point of view.

/S/ 12/28/98

Iftekhar Mahmood, Ph. D.
Division of Pharmaceutical Evaluation I

RD/FT initialed by Chandra Sahajwalla, Ph. D. /S/ 12/28/98

CC: NDA 19-839 (S-026)
HFD-120, HFD-860 (Mahmood, Sahajwalla, Mehta), CDR (Barbara Murphy for Drug Files).

EXCLUSIVITY SUMMARY FOR NDA # 19-839 SUPPL # S-026

Trade Name Zoloft Tablets Generic Name sertraline HCl

Applicant Name Pfizer HFD # 120

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO / /

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /✓/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /__/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /✓/

APPEARS THIS WAY
ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 640

Study 671

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Study 640

Study 671

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND [redacted] YES /✓/ ! NO /___/ Explain: _____

!

! _____

Investigation #2 !

!

IND # [redacted] YES /✓/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

!

!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____ _____
Signature Date
Title:_____

APPEARS THIS WAY
ON ORIGINAL

_____ _____
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

SECTION 13. PATENT AND EXCLUSIVITY INFORMATION

1.	Active Ingredient:	(1S-cis)-4(3,4-dichlorophenyl) -12,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride
2.	Strength:	25, 50, and 100mg sertraline
3.	Trade Name:	Zoloft
4.	Dosage Form/Route of Administration:	Tablets/Oral
5.	Application Firm Name:	Pfizer Inc.
6.	NDA Number:	19-839
7.	Exclusivity Period:	Thirty-six months (3 years) from the date of approval of this supplement to NDA 19-839
8.	Applicable Patent Numbers And Expiration Dates:	4,536,518 December 30, 2005 4,962,128 November 2, 2009 5,248,699 August 13, 2012

SECTION 14. PATENT CERTIFICATION

Pfizer certifies that patent numbers 4,536,518 (expires December 30, 2005), 4,962,128 (expires November 2, 2009) and 5,248,699 (expires August 13, 2012), which are listed in section 13 of this application, claim, respectively, the drug sertraline, a method of treating anxiety related disorders (including post-traumatic stress disorder) using sertraline, and a crystalline polymorphic form of sertraline hydrochloride, and that sertraline is the subject of this application for approval under section 505 of the Federal Food, Drug, and Cosmetic Act.

APPEARS THIS WAY
ON ORIGINAL

Memo

NDA #: 19-839

Applicant: Pfizer, Inc.

Name of Drug: Zoloft (sertraline)

Indication: Patients with posttraumatic stress disorder

Regarding: Two statistical reviews for sertraline for PTSD

A statistical review dated 22 June 1999 was completed and signed for NDA 19-839. A programming error that affected results given in Tables 4.12 through 4.16 was found, subsequent to the statistical review being entered into the permanent NDA 19-839 file. The statistical reviewer's conclusions about the interpretation of Tables 4.12 through 4.16 were incorrect due to this programming error.

After the error was corrected, Tables 4.12 through 4.16 were updated to reflect the corrected results. Furthermore, Table 4.12 became Table 4.12a, and a new table, Table 4.12b, was created. The conclusions based on the corrected results were also updated.

The statistical review dated and signed off on 27 September 1999 completely supplants the statistical review dated 22 June 1999, even though the statistical review dated 22 June 1999 was signed off and entered into the permanent NDA 19-839 file.

/S/

David Smith, Ph.D.
Mathematical Statistician

Concur: Dr. Ji /S/

APPEARS THIS WAY
ON ORIGINAL

cc:

Archival NDA #19-839
HFD-120/Ms. Homonnay-Weikel
HFD-120/Dr. Hearst
HFD-120/Dr. Laughren
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Smith
HFD-710/Chron

SMITH / 30 Sep 99 / WordFiles / 19839twostatreviewsmemo.doc

MEMO OF TELEPHONE CALL

Date:	November 30, 1999
NDA:	20-990
NDA:	19-839/SE1-026
Subject:	Final labeling for Pending NDA
Drug:	Zoloft (sertraline hydrochloride) tablets (19-839) and oral concentrate (20-990)
Indication:	OCD/Depression/Panic Disorder/PTSD
Firm:	Pfizer
Contact:	Martha Brumfield, Ph.D
Phone #:	(212) 573-5406

At the request of Dr. Laughren, I contacted Dr. Brumfield in reference to their faxed labeling counterproposal dated 11-19-99, responding to the labeling proposal faxed by the Agency on 11-2-99. The labeling revisions reflected changes to the labeling to provide for the new oral concentrate formulation, additional safety related changes previously requested by the Agency or in pending supplemental applications, and corrections to Table 3 in the Adverse Reactions section of labeling. The attempt of these faxes was to secure labeling agreement at the Team leader level.

I informed Dr. Brumfield that the Agency was willing to accept some of Pfizer's proposed changes (see attached e-mail from Dr. Mosholder). Dr. Brumfield was additionally informed that the Agency wished to have a tabular format in lieu of a narrative format for the Adverse Reactions-Sexual Dysfunction section of labeling. Dr. Brumfield replied that Pfizer was willing to accept all of these changes.

I also noted that the PTSD efficacy supplement, 19-839/SE1-026, was to be acted on at the same time as the oral concentrate application, NDA 20-990. Pfizer had previously informed me that they did not wish to have the oral concentrate labeling and the PTSD labeling together for the following reasons: 1) their detail people need to be trained on the appropriate use of the concentrate and the new indication of PTSD, and 2) they are not able to commercially distribute the concentrate until 3/2000.

I informed her that the Agency would be willing to provide separate labeling for the PTSD and the oral concentrate (with the understanding that Pfizer would combine the labeling once the FPL for the oral concentrate was submitted). However, all of the safety related changes in our agreed upon labeling (attached) would also be incorporated into the PTSD labeling so that these changes would be in the marketplace as soon as possible. Dr. Brumfield agreed with this approach.

APPEARS THIS WAY
ON ORIGINAL

/S/

Paul A. David, R.Ph.
Regulatory Project Manager

NDA 20-990
NDA 19-839/SE1-026
NDA:DIV FILES
HFD-120/TLaughren/AMosholder
/PDavid/AMHomonnay
ATTACHMENTS (2)

NDA 19-839/S-026

Homonney

SEP 13 1999

Pfizer Inc.
Attention: Margaret A. Longshore
Director
235 E. 42nd Street
New York, New York 10017

Dear Ms. Longshore:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zoloft (sertraline Hydrochloride) Tablets

NDA Number: 19-839

Supplement Number: S-026

Therapeutic Classification: Standard (S)

Date of Supplement: September 10, 1999

Date of Receipt: September 10, 1999

This supplement provides for Zoloft Tablets for the treatment of post-traumatic stress disorder as a new indication.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 10, 1999, in accordance with 21 CFR 314.101(a).

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, contact Anna M. Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely,

/S/ 9/13/99

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

NDA 19-839/S-026

SEP 13 1999

Homonnay

Pfizer Inc.
Attention: Margaret A. Longshore
Director, Regulatory Affairs
235 E. 42nd Street
New York, New York 10017

Dear Ms. Longshore:

We acknowledge receipt of your September 9, 1999, correspondence notifying us that you are withdrawing your October 7, 1998, supplemental new drug application (NDA) for Zoloft (sertraline hydrochloride) Tablets for the treatment of post-traumatic stress disorder.

Therefore, in accordance with 21 CFR 314.65, this application is withdrawn as of the date of our receipt of your notification, September 9, 1999. This withdrawal does not prejudice any future filing of the application. You may request that the information contained in this withdrawn application be considered in conjunction with any future submission.

If you have any questions, contact Anna M. Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely,

/S/ 9/13/99

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-839/S-026

Pfizer Inc.
235 E. 42nd Street
New York, New York 10017

OCT 15 1998

Attention: Margaret A. Longshore, Director

Dear Ms. Longshore:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Zoloft

NDA Number: 19-839

Supplement Number: S-026

Date of Supplement: October 7, 1998

Date of Receipt: October 7, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 6, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/ (for)

10/13/98

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	19839	**Trade Name:**	ZOLOFT (SERTRALINE HCL) TABLET
Supplement Number:	26	**Generic Name:**	SERTRALINE HYDROCHLORIDE
Supplement Type:	SE1	**Dosage Form:**	Tablet; Oral
Regulatory Action:	AP	**Proposed Indication:**	post-traumatic stress disorder

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) _X_Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ANNA MARIE HOMONNAY-WEIKEL

/S/ 12-5-99

Signature Date

APPEARS THIS WAY
ON ORIGINAL