CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 19-839/S-035
20-990/S-003

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

sNDA #:	19-839/S-035 and 20-990
Applicant:	Pfizer Pharmaceuticals
Name of Drug:	Zoloft® (sertraline hydrochloride)
Indication:	Post-traumatic stress disorder
Document reviewed:	Volumes 1-16
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1. Introduction

Sertraline hydrochloride, marketed under the tradename Zoloft by Pfizer pharmaceuticals, is a selective serotonin reuptake inhibitor for oral administration. The drug is currently available in an oral concentrate in addition to 25, 50, and 100 mg tablets. The FDA previously approved these formulations under NDA 20-990 and NDA 19-839 respectively. It was initially approved for the treatment of depression on December 30, 1991. Subsequently, it was approved for the treatment of obsessive-compulsive disorder in October 1996, panic disorder in July 1997, and post-traumatic stress disorder in December 1999. Regarding the indication for post-traumatic stress disorder (PTSD), the label states that the effectiveness of Zoloft has not been evaluated in clinical trials for a treatment duration longer than 12 weeks. The efficacy supplement under review here is for the long-term treatment of PTSD.

2. Study Design

The long-term efficacy of Zoloft in treating patients with PTSD was studied in two clinical trials. Protocol 95CE21-0672 was a 24-week open-label extension study in outpatients with PTSD. Protocol 95CE21-0703 was a 28-week double-blind placebo controlled continuation study in outpatients with PTSD.

2.1 Study 672

Initially, 380 patients with a DSM-III-R diagnosis of PTSD were randomized in two double-blind placebo-controlled studies. The results of these two studies were previously reviewed by the FDA and are referred to as the "feeder studies" for the studies under review in this efficacy supplement.

Subjects who completed either of these two studies were eligible for entry into the 24-week open-label extension study (Study 672). Of the 275 patients who completed the feeder studies, 252 patients entered Study 672. The subjects' treatment assignments in

the feeder studies were not revealed at that time. Subjects received 25 mg/day of the drug for one week followed by 50 mg/day in the absence of dose-limiting adverse events. Subjects who failed to respond could be titrated up to 200 mg/day in 50 mg/day increments. The study was conducted at 24 sites.

The demographic composition of the 252 patients who entered the study was as follows: 184 were female and 68 were male, 224 were white, 19 were black, and 7 were Asian. 144 of the patients were victims of physical or sexual assault, 36 witnessed someone get hurt or die, 23 were involved in a serious accident, fire, or injury, 14 were involved in war or combat, 1 was a victim of a natural disaster, and 34 were classified as "other".

During the study, a series of efficacy assessments was completed to rate the subject's progress. These assessments included the Clinician-Administered PTSD Scale Part 2 (CAPS-2), the Impact of Event Scale (IES), as well as the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) ratings. Patients also completed Quality of Life questionnaires periodically.

2.2 Study 703

This study was designed to evaluate the comparative safety and efficacy of Zoloft and placebo in the prevention of PTSD relapse in subjects who completed and responded to 24 weeks of open-label treatment in Study 672. Subjects who met both of the following criteria were classified as responders:

1) A CGI Global Improvement score of "1" (very much improved) or "2" (much improved) and
2) a decrease in the CAPS-2 score by 30% or more relative to the baseline of the initial double-blind feeder study.

139 of patients completed Study 672 and were classified as responders. Of these, 96 were randomized to double-blind treatment. The participants who were randomized to treatment received the same amount Zoloft as they were taking in Study 672, but could be titrated upward or downward during the study. The study was conducted at 24 sites.

Of the 96 patients who entered the study, 46 were randomized to treatment and 50 to placebo. Demographically, 67 were female (36 in the treatment group/31 placebo) and 29 were male (10/19), 88 were white (40/48), 4 were black (4/0), and 4 were Asian (2/2). 53 of the patients were victims of physical or sexual assault. The remaining patients witnessed someone get hurt or die, were involved in a serious accident, fire, or injury, were involved in war or combat, were victims of a natural disaster, or experienced some other traumatic event.

During the study, a series of efficacy assessments was completed to rate the subject's progress. These assessments included the Clinician-Administered PTSD Scale

Part 2 (CAPS-2), the Impact of Event Scale (IES), as well as the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) ratings. Patients also completed Quality of Life questionnaires periodically.

3. Primary Efficacy Variables

3.1 Study 672

In Study 672, there were four primary efficacy variables specified in the protocol: 1) the CAPS-2 total severity score 2) IES 3) CGI-S rating and 4) CGI-I rating. The CPAS-2 total severity score is computed as the sum of the frequency and intensity of each of the first 17 items in the scale. The frequency and intensity for each item were assigned numeric values of 0 through 4, increasing with higher numbers. The CAPS-2 ratings were performed at baseline and every 2 weeks thereafter. The IES consists of the subject's response to 15 statements describing the symptoms during the past week. For each item, the patient's responses were assigned numeric values of 0, 1, 3. or 5 with increasing values representing more severe symptoms. The total score for these 15 items was then computed. The subject completed this exam at the end of Weeks 1, 2, 3, 4, and every 2 weeks thereafter. The CGI-S was a rating by the investigator of 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 ranged from 1=normal, not at all ill to 7=among the most severely ill. The CGI-I was a rating by the investigator of the subject in response to the following question, "Compared to the subject's condition at the beginning of the double-blind study, how much has he/she changed?" The ratings ranged from 1=very much improved to 7=very much worse. Both the CGI ratings were administered at the end of Weeks 1, 2, 3, 4, and every 2 weeks thereafter.

3.2 Study 703

In Study 703, there were two primary efficacy variables specified in the protocol: 1) the time to relapse and the rate of relapse and 2) the time to relapse or discontinuation due to insufficient clinical response and the rate of relapse or discontinuation due to insufficient clinical response Data for evaluation of the primary efficacy variables were based on the CAPS-2 total severity score and CGI-I, as well as on the investigator's opinion of the subject's overall clinical condition. A subject was classified as "relapsed" and discontinued if on two consecutive visits the following three conditions were met: 1) CGI Improvement rating was 3 or greater 2) CAPS-2 score increased by at least 30% and by at least 15 points relative to the baseline measurement at the start of Study 703 and 3) in the investigator's opinion, the subject's clinical condition had significantly worsened. The time to relapse is the time to the first of the two consecutive visits that meet the relapse criteria.

4. Secondary Efficacy Variables

4.1 Study 672

The CAPS-2 consists of 30 questions that are grouped into several clusters that were used as secondary efficacy variables. In addition, secondary efficacy variables were derived from the Davidson Self-Rating PTSD Scale total score, the Hamilton Depression Scale and the Quality of Life Enjoyment and Satisfaction Questionnaire.

4.2 Study 703

Secondary efficacy variables were derived from the following: CAPS-2 total severity score, CAPS-2 clusters and global ratings, IES total score and clusters, Davidson Self-Rating PTSD Scale total score and clusters, CGI-S, CGI-I, Hamilton Depression Scale and the Quality of Life Enjoyment and Satisfaction Questionnaire.

5. Protocol Specified Planned Statistical Analysis

5.1 Study 672

Changes in the primary efficacy variables from baseline to each visit and endpoint were summarized. 95% confidence intervals were computed around the mean changes and two-sided p-values from a one-sample t-test were calculated. No adjustment for multiple comparisons was made.

Response was defined as at least 30% decrease in the CAPS-2 total severity score compared to the baseline of the feeder study and a CGI-I score of 1 or 2 (very much or much improved). Number and percent of responders were reported by gender and by previous treatment in the feeder studies. Response rates were further investigated by comparing proportions of responders at the baseline of Study 672 and at the endpoint of Study 672 using McNemar's test. This analysis was performed by gender group and by previous treatment in the feeder studies.

5.2 Study 703

For the time to relapse analysis, a subject who discontinued for any reason other than "relapse" was considered censored. The probability of remaining in the study for 28 weeks was determined by the Kaplan-Meier estimate. Statistical significance of the treatment effect was tested using the logrank test. Relapse rates were summarized by treatment as the proportion of subjects who experienced the event. Comparisons were made between treatment groups using Fisher's exact test.

These two analyses were repeated for time to relapse or discontinuation due to insufficient clinical response. Subjects who discontinued for some other reason were considered censored in this analysis.

6. Analysis of Primary Efficacy Variables

6.1 Study 672

There were highly significant differences ($p<0.0001$) in changes from baseline of this study to the endpoint of this study in all four primary efficacy variables (CAPS-2 total severity score, IES, CGI-S rating, and CGI-I rating). These p-values are from the one-sample t-test used to test if the change from baseline has mean 0.

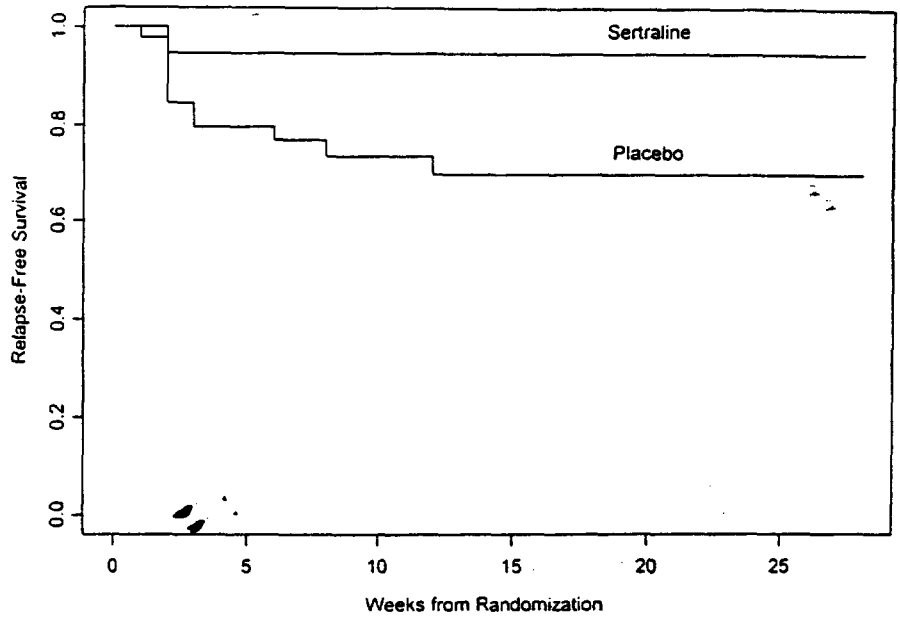
Responders were defined as subjects with at least a 30% improvement in CAPS-2 total score and a CGI-I score of "1" or "2". Of the 249 ITT subjects, 188 (75.5%) were responders at the end of this study. Among the 126 patients who received sertraline in the feeder studies 74 (58.7%) were already classified as responders at the baseline of this study and 96 (76.2%) were classified as responders at the endpoint. Among the 123 patients who received a placebo in the feeder studies 55 (44.7%) were already classified as responders at the baseline of this study while 92 (74.8%) were classified as responders at the endpoint. The difference in the proportion of responders at baseline and endpoint was significant ($p<0.05$) in the following subgroups: females and all subjects who received sertraline in the feeder studies and females, males, and all subjects who received a placebo in the feeder studies.

6.2 Study 703

The Kaplan-Meier estimates of the probability of remaining relapse-free for the entire 28-week treatment period are 0.9474 for the sertraline group and 0.6989 for the placebo group. The difference in the distribution of time to relapse in the two groups was statistically significant ($p=0.007$, logrank test, ITT approach). The Kaplan-Meier curves are shown in Figure 6.2.1. These curves show that most of the difference in the curves occurred early in the study.

The Kaplan-Meier estimates of the probability of not discontinuing due to relapse or insufficient clinical response for the entire 28-week treatment period are 0.8194 for the sertraline group and 0.5125 for the placebo group. The difference in the distribution of time to discontinuation due to relapse or insufficient clinical response in the two groups was statistically significant ($p=0.0016$, logrank test, ITT approach).

Figure 6.2.1 Kaplan-Meier estimates of probability of relapse-free survival for the two treatment arms [*Source: Table 5.6.1 of Study Report*].



7. Analysis of Secondary Efficacy Variables

7.1 Study 672

The changes from baseline to endpoint in CAPS-2 clusters were all significant ($p<0.0001$) except for rating validity. Changes in all IES clusters and Davidson Scale clusters were all significant ($p<0.0001$). Changes in Hamilton Depression Scale and the Davidson Scale total score were significant ($p<0.0001$) as well as the changes in the Quality of Life Enjoyment and Satisfaction Questionnaire ($p=0.0064$).

7.2 Study 703

The adjusted mean change in the CAPS-2 total severity score were significantly different ($p=0.001$). For this and all other secondary efficacy variables, analysis of covariance using the ITT approach was used to compare the changes in the scores of the two treatment groups after adjusting for site and baseline scores. All comparisons of CAPS-2 clusters and global ratings were significant ($p<0.05$) except for the global ratings of social rating and rating validity. The following between group comparisons were also significant: IES total score ($p=0.028$), IES cluster of avoidance ($p=0.016$), Davidson Self-Rating PTSD Scale total score ($p=0.008$), Davidson cluster of arousal ($p=0.045$),

Davidson cluster of avoidance/numbing (p=0.031), CGI-S (p=0.002), CGI-I (p=0.001), Hamilton Depression Scale (p=0.022), and the Quality of Life Enjoyment and Satisfaction Questionnaire (p=0.014).

8. Exploratory Subgroup Analysis

8.1 Study 672

There were highly significant differences (marginal p-values from t-test less than 0.0001) in changes from baseline of this study to the endpoint of this study in all four primary efficacy variables (CAPS-2 total severity score, IES, CGI-S rating, and CGI-I rating) in both male and female subgroups analyzed separately. This was also true for the subgroup of patients who received sertraline in the feeder studies and for the subgroup who received placebo in the feeder studies.

8.2 Study 703

Among females, there were 2/29 (6.9%) relapses in the sertraline group and 7/28 (25%) relapses in the placebo group. Among males, there were 0/9 relapses in the sertraline group and 5/18 (27.8%) relapses in the placebo group.

9. Adverse events

9.1 Study 672

There were thirteen patients who discontinued due to adverse events attributed to study drug. One female subject had moderate weight gain from 136 lbs. to 148 lbs. One female patient experienced moderate dizziness, nausea, and syncope. One female had moderate decreased libido. One female patient had moderate insomnia, bladder pain, mild hypertonia, and twitching. A female patient experienced moderate apathy. A male patient had mild fatigue, impotence, and dry mouth. A male patient had moderate decreased libido and mild insomnia. A male patient had moderate rash on chest. A female patient had moderate insomnia. A female patient had moderate fatigue, insomnia, and increased sweating. A male patient had moderate forgetfulness. A male patient had moderate ejaculation failure. A female patient had mild dizziness, headache, nausea, and tremor. None of these were classified as serious adverse events. There were no serious adverse events reported that were attributed to the study medication.

9.1 Study 703

In the sertraline group, three patients discontinued due to an adverse event that was attributed to study drug. One female patient experienced mild insomnia and palpitation. A female patient had moderate depression. A female patient had mild body weight gain from 135 lbs. at baseline to a maximum of 138.5 lbs.

In addition, there was one serious adverse event that was not attributed to the study drug, but the cause was unknown. A 32-year old female became pregnant despite barrier contraception. The subject discontinued treatment upon knowledge of pregnancy. One month later, a sonogram revealed fetal death. The cause was unknown but not considered treatment-related.

Three patients discontinued treatment from the placebo group due to adverse events attributed to study drug (dizziness, mild agitation, and moderate increased sweating).

10. Conclusions

The study medication appears to be safe and well-tolerated at the doses studied. The long-term efficacy was established in one double-blind study (Study 703; p=0.007).

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This review consists of 9 pages of text, tables, and figures.

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NDA 20-990
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