CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 019839/S011

TRADE NAME: Zoloft 25 mg, 50 mg, and 100 mg Tablets

GENERIC NAME: Sertaline HCl

SPONSOR: Pfizer Pharmaceuticals

APPROVAL DATE: 07/08/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-839/S-011

JUL - 8 1997

Pfizer Pharmaceuticals
Attention: Margaret Longshore, Ph.D.
Director, Regulatory Affairs
235 East 42nd Street
New York, New York 10017-3184

Dear Dr. Longshore:

Please refer to your December 20, 1995, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoloft (sertraline Hydrochloride) 25, 50 and 100 mg tablets.

Reference is also made to an Agency approvable letter dated November 19, 1996, and we also acknowledge receipt of your additional communications dated January 29, February 4, and June 6, 1997.

The User Fee goal date for this application is July 30, 1997.

Supplemental application S-011 provides clinical data supporting the use of Zoloft in the treatment of panic disorder in a recommended dose range of 50 to 200 mg/day.

We have completed our review of this supplemental application, as amended, 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 marked-up draft labeling (see ATTACHMENT). Accordingly, this supplemental application is approved effective on the date of this letter.

Labeling

1. The labeling accompanying this letter should be used for marketing this drug product. This final labeling is based on Agency telefacsimiles sent to you dated May 22, and May 28, 1997. We note your agreement to the Agency's proposed labeling in a telephone conversation dated July 1, 1997, between Dr. Martha Brumfield of your firm and Mr. Paul David of this Agency. For convenience, all labeling changes made since your last approved labeling (Label Code: 69-4721-00-2) appear as shaded text (redlined) in the attached labeling.

2. As requested by you, below is a listing of the adverse event terms removed from the Other Events Observed During the Premarketing Evaluation of Zoloft section. We note that these event terms were removed at the request of the Agency since we considered them either to be too general to be informative or very unlikely to be caused by drug. In our view, the presence of such terms in labeling serves no clinical purpose and, in fact, tends to distract the prescriber from other, more informative terms. The event terms are:

   injection site fibrosis, tolerance decreased, heart disorder, varicose veins, sensory disturbance, local anesthesia, speech disorder, neuralgia, nail disorder, abnormal hair texture, skin disorder, fungal dermatitis, abnormal skin odor tooth disorder, tongue disorder, hemorrhoids, pain, halitosis, herpes simplex, viral infection, otitis media, deafness, arrhythmia, lymphadenopathy, cervical lymphadenopathy, dehydration, bone disorder, hernia, accidental injury, medical surgical procedure, neurosis, personality disorder, hysteria, drug abuse, drug dependence, abnormal thinking, sleep disorder, testes disorder, infection, abscess, fungal infection, moniliasis, respiratory disorder, taste perversion, eye abnormality, urine abnormal, bladder carcinoma, micturition disorder, and urinary tract infection.

Phase 4 Commitment

We note that you have already submitted the first packet of promotional materials for the indication of panic disorder. Please submit three copies of any subsequent introductory promotional material 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 material and the package insert directly to:

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

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. These revisions are terms of the supplemental NDA approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

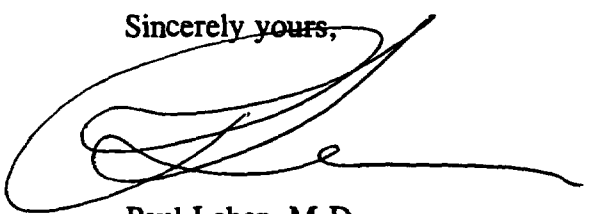
Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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, please contact Mr. Paul David, Project Manager, at (301) 594-5530.

Sincerely yours,



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

ATTACHMENT

cc:
ORIG NDA 19-839/S-011
HF-2/MedWatch
HFD-2/ORM
HFD-92/DDM-DIAB
HFD-101/LCarter
HFD-102/NSager
HFD-120/DIV FILE 7-3-97
HFD-120/PLeber/TLaughren/AMosholder/HLee
HFD-120/GFitzgerald/BRosloff
HFD-120/SBlum/MZarifa
HFD-120/PDavid 7/3/97
HFC-130/JAllen
HFD-40/LStockbridge
HFD-222/New Drug Chemistry Division Director
HFD-613
HFD-713/TSahlroot/JChoudhury
HFD-735/DPE
HFD-40/DDMAC (with draft labeling)
HFI-20/Press Office
District Office
rd:07/02/97pd;rev:07/03/97tl
ft:07/03/97pd
Doc #DAVID\LTRZLFPD.AP1
SUPPLEMENTAL APPLICATION APPROVAL [with Phase 4 Commitments]

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 8, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

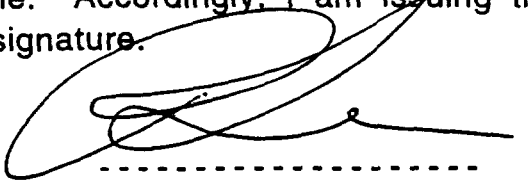
SUBJECT: Zoloft™ [sertraline hydrochloride] for Panic Disorder
NDA 19-839/S-011
Approval Action Memorandum

TO: File NDA 19-839

This memorandum conveys for the record my determination that S-001 to NDA 19-839, which provides for Zoloft's use in the management of Panic Disorder, may be approved. The determination reflects both the substantive considerations regarding the clinical evidence supporting the conclusion that Zoloft is safe for use and effective in use (addressed in my approvable action memorandum of 11/19/96), and the results of negotiations (concerning largely technical details regarding labeling) conducted since the approvable action was taken (see Dr. Laughren's July 3, 1997 summary).

As anticipated in the case of a product already marketed for use, the Safety Update, reviewed by Dr. Mosholder, provides no unusual or unexpected reports of adverse sertraline associated events.

I have reviewed the labeling text negotiated by the review team under Dr. Laughren's direction and find it acceptable. Accordingly, I am issuing the approval action letter prepared for my signature.



Paul Leber, M.D.
July 8, 1997

M E M O R A N D U M

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

DATE: July 3, 1997

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

SUBJECT: Recommendation for Approval Action for
Zoloft (sertraline) for Panic Disorder (PD)

TO: File NDA 19-839/S-011
[**Note:** This overview should be filed with the 1-29-97 submission.]

1.0 BACKGROUND

In our 11-19-96 approvable letter, we requested a safety update, a foreign regulatory update, a world literature update, and a commitment to conduct We also attached our proposal for labeling. Pfizer responded formally to the approvable letter with the 1-29-97 submission.

The review team, up to the level of Team Leader, interacted with the sponsor over a period of several weeks to arrive at the version of labeling [LABZLFPD.AP1] that is included with the approval letter. The sponsor's initial counter-proposal to our approvable labelng was included in the 1-29-97 submission. We responded with a counter-proposal that was faxed to Pfizer on 5-22-97 and 5-28-97. This counter-proposal included finalized language from several other labeling supplements, including SLR-021, SLR-019, and SLR-022. The sponsor responded with a fax dated 6-6-97. The sponsor agreed to our counterproposal, with slight modifications, and this agreement was confirmed in a telephone call with Paul David, the project mangager, on 7-1-97.

Dr. Andrew Mosholder reviewed the clinical sections of the 1-29-97 response to the approvable letter, including the safety update, the literature update, the regulatory status update, and labeling.

2.0 SAFETY UPDATE

The safety update included reports of deaths, serious adverse events, and adverse dropouts. This update covered a period from 6-30-95, the cutoff date for the original submission, through 11-15-96. The number of sertraline-exposed patients for whom safety data have now been provided has been expanded from the 430 patients in the original submission to a total of 1157 patients as of this 1-29-97 safety update.

There was 1 death and 9 other serious adverse events among sertraline-exposed patients in this safety update. Dr. Mosholder reviewed these cases and concluded that none of them could be reasonably attributed to sertraline treatment. There were an additional 5 sertraline-exposed patients discontinued for adverse events, and Dr. Mosholder concluded that none of the events was unusual for sertraline. Of interest, there were suicide attempts reported, among all treatment groups, a reminder that depression and suicidality are commonly associated with panic disorder.

In summary, none of these reports contained new or unusual findings that would change my view about the approvability of this drug. Dr. Mosholder has proposed broadening the standard suicide precautions statement to all indications for which Zoloft is approved, and I agree.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period from the cutoff date for the original NDA submission to November, 1996, and included 16 references. These were reviewed by Pfizer staff and they provided a warrant that they contained no unrecognized adverse events relevant to this supplement. We were provided with only the titles of these papers. Dr. Mosholder reviewed the titles and concurred that, at least from the titles, there was no indication of important new safety findings that would adversely affect our conclusions about the safety of Zoloft for panic disorder.

4.0 FOREIGN REGULATORY UPDATE

The sponsor warranted in the 1-29-97 submission that Zoloft is not approved for the treatment of panic disorder in any countries at the present time, and that no negative regulatory actions have been taken with regard to this indication. It is apparently under review in Canada.

5.0 REQUEST FOR RELAPSE PREVENTION TRIAL

The sponsor has committed to completing a relapse prevention trial involving Zoloft in panic disorder (#93CE21-0631) to adequately address the question of long term effectiveness.

6.0 LABELING

Lilly proposed numerous changes to the labeling for Zyprexa, many of which we found acceptable, while others were the subject of negotiations with the review team over the roughly 2-week time period described under Background. As noted, we were able to reach agreement at a Team Leader level on labeling.

7.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Pfizer has submitted sufficient data to support the conclusion that Zoloft is effective and acceptably safe in the treatment of panic disorder. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:
Orig NDA 19-839/S-011
HFD-120
HFD-120/TLaughren/PLeber/AMosholder/HLee/MMille/PDavid

DOC: MEMZLFPD.AP1

M E M O R A N D U M

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

DATE: May 28, 1997

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

SUBJECT: 2-20-97 submission providing for labeling language to incorporate findings from a relapse prevention trial in depression (Study 320)

TO: File, NDA 19-839/SLR-021 (Zoloft)

See my 1-17-97 memo for details on the study.

Pfizer has proposed changes to three sections of labeling: Clinical Trials subsection of Clinical Pharmacology; Indications and Use; and Dosage and Administration.

Their proposed language is mostly acceptable, but I do have a few changes to propose:

-For another SSRI, we have recently reviewed a relapse prevention trial and included labeling language that does not include actual relapse rates. The rationale for excluding the actual rates was a concern that there may be attempts to do cross study comparisons of such rates, when in fact, the actual rates depend very much on the populations studied and such comparisons are not valid. Since the important question is whether or not any of these drugs is active in delaying relapse (i.e., beats placebo), it didn't seem important to include the actual rates. Consequently, I would propose deleting the rates here as well.
-The dosage range for the trial (i.e., 50-200 mg/day) should be included, as well as the mean dose.
-The relapse prevention phase of the trial should be characterized as a 44-week phase and not 1 year, although the total trial duration can be referred to as 1 year.

I propose the following alternative language for these 3 sections:

-For Clinical Trials, under Clinical Pharmacology:

> "Study 3 involved depressed outpatients who had responded by the end of an initial 8-week open treatment phase on Zoloft 50-200 mg/day. These patients (N=295) were randomized to continuation for 44 weeks on double-blind Zoloft 50-200 mg/day or placebo. A statistically significantly lower relapse rate was observed for patients taking Zoloft compared to those on placebo. The mean dose for completers was 70 mg/day."

-For Indications and Usage:

> "The efficacy of Zoloft in maintaining an antidepressant response for up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving Zoloft for extended periods should be reevaluated periodically (see Clinical Trials under Clinical Pharmacology).

-For Dosage and Administration:

> "It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown. Systematic evaluation of Zoloft has shown that its antidepressant efficacy is maintained for periods of up to 44 weeks following 8 weeks of open-label acute treatment (52 weeks total) at a dose of 50-200 mg/day (mean dose of 70 mg/day). (see Clinical Trials under Clinical Pharmacology)

cc:
Orig NDA 19-839 (Zoloft)
HFD-120/DivFile
HFD-120/TLaughren/HLee/AMosholder/PDavid

DOC: NDA19839.11

M E M O R A N D U M

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

DATE: January 17, 1997

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

SUBJECT: Reconsideration of Data from Relapse Prevention Trial (Study 320)

TO: File, NDA 19-839 (Zoloft)

Background

As part of a larger discussion regarding FDA s concern that Pfizer was engaging in violational promotional activities for Zoloft (see 8-1-96 letter), there has been some discussion of the interpretation and description in labeling of study 320, a long-term trial submitted with the original NDA for Zoloft. This was a European trial (37 sites) involving an initial open 8-week treatment phase of 467 depressed outpatients with Zoloft 50-200 mg/day. 295 responders entered a 44-week double-blind phase involving the 2:1 randomization to either Zoloft (50-200 mg/day) or placebo. The protocol for this trial was lacking in detail, and in fact, it was not even clear that the goal of this study was to look at relapse prevention. There were no definitions provided for either responders during the open phase or relpase during the double-blind phase. The protocol focused on change from baseline in CGI as the primary outcome of interest, and that was also the focus of our original reviews of this study. On that measure, the study fails to show significant drug-placebo differences beyond about 8 weeks in the observed cases analyses. Thus, despite the fact that sponsor in analyzing the data from this trial provided a definition for relapse and analyzed for relapse rate, we characterized this as a 16-week study in the labeling for Zoloft (8 weeks of open treatment plus 8 weeks in the double-blind phase). In retrospect, this is not the way we currently approach a study of this design, and it seemed reasonable to revisit the data from study 320.

Reconsideration of Study 320 Data

I met with Dr. Hillary Lee, the clinical reviewer of the efficacy data for the original NDA, with Dr. Japo Choudhury the statistical reviewer of the efficacy data for the original NDA,

and with Dr. Todd Sahlroot, Team Leader for the Biometrics group assigned to this NDA. Overall in study 320, 58% of Zoloft patients completed to 44 weeks compared to 34% of placebo patients. The sponsor had defined relapse in terms of changes on the CGI, i.e., a patient who moved from a CGI rating of 1-3 to $\geq$ 4 and either stayed at that level or discontinued for lack of efficacy was considered to have relapsed. Using that measure, 13% of Zoloft patients had relapsed at 44 weeks compared to 46% of placebo patients ($p < 0.001$). We also asked the sponsor to perform a life table analysis for time to relapse and this analysis also highly favored Zoloft over placebo. Although there is the problem of the protocol not clearly stating the goals of the study and not providing a definition for relapse, we were in agreement that, were we to look at this study today, we would likely characterize it as a successful, 44-week relapse prevention trial.

Comment/Recommendations

I have discussed this matter with Dr. Leber, and he is in agreement that it would not be unreasonable for the sponsor to be permitted to recharacterize this study in labeling. We will invite them to propose an alternative description of this trial in labeling, but now in the newly created Clinical Trials subsection of Clinical Pharmacology rather than in Indications and Use. A mention of long-term efficacy can be made in Indications and Use, with a reference back to Clinical Trials for the details.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 19-839 (Zoloft)
HFD-120/DivFile
HFD-120/TLaughren/PLeber/HLee/AMosholder/PDavid
HFD-710/TSahlroot/JChoudhury
HFD-101/RTemple
HFD-40/DDMAC (NDrezin)

DOC: NDA19839.10

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 19-839/S-011

Food and Drug Administration
Rockville MD 20857

Pfizer Inc.
ATTENTION: Margaret A. Longshore, Ph.D.
235 East 42nd Street
New York, New York 10017

Dear Dr. Longshore:

Please refer to your December 20, 1995 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the Zoloft (sertraline HCl) Tablets, 25, 50, 100, and 200 mg.

We acknowledge receipt of the following amendments:

February 16, 1996	March 6, 1996	March 21, 1996	March 29, 1996
April 18, 1996	May 28, 1996	July 24, 1996	August 12, 1996
August 20, 1996			

Supplemental application S-011 provides clinical data supporting the use of Zoloft in the treatment of panic disorder in a recommended dose range of 50 to 200 mg/day.

We have completed our review of supplemental application S-011 and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following clinical issues:

1. **Labeling**

   Accompanying this letter (See Attachment) is the Agency's proposal for the labeling of Zoloft. Our proposal is based on your labeling proposal submitted on December 20, 1995.

   We have proposed a number of changes to your draft labeling and explanations for these changes are provided in the bracketed comments embedded within the proposed text. In certain instances, we have asked you to further modify labeling. Division staff would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

2. **Safety Update**

   Our review of the safety of Zoloft in the treatment of panic disorder was based on data accumulated through 6-30-95. You will need to submit a final safety update including safety data accumulated since these cutoff dates. This safety update can focus on deaths, serious adverse events, and patients dropping out of clinical trials

for adverse events in studies of panic disorder. It should include a line listing, along with narrative summaries, for all such patients. We may ask for copies of case report forms for selected patients from this list.

3. World Literature Update

This report should cover all relevant published papers, including clinical or preclinical data, that were not submitted with the original NDA or in subsequent amendments.

We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conditions about the safety of Zoloft in this population. The report should also detail how the literature search was conducted, by whom, (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

4. Foreign Regulatory Update/Labeling

We require a review of the status of all actions with regard to Zoloft in the treatment of panic disorder, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If Zoloft is approved for use in panic disorder in any countries, we ask that you provide current labeling for Zoloft in those countries, along with English translations when needed.

5. Post-Marketing Studies

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. For administrative purposes, all submissions, including labeling

supplements, relating to Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar paper.

In addition, please submit three copies of the introductory promotional and/or advertising campaign that you propose to use for this new indication. 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 material and the package insert, directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-040, Room 17B-17
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

In accordance with the policy described in Section 314.102(d) of the new drug regulations and in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with the division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. Alternatively, you may choose to receive such a report via a telephone call. Should you wish this conference or a telephone report, please call Mr. Merril Mille, Senior Regulatory Management Officer, at (301) 594-5528.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

Sincerely yours,

11/19/96

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

ATTACHMENT

CC: ORIG NDA 19-839/S-011
HFD-120
HFD-2/MLumpkin
HFD-040(with draft labeling)
HFD-92
HFD-100/RTemple (with Labeling)
HFD-120/PLeber AM 11/7/96 HLee 11/7/96
HFD-120/HLee/AMosholder/TLaughren: JM 11-8-96
HFD-120/BRosloff/GFitzgerald:
HFD-120/~~JRzeszotarski~~/SBlum: MZaniFa MZ 11/7/96
HFD-120/MMille: 10/22/96
HFD-860/RBaweja:
HFD-638(with draft labeling)
HFD-713/Jchoudhury/JTSahlroot:
HFD-735/Barash (with draft labeling)
District Field Office

SPELLCHECK: 11-07-96/mjm
DT:
REVISED: 11-7-96/tpl
FT:

DOC# n:\mille\LTRZLFPD.AE1

SUPPLEMENTAL APPLICATION
APPROVABLE

NDA: 19-839/S-011
Trade Name: ZOLOFT
Generic Name: sertraline
Applicant Name: Pfizer Central Research
Division: HFD-120
Project Manager: Merril J. Mille, R.Ph.
Approval Date: 07-08-97

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 questions about the submission.

   a) Is it an original NDA? **NO**

   b) Is it an effectiveness supplement? **YES**
   If yes, what type? (SE1, SE2, etc.) **SE-1**

   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**

   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:

   d) Did the applicant request exclusivity? **YES**

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

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

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? **NO**

If yes, NDA # Drug Name:

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

3. Is this drug product or indication a DESI upgrade? **NO**

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). **NDA 19-839/Zoloft Tablets (original approval)**

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.) **N/A**

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

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

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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**

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

(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?

NO

(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.

NO

(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? **NO**

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:

Investigation #1, **Study #: 93CE21-0629**
Investigation #2, **Study #: 93CE21-0630**

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	**NO**
Investigation #2	**NO**

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

NOT APPLICABLE

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	**NO**
Investigation #2	**NO**

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

NOT APPLICABLE

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"):

Investigation #: 1, **Study #:93CE21-0629**
Investigation #: 2, **Study #:93CE21-0630**

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	**YES**	**IND#:**
Investigation #2	**YES**	**IND#:**

(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?

NOT APPLICABLE

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.)

NO

Merril J Mille 11/19/96

Merril J. Mille, R.Ph.
Sr. Regulatory Management Officer
DNDP, HFD-120

11/19/96

Paul Leber, M.D.
Director
DNDP, HFD-120

cc:
Original NDA
Division File
HFD-120/MMille
HFD-85/Holovac

ITEM 13. PATENT AND EXCLUSIVITY INFORMATION

1.	Active Ingredient:	(1S-cis)-4-(3,4-dichlorophenyl) -1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride
2.	Strength:	25, 50, and 100 mg sertraline hydrochloride
3.	Trade Name:	Zoloft
4.	Dosage Form/Route of Administration:	Capsules/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

APPEARS THIS WAY
ON ORIGINAL

ITEM 14. PATENT CERTIFICATION

Pfizer certifies that patent nos. 4,536,518 and 4,962,128, which are listed in section 13 of this application, claim, respectively, the drug sertraline and a method of treating anxiety related disorders (including panic disorder) using sertraline, and that sertraline is the subject of this appplication for approval under Section 505 of the Federal Food, Drug, and Cosmetic Act.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 19-839 Supplement # 011 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-120 Trade (generic) name/dosage form: Sertraline Tablets Action: AP [redacted]A

Applicant Pfizer Therapeutic Class _____
Indication(s) previously approved Depression / O.C.D. Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Panic Disorder (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ ___ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed. for this indication

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Thomas P. Laughren 11-14-96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 19-839
HFD-120 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 19-839 Supplement # 011 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-120 Trade (generic) name/dosage form: Sertraline Tablets Action: AP (AE) NA

Applicant Pfizer Therapeutic Class _____
Indication(s) previously approved Depression / O.C.D. Pediatric labeling of approved indication(s) is adequate __ inadequate __

Indication in this application Panic Disorder (For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

__ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. The applicant has committed to doing such studies as will be required.
- __ (1) Studies are ongoing,
- __ (2) Protocols were submitted and approved.
- __ (3) Protocols were submitted and are under review.
- __ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

__ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

for this indication

__ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

__ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Thomas P. Laughren 11-14-96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 19-839
HFD-120 /Div File
~~NDA/PLA Action Package~~
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

3/96

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 19-839
Drug: Zoloft (sertraline HCl)
Sponsor: Pfizer
Date of Submission: 1/29/97
Date Received: 1/30/97
Material Submitted: Supplement 11, for Zoloft in the treatment of Panic Disorder: Safety Update and Response to Approvable Letter
Medical Officer: Andrew Mosholder, M.D.

I. Background

In the Division's letter of 11/19/96, this supplement was designated "approvable." The letter made several requests of Pfizer: modifications of the proposed labeling, a safety update for panic disorder clinical trial experience focusing on serious adverse events and adverse dropouts, a world literature update, a foreign regulatory status update for this indication, and a committment to complete the ongoing
This submission is Pfizer's response to the approvable letter. Also included in the submission are draft promotional materials; however, these materials were submitted to the Division of Drug Marketing, Advertising and Communications and will not be covered in this review.

II. Safety Update

Please refer to the clinical safety review of 11/1/96 for details of the sponsor's clinical development program. Pfizer reports that for the panic disorder indication there have been a total of 8 completed clinical studies, with 8 ongoing clinical studies. Since the original submission, studies 603 and 003 (Japan) have been completed. In addition, the following 5 new studies have been initiated and are ongoing.

Table: Panic disorder studies initiated since the original submission. All studies listed are ongoing.

Protocol	Description
001 (Brazil)	DB, multicenter, 12 week flexible dose trial, sertraline v. placebo, panic disorder (n=78 total); sertraline 50-100 mg/d
003 (Canada)	DB, multicenter, 52 week flexible dose trial, sertraline v. placebo v. Cognitive-Behavioral therapy, panic disorder (n=8); sertraline 25-200 mg/d
003 (multinational)	DB, multicenter, 29 week flexible dose trial, sertraline v. placebo v. Imipramine, panic disorder and concurrent depression (n=173); sertraline 25-100 mg/d, imipramine 25-200 mg/d
003C (multinational)	DB, multicenter, 18 week extension of study 003 (n=19)
337B (Australia)	Open label flexible dose extension of study 337; (n=35) sertraline 50-200 mg/d

Additional Exposure

The cutoff date for the original submission was 6/30/95; the cutoff date for the safety update is 11/15/96. Pfizer estimated the exposure in the ongoing studies according to the randomization schemes, arriving at total numbers of patients as shown.

Number of patients by treatment:	Sertraline	Placebo	Imipramine
Total with safety update (estimated)	1157	571	166
Original database	430	275	19

Serious Adverse Events

Between 7/1/95 and 11/15/96, Pfizer reports that 22 patients suffered serious adverse experiences in panic disorder clinical trials, including one death. Narrative summaries and line listings were provided for these patients. Of these, 10 received sertraline, 6 placebo, 1 imipramine, and 5 were still blinded. In addition, one additional serious adverse event was found that should have been included in the original submission, and Pfizer submitted this case report also. In my judgement, none of these serious adverse events could be reasonably attributed to sertraline treatment. The following table summarizes these events.

Protocol and patient number	**Treatment**	**Serious Adverse Event**
Death		
001 (Brazil) #73	Sertraline	42 year old female died with pneumonia after 56 days of sertraline 50 mg/d
Cardiovascular		
337B #18	Sertraline	55 year old female hospitalized for supraventricular tachycardia treated with atenolol; did not d/c sertraline
#113	Sertraline	48 year old female developed trigeminy; completed study
Gastrointestinal		
337 #162	setraline	46 year old male with peri-anal abscess
631 #1128	sertraline	48 year old female with diverticulitis
003 #63	blinded	48 year old female with bleeding gastric ulcer
337 #99	placebo	44 year old male with duodenal ulcer
337 #291	placebo	34 year old male with possible dysentery

Metabolic/ Endocrine		
646 #1039	blinded	50 year old female with diarrhea and electrolyte disturbance
Musculoskeletal		
# 1213	sertraline	39 year old male injured knee in horse riding accident
Nervous/ Psychiatric		
♀ 541	sertraline	20 year old female with syncope after 44 weeks on sertraline 200 mg/d, and suicide gesture at 48 weeks on sertraline
#523	sertraline	72 year old male hospitalized for observation after falling and hitting his head; fall attributed to chronic knee arthritis
337 # 226	sertraline	41 year old female hospitalized for worsening panic disorder
337 #122	imipramine	35 year old male attempted suicide by overdose
603 #15-4	placebo	43 year old male hospitalized for increased anxiety
337 #34	placebo	48 year old female made suicide attempt by overdose
Respiratory		
337 #302	placebo	43 year old female with carcinoid tumor of lung
Genitourinary/ Reproductive		
003 #168	blinded	31 year old female underwent elective abortion
337 #348	placebo	54 year old female with cervical intraepithelial neoplasm
Miscellaneous		
#1031	sertraline	35 year old female hospitalized for treatment of a cat bite
#140	blinded	60 year old female with breast carcinoma
# 671	blinded	37 year old female hospitalized with suicidal ideation and intoxication

As noted, in my judgment none of these events are likely to be causally related to sertraline treatment. There were a number of suicide attempts, consisitent with the association of panic disorder and suicidality reported in recent clinical literature.

Adverse Dropouts

The sponsor reported on an additional 5 sertraline treated panic disorder patients who discontinued treatment for adverse experiences. Of these 5 patients, 3 had symptoms related to gastrointestinal distress, 2 had anorexia, 2 had tremor, and one had palpitations (3 patients had more than one adverse event leading to discontinuation). These adverse events do not

appear unusual for sertraline treated patients.

Conclusions

There is no evidence from these cases of serious adverse events or adverse dropouts that would alter the previous conclusions about the safety profile of sertraline administered to panic disorder patients. The suicide attempts reported suggest that this patient population is vulnerable to suicidality, which has implications for the labeling (see below).

III. World Literature Update

Pfizer conducted an electronic literature search using a variety of databases, covering the period from January 1995 to November 1996. This yielded 16 publications. These were reviewed by Thomas F. Miller, Ph.D., who is a post-doctoral fellow at Pfizer (his post-doctoral fellowship discipline is not specified). He concluded that there were no unrecognized adverse safety findings relevant to this supplement. Please note that no copies of these references were submitted; however, there is no indication of important new data from the titles provided.

IV. Foreign Regulatory Update

This indication is currently under review by the Canadian regulatory agency; no other foreign submissions have been made as of 11/15/96.

V. Phase IV Committments

Pfizer plans to complete the

VI. Labeling

I will summarize here the changes in Pfizer's proposed labeling subsequent to the approvable letter. Some of these changes were apparently discussed with Dr. Laughren by telephone.

Pfizer has made a counter proposal for the description under Clinical Trials of the panic disorder studies. The chief differences between their counterproposal and the approvable letter are that they have added a description of study 529, which they state Dr. Laughren requested; and that they have added positive findings on a variety of secondary outcome measures such as quality of life and phobic avoidance.

In the Precautions section, Pfizer has deleted references to specific indications in several places. I have one recommendation pertaining to this, which is that the suicide precaution statement likewise not be limited to depressed patients; as noted earlier, there were a number of suicide attempts among these panic disorder patients. For that matter, OCD patients may also be prone to suicide attempt considering the comorbidity between depression and OCD. I propose a suicide precaution statement similar to the Prozac labeling which includes all the indications.

In the Adverse Reactions section, it appears that Pfizer has generated the new tables

requested in the approvable letter, namely, a "5% table" showing incidence of adverse events by indication, a "2%" adverse event incidence table combining indications, and an expanded "Other Events" table including data on roughly 3800 patients who received Zoloft for any of the three current indications. In the revised "Other Events" table, contrary to our suggestion in the approvable letter, Pfizer has elected not to omit terms for which a drug cause could be considered remote or non-serious events reported only once. This also was apparently discussed by telephone with Dr. Laughren.

VII. Conclusions and Recommendations

I recommend that the supplement for the indication of panic disorder be approved. The sponsor's proposed labeling may need some minor revisions; specifically, the description of secondary outcome measures in the Clinical Trials section is questionable, and the Suicide precaution should no longer be limited to the indication of depression.

5/2/97

Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 19-839
Div File
HFD-120 Laughren/Mille/Mosholder

7-3-97
We have now agreed upon final labeling and this supplement can be approved. See memo to file for more detailed response.
Thomas P. Laughren, MD
TL, PDP

REVIEW AND EVALUATION OF CLINICAL DATA

IND/NDA:	N19-839
SPONSOR:	Pfizer
DRUG:	Sertraline (Zoloft)
DRUG CATEGORY:	SSRI
MATERIAL SUBMITTED:	Labeling supplement re: gender effect for efficacy (SLR-022)
CORRESPONDENCE DATE:	5/7/97
DATE RECEIVED:	5/7/97

This supplement provides for a statement to appear in the Clinical Trials/Depression section of labeling that states: "Analyses for gender effects on outcome did not suggest any differential responsiveness on the basis of sex" (pg. 4 of this submission). The analyses of depression efficacy data by gender submitted here were previously submitted to DDMAC and reviewed by this Division; I have attached a copy of that review. As stated in the previous review, the sponsor's analyses support their conclusion that evidence for a differential effect by gender in the treatment of depression is absent. Note that this labeling supplement does not include any statement about the adverse event profile by gender.

I recommend approval of this labeling supplement.

[signature] 6/6/97

Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 19-839 / SLR-022
Div. File
HFD-120:Laughren/David/Mosholder

6-16-97
as noted in the
4-15-97 minutes, the
proposed addition to
labeling is acceptable
— James P. Laughren, MD
TL, PDP

MEDICAL OFFICER CONSULT REVIEW

DATE RECEIVED: 4/8/97
CONSULT FROM: DDMAC, HFD-040
SUBJECT: ZOLOFT--RESPONSE REGARDING GENDER ANALYSES
REVIEWER: ANDREW MOSHOLDER, M.D.
DATE OF REVIEW: 4/15/97

The Division of Drug Marketing Advertising and Communications has requested our evaluation of Pfizer's response to a recent warning letter regarding inappropriate promotional materials for Zoloft (sertraline HCl, NDA 19-839). The response is dated 4/3/97, and concerns the issue of safety and efficacy of sertraline in the treatment of women with major depression.

The data presented were originally submitted with the Zoloft NDA; i.e., these data are not from new studies.

Efficacy

Pfizer has pooled data from two double blind controlled studies, 103 and 104; both studies were placebo controlled, and Pfizer combined dose groups in the fixed dose study 103 for this analysis. The rationale for selecting these two studies was not provided. However, I consulted with Dr. Hillary Lee, who reviewed the clinical efficacy for the Zoloft NDA, and it seems that these were in fact the only two positive pivotal studies in the original NDA submission.

This combined analysis showed a statistically significant difference between placebo and sertraline patient groups on Total HAMD scores with the pooled data, for men, women, and both sexes together. The "effect size" (mean change from baseline for sertraline minus that for placebo) was -3.0 for females, -2.8 for males, and -2.9 overall. Additionally, there was not a statistically significant gender by treatment interaction.

This data supports Pfizer's assertion that there is no significant differential response on the basis of gender.

Adverse Effects

The analysis of the adverse event profile presented in this submission used the pool of depression/other trials corresponding to Table 1 of the current Zoloft labeling. This data set comprised 861 sertraline patients (271 men and 590 women), and 853 placebo patients (271 men and 582 women). Pfizer did not provide details of their analysis, but they report that the method they used was to subtract the placebo incidence from the sertraline incidence for each particular adverse event, comparing these for men and women. This is in a sense a comparison of attributable risks for men and women, and may not be the most sophisticated method; better might have been to compare relative risks for men and women. In any event, the sponsor reported statistically significant

differences between males and females for the following adverse events at a $p<0.05$ level of significance: libido decreased, sweating increased and agitation (higher in men), and paresthesia (higher in women). Additionally, the adverse event of dizziness was marginally significantly increased in men compared to women ($p<0.1$). It is interesting to note that agitation was actually more frequent in females receiving placebo (4.6%) than in females receiving sertraline (4.4%), while for men the incidences were 8.1% and 2.6% for sertraline and placebo, respectively.

On balance, I would tend to agree with Pfizer that these differences in adverse event incidences by gender do not represent clinically meaningful dissimilarities in adverse drug reactions for men and women.

4/15/97

Andrew Mosholder, M. D.
Medical Officer, HFD-120

Cc:Orig. HFD-040
Division Consult File
NDA 19-839 File
HFD-120/Laughren/David/Mosholder/Lee

4-23-97

I agree with Dr. Mosholder that the data submitted in this 4-3-97 submission are not suggestive of any important differences in antidepressant effectiveness or safety between men and women. The efficacy analyses would be supportive of the following standard labeling statement in the Clinical Trials subsection under Depression: "Subgroup analyses did not indicate any differential responsiveness on the basis of gender." While the safety analyses also did not suggest any gender differences in safety, we have generally not included statements about such findings in labeling, and I would prefer not to set a precedent by doing that here. Regarding what promotional claims might arise from these findings, I would think very little. I think it would be reasonable for Pfizer to suggest that "subgroup analyses did not indicate any differential responsiveness or safety problems on the basis of gender," however, I do not think it would be reasonable to suggest, for example, that Zoloft is specifically effective in women or is specifically safe in women, since that would imply that it may be superior to other products in this regard, and that clearly has not been shown.

Thomas P. Laughren, MD
TL, ADP

REVIEW AND EVALUATION OF CLINICAL DATA

IND/NDA:	N19839
SPONSOR:	Pfizer
DRUG:	Sertraline
DRUG CATEGORY:	SSRI
MATERIAL SUBMITTED:	SLR-021 Labeling Amendment
CORRESPONDENCE DATE:	2/20/97
DATE RECEIVED:	2/21/97

In a letter to Pfizer 1/31/97, this Division requested a labeling change to the Clinical Pharmacology and Dosage and Administration sections to reflect findings from a long term relapse prevention trial, Study 320. This request was prompted by a reconsideration of the findings from that study, following review of recent promotional materials for Zoloft which included data from that trial. Please refer to Dr. Laughren's memo to the NDA file dated 1/17/97.

Pfizer, in this supplement, has proposed the following language under Clinical Pharmacology/Clinical Trials/Depression: " Study 3 was a relapse prevention trial. In this study, depressed outpatients, aged 18-79, who had responded to an 8 week open trial of ZOLOFT were randomized to continue on ZOLOFT or placebo for an additional 44 weeks. A significantly lower relapse rate was demonstrated for patients taking ZOLOFT (13%) compared to those on placebo (46%). The mean dose for completers was 70 mg per day." Additional new language is proposed under Indications and Usage/Depression, to replace the current description of Study 320: "The effectiveness of ZOLOFT in long-term use, that is, up to one year, has been demonstrated in a study of depressed outpatients. In this study, depressed patients who had responded to ZOLOFT during an initial acute open treatment phase and were then randomized for continuation on ZOLOFT or placebo demonstrated a significantly lower relapse rate for patients on ZOLOFT compared to those on placebo." Finallly, under Dosage and Administration /Maintenance Continuation Extended Treatment, the language stating that efficacy has not been shown beyond 16 weeks has been deleted, and the following sentence has been added: "Systematic evaluation of the efficacy of ZOLOFT has shown that efficacy is maintained for periods of up to one year."

Conclusions and Recommendations

Note that the sponsor's definition of relapse involved a patient who had a sustained increase in CGI from 1, 2, or 3 to 4 or greater, or a patient who discontinued for lack of efficacy. Pfizer has chosen to highlight this result rather than the difference in completion rates at 44 weeks (58% for sertraline and 34% for placebo). It might be more precise to describe this as a 44 week trial rather than a one year trial, although it is true that the total duration of sertaline treatment was one year. These details notwithstanding, I believe that Pfizer has made a reasonable response to our request.

I recommend approval of this supplement.

4/8/97
Andrew Mosholder, MD
Medical Officer, HFD-120

5-22-97
I have proposed some alternative language for labeling. See memo & file.
T. Laughren

NDA 19-839
D.U. File

REVIEW AND EVALUATION OF CLINICAL DATA

IND/NDA:	N19839
SPONSOR:	Pfizer
DRUG:	Sertraline
DRUG CATEGORY:	SSRI
MATERIAL SUBMITTED:	SLR-019 Labeling Amendment
CORRESPONDENCE DATE:	1/16/97
DATE RECEIVED:	1/17/97

In a letter to Pfizer dated 10/17/96, this Division asked the sponsor to add language to the Zoloft labeling under Precautions describing the association of severe cutaneous reactions with sertraline use. This language would have recommended discontinuation of sertraline in the event of a significant dermatologic adverse reaction such as TEN or Stevens-Johnson syndrome. This submission is the sponsor's counter-proposal, which provides for the following addition to the Other Events Observed During the Postmarketing Evaluation of Zoloft subsection:

"...severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders,..."

Conclusions and Recommendations:

Pfizer does not feel that the clinical evidence warrants stronger labeling at present. My own opinion is unchanged from my previous recommendation (please refer to the Monitored Adverse Reaction (MAR) document from HFD-730 dated 8/6/96, and to my review of the MAR dated 9/16/96); namely, that these data warrant a statement under Precautions.

As a practical matter, it would be appropriate to accept Pfizer's counter proposal for now. In the mean time, I propose consulting the Division of Pharmacovigilance and Epidemiology, to provide estimates of reporting rates of dermatologic reactions to sertraline as a further evaluation of the reporting "signal." Then, if more persuasive evidence emerges from this analysis, Pfizer could be approached again regarding a labeling change. If desired, other recently approved antidepressants could be included in this consult request.

6/17/97

Andrew Mosholder, MD
Medical Officer, HFD-120

NDA 19-839
Div File
HFD 120:TLaughren/PDavid/AMosholder/GBurkhart

6-27-97
I agree with the above interim measure while we gather additional information
T. Laughren

REVIEW AND EVALUATION OF CLINICAL SAFETY DATA

NDA: 19-839
Drug: Zoloft (sertraline HCl)
Sponsor: Pfizer
Date of Submission: 12/20/95
Date Received: 12/21/95
Material Submitted: Supplement 11, for Zoloft in the treatment of Panic Disorder
Medical Officer: Andrew Mosholder, M.D.
Review Completion Date: 11/1/96

Contents

1.0 Material Utilized in Review

1.1 Material from NDA/IND

The following is a list of specific items reviewed.

Volume	Submission Date	Material
1	12/20/95	Application Summary
29	"	ISS and ISE
3,8,13,19,26,28	"	Individual study reports

Case Report Forms/Tabulations

Protocol	Patient #
529	404
514	176

1.2 Related Reviews

The safety review of the Zoloft for Obssessive Compulsive Disorder (OCD) supplement by Dr. James Knudsen provided relevant information.

2.0 Background

2.1 Indication

Panic Disorder (PD) is described in the Diagnostic and Statistical Manual IV of the American Psychiatric Association as an anxiety disorder involving recurrent Panic Attacks accompanied by fearfulness about future panic attacks. The panic attacks themselves involve episodes of intense anxiety and concurrent somatic symptoms. Associated clinical features include excessive somatic concerns (which might decrease the patient's tolerance for minor side effects of medication) and comorbidity with other psychiatric disorders, notably Major Depressive Disorder, substance abuse, and other anxiety disorders, particularly agoraphobia. Certain laboratory findings have been associated with panic disorder, such as decreased bicarbonate. Some studies have suggested that mitral valve prolapse and thyroid disorders are more prevalent in panic disorder patients than the general population. Panic disorder is thought to be 2-3 times more common in women than men. Onset is usually in adolescence or early adulthood, and the course is frequently chronic. Lifetime prevalence is estimated to be 1.5-3.5% [DSM-IV, 1994].

Presently, Xanax (alprazolam) is the only drug marketed in the U.S. for the indication of panic disorder. Efficacy supplements for a panic disorder indication are currently under review for the marketed drugs Paxil (paroxetine) and Klonopin (clonazepam).

2.2 Important Information from Related INDs and NDAs and from Pharmacologically Related Agents

Pfizer has sponsored 2 INDs with sertraline:

In addition, there have been numerous sertraline single investigator INDs.

I am not aware of any critical data from these INDs which would not be found in the present submission.

Sertraline is a selective serotonin reuptake inhibitor (SSRI) and is known to share various adverse drug reactions with other drugs in its class. The approved dosage for depression is 50-200 mg/day.

2.3 Administrative History

- NDA 19-839 for Zoloft in the treatment of depression was approved 12/30/91. The protocol for study 0529, a fixed dose study with sertraline in panic disorder patients, was submitted to IND by Pfizer

on 4/22/91. Subsequently, 3 other U.S clinical studies were conducted under this IND. There was no End of Phase II or Pre-NDA Meeting with Pfizer for this supplement.

2.4 Directions for Use

The sponsor's draft labeling advises a starting dose of 25 mg sertraline once daily, increasing to 50 mg daily after one week. The labeling also advises that unresponsive patients may benefit from an increased dose, up to 200 mg/day maximum. The labeling further advises that responding patients may benefit from continued treatment beyond the 12 week duration administered in clinical trials.

2.5 Foreign Marketing

Although Zoloft is marketed in other countries for depression, it is not approved elsewhere for the indication of panic disorder.

3.0 Chemistry

This supplement proposes a starting dose of 25 mg; a chemistry supplement providing for a new 25 mg tablet strength was approved 3/6/96.

4.0 Animal Pharmacology

Pfizer conducted no new preclinical studies for this supplement.

5.0 Description of Clinical Data Sources

For this safety review, the sponsor's integrated primary database encompassed 6 clinical trials with 430 sertraline patients, 19 imipramine patients, and 275 placebo patients. The cutoff date for safety data was 6/30/95, at which time all 6 trials had been completed.

For serious adverse experiences, data from 4 ongoing clinical trials along with data from the 6 completed trials was provided. The cutoff date for serious adverse event safety data was also 6/30/95. Since 3 of the 4 ongoing trials are still blinded, the sponsor had to estimate the exposure for the serious adverse event data base based on the randomization schemes in the trials, yielding totals of 802 sertraline patients, 407 placebo patients and 52 imipramine patients.

Additional safety data was obtained from a Japanese open label sertraline study involving 47 patients; this data was not incorporated into the integrated primary database.

5.1 Primary Development Program

As noted, the integrated primary database created by the sponsor included 430 sertraline, 275 placebo and 19 imipramine treated patients. All six studies in the integrated primary database were completed at the time of the 6/30/95 cutoff date for collection of safety data. The mean duration of treatment for these patients was 61 and 66 days for sertraline and placebo, respectively. This is equivalent to an total exposure (expressed in patient years) of 72 patient years for sertraline and 50 patient years for placebo.

In addition, ongoing studies involved an estimated 372 sertraline patients, 195 placebo patients and 33 imipramine patients. Data from these patients regarding serious adverse events was available as of the 6/30/95 cutoff date, but these studies were not incorporated in the integrated primary database.

5.1.1 Study Type and Design/Patient Enumeration

Table 5.1.1 displays a summary of all studies included in the integrated primary database. All of these studies were placebo controlled.

Table 5.1.1 Summary of all studies in the integrated primary database

Pools by Study Design	Enumeration by Treatment Group		
	Sertraline	Imipramine	Placebo
Fixed dose	246	-	83
Flexible dose	184	19	192
Placebo controlled (total)	430	19	275

The following table enumerates the numbers of patients in the 6 completed controlled studies constituting the integrated primary database.

Completed Controlled Clinical Trials (=integrated primary database)

Study	Location	Study type	Sertraline	Imipramine	Placebo
629	U.S.	flexible dose	80	-	88
630	U.S.	flexible dose	88	-	88
326	Germany	flexible dose	14	17	14
326A	U.K.	flexible dose	2	2	2
529	U.S.	fixed dose	132	-	45
514	U.S.	fixed dose	114	-	38
Total		-	430	19	275

A description of these and all other studies, ongoing and completed, may be found in Appendix Table 5.1.1.

5.1.2 Demographics

The following table depicts the demographic profile for patients enrolled in the sertraline panic disorder integrated primary database.

TABLE 5.1.2.1 Demographic Profile for Sertraline PD Studies

PARAMETER	Sertraline (N = 430)	Placebo (N=275)
AGE (years)		
Mean	38.9	36.8
Range	18-79	19-63
Groups		
18-44 Years	310	216
45-64 Years	110	59
>= 65 Years	10	0

SEX		
Male	216	134
Female	214	141
RACE		
White	366	228
Black	17	20
Asian	5	0
Hispanic	24	9
Other	2	2
Missing	16	16
MEAN WT (lb)	173	175

5.1.3 Extent of Exposure (dose/duration)

Table 5.1.3 below displays the duration of exposure by the maximum daily dose for each patient.

TABLE 5.1.3
Number of all Patients Receiving Sertraline According to Maximum Daily Dose and Duration of Therapy in PD Studies (N = 430)

Duration (Days)	25 mg	50 mg	100mg	150 mg	200mg	>200 mg	TOTAL	(%)
1	0	4	0	0	0	0	4	0.9
2-10	10	27	10	1	0	0	48	11.2
11-31	1	23	9	5	3	0	41	9.5
32-90	0	63	108	30	119	9	329	76.5
91-100	0	3	3	1	1	0	8	1.9
TOTAL	11	120	130	37	123	9	430	100
(%)	2.6	27.9	30.2	8.6	28.6	2.1	100	

5.2 Secondary sources

5.2.1 Non-IND Studies

Protocol 003 was an open label Japanese study of sertraline for panic disorder which involved 47 patients. Pfizer elected to report the safety data from this study separately from the primary integrated database, as data had been incompletely analyzed.

5.2.2 Post Marketing Experience

Sertraline has been approved in the U.S. for the treatment of depression since 12/30/91; the drug is also marketed over 40 countries as well. Sertraline is not marketed for treatment of panic disorder in any country at this time. No analysis of postmarketing events related to treatment of panic disorder was included in this supplement.

5.2.3 Literature

The sponsor conducted a literature search using the Medline, EMBASE, Biosis, and PsycInfo databases, through August 1995. This provided approximately 50 citations from the world literature regarding

sertraline treatment of panic disorder, many of them review articles. Gail Farfel, Ph.D., from Pfizer reviewed these articles and concluded that there were no adverse findings with respect to sertraline in the treatment of panic disorder. Pfizer provided copies of only two of these references: Varon et al., J Emerg Med 1995;13(2):246 and Zinner SH, Am J Psychiatry 1994;151(1):147-148. These reports describe cases of treatment emergent panic attacks with sertraline therapy. As other references were not provided, I have reviewed only these two publications; however, there were no other citations in the sponsor's bibliography that appeared to have specific information bearing on the safety of sertraline in the treatment of panic disorder.

6.0 Human Pharmacokinetics

The terminal half life of sertraline is roughly 26 hours. Tmax after multiple oral doses is from 4-8 hours. Sertraline exhibited linear pharmacokinetics over the dose range of 50-200 mg (single doses). Food increased sertraline Cmax by 25% (compared to fasting) and shortened Tmax from 8 to 5.5 hours. The major sertaline metabolite is N-desmethysertraline, formed through an extensive first pass metabolism; it is less pharmacologically active than sertraline and has an elimination half life of over 60 hours. In addition, the AUC for desmethylsertraline increases with significantly chronic dosing. Sertraline and desmethylsertraline are further metabolized and conjugated; the metabolites are eventually excreted in feces and urine. Sertraline is 98% plasma protein bound. Sertraline clearance was found to be decreased in elderly subjects and subjects with liver disease.

7.0 Safety Findings

7.1 Backgroung and Methodology for Safety Review

The primary source for this safety review was the sponsor's integrated summary of safety and supporting data displays. Individual study reports were consulted as necessary to provide clarification on certain points.

7.1.1 Deaths

There have been no deaths in sertraline clinical trials for panic disorder.

7.1.2 Dropouts

7.1.2.1 Overall Pattern of Droupouts

The following table presents the reasons for premature discontinuations from the studies in the integrated primary database.

Table 7.1.3.1 Rates of Dropout by Treatment Group and Reason for Primary Integrated Database

Reason for Dropout	% Dropping Out Sertraline (n=430)	% Dropping Out Placebo (n=275)
Adverse Event	14.2	2.9
Insufficient Clinical Response	3.7	8.4
Lost to Follow Up	4.7	3.3
Protocol Violation	2.6	2.2
Intercurrent Illness	1.4	1.5

Withdrew Consent	0.9	1.8
Laboratory Abnormality	0.5	0.4
Other	4.0	2.5
Total	31.9	22.9

7.1.2.2 Adverse Events Associated with Dropout

Those adverse events leading to dropout by 1% or more of sertraline patients in the integrated primary database are listed in the table below. (Patients dropping out may have had more than one adverse experience recorded.)

Adverse Events Causing Dropout in ≥1% of Sertraline Patients in Integrated Primary Database

Adverse Event	Percent Dropping Out	
	Sertraline (n=430)	Placebo (n=275)
Nausea	2.6	0.4
Insomina	2.3	0
Somnolence	2.3	0
Agitation	2.1	0
Nervousness	1.9	1.1
Ejaculation failure	1.9 (males)	0
Diarrhea	1.4	0
Dyspepsia	1.2	0.4

In a few cases, the sponsor classified the reason for discontinuation as an intercurrent illness rather than an adverse event. Although the reasons for this classification were not always consistent (e.g., in one placebo patient insomnia was considered an intercurrent illness rather than an adverse event), such cases were few (i.e., only 10 patients total) and did not materially affect the tabulation shown in the above table.

For comparison, as stated in the current Zoloft labeling, the adverse events associated with discontinuation of treatment in at least 1% of subjects in premarketing clinical trials were as follows: agitation, insomnia, male sexual dysfunction, somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea, fatigue. Note the substantial overlap with the list of adverse events from panic disorder studies.

The sponsor presented data on dropouts for adverse events by dose for the two fixed dose studies (529 and 514) pooled. The doses of sertraline in these protocols were 50, 100 and 200 mg/d; dosage was started at 50 mg and titrated upwards by 50 mg/week for the higher doses. Inspection of this data for the above listed adverse experiences did not reveal any clearcut dose dependency, with one possible exception: all 4 male patients who discontinued for ejaculation failure recieved the high dose (200 mg). Of course, the numbers of patients dropping out in each dose group for a particular adverse event were quite small, making it difficult to draw conclusions from the data.

Pfizer also analyzed the incidence of dropout for adverse events in the first week, comparing protocols 529 and 514 in which patients received 50 mg during week 1, to protocols 629 and 630 in which patients recieved 25 mg during week 1. A total of 8% of 246 sertraline patients initially treated with 50 mg dropped out for adverse events, compared to 2% of 168 sertraline patients initially treated with 25 mg. From the same pool of studies, the adverse dropouts in the placebo groups were 2% and 1%, respectively.

Although it is not always reliable to compare such findings across different studies, these data suggest that reducing the starting dose from 50 mg to 25 mg, as the sponsor proposes, is reasonable.

7.1.3 Other Serious Adverse Events

For the safety analysis, the sponsor defined a serious adverse experience as one that was fatal, life threatening, disabling, requiring or prolonging hospitalization, involving cancer, congenital anolmaly or drug overdose, or suggesting a significant hazard to the patient. As noted previously, data on serious adverse events was available from both completed short term and ongoing (short and long term) studies, comprising estimated totals of 802 sertraline patients, 407 placebo patients, and 52 imipramine patients. Of these, there were 7 serious adverse events among sertraline patients, 4 among placebo patients and 1 for which the blind was not broken. Serious adverse events among sertraline patients were motor vehicle accidents (3 patients); and syncope (attributed to panic attack), labrynthitis, bladder carcinoma, and diabetes (1 patient each). There do not appear to have been any serious adverse events in Japanese study 003, although only a partial report was available.

7.1.4 Safety Findings Discovered with Other Specific Search Strategies

7.1.5 Adverse Event Incidence Tables

7.1.5.1 Establishing Appropriateness of Adverse Event Categorization and Preferred Terms

In the primary integrated database, Pfizer employed the World Health Organization Adverse Event Coding Glossary for translation of investigator reports of adverse events to standardized terminology.

For the majority of clinical studies in the primary integrated database, verbatim investigator terms were not provided, and so no comparison of investigator terms to the corresponding preferred terms for particular adverse events was possible. Where such information was available (i.e., in reports from the two European studies 0326 and 0326A), translation of investigator terms to preferred terms seemed appropriate.

7.1.5.2 Selecting the Key Adverse Event Tables for Characterizing the Adverse Event Profile

For the table of adverse events in short term placebo controlled trials, please refer to appendix 8.1.5.2.

In examining the common adverse event profile for sertraline in panic disorder patients, Pfizer has chosen to pool all 6 completed short term (10-12 week) placebo controlled trials. In my opinion, this is acceptable, particularly since it parallels the adverse event table in the present Zoloft labeling. The majority of patients represented in this pool were from the 4 domestic clinical studies. By inspection, the common adverse experiences were not very dissimilar between the different individual studies, so that combining the data seems appropriate. One could argue that presenting data from the fixed dose studies would illustrate dose relationships, and in fact the sponsor has included such a table in the Integrated Safety Summary. However, the numbers of patients for each dose were somewhat small (roughly 80 per dose for studies 529 and 514 pooled); furthermore, inspection of this data fails to reveal consistent dose response relationships for the more common adverse events.

7.1.5.3 Identifying Common and Drug Related Adverse Events

To determine common, possibly drug related adverse events, the following criteria were applied to the adverse event incidences for the pooled placebo controlled short term trials: adverse events that occurred at least twice as often among sertraline treated patients as among placebo treated patients, and which occurred in at least 5% of sertraline patients. Application of this criteria generated the following list of

possibly drug related adverse events. The more precise table in the Integrated Safety Summary was used rather than the table from the draft labeling (which rounded incidences to the nearest integer).

diarrhea	constipation	libido decreased	agitation
tremor	ejacualtion failure	anorexia	

[For comparison, the same criteria were applied to the premarketing clinical trial adverse event data as shown in the present Zoloft labeling. This yielded the following list of possibly drug related adverse events:

sweating increased	tremor	nausea dyspepsia
somnolence	male sexual dysfunction	

There are some differences between the two lists, but whether these differences relfect true distinctions between different clinical populations, or simply chance variabliity, is not clear.]

7.1.5.4 Additional Analyses and Explorations

To address gender effects, the sponsor analyzed the placebo subtracted incidence of adverse experiences in all 6 studies pooled, comparing men to women. Two adverse events showed statistically significant differences by gender: agitation (excess incidence for sertraline treated men over placebo treated men of 8% versus 0% for women) and vision abnormal (excess incidence for sertraline treated men over placebo treated men of 4% versus -3% for women). These findings are not likely to be of clinical significance.

Regarding age effects, only 10 patients older than 64 years of age received sertraline in these clinical trials, a number insufficient to permit conclusions about tolerability in elderly patients with panic disorder. Similarly, with respect to race, in the four protocols with data on race (629, 630, 529 and 514) only 48 nonwhite patients were exposed to sertraline, making generalizations about racial differences in adverse events difficult.

With respect to suicidal ideation, which has been reported to be associated with panic attacks, one placebo treated patient and no sertraline treated patients were listed as having suicidal ideation as an adverse experience.

7.1.6 Laboratory Findings

7.1.6.1 Extent of Laboratory Testing in the Development Program

Pfizer performed laboratory testing on all subjects in the clinical development program. Laboratory testing included complete blood counts, selected clinical chemistry tests, and urinalysis for glucose and protein. Roughly 400 sertraline and 250 placebo patients underwent clinical laboratory testing in the U.S. placebo controlled studies. In protocols 629 and 630, clinical laboratories were obtained at weeks 2 and 10, while in studies 514 and 529, clinical laboratories were obtained at weeks 2,4, 8, and 12.

7.1.6.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The primary pool for analysis of clinical laboratory findings was the pool of U.S placebo controlled studies (protocols 629, 630, 529, and 514). Foreign laboratory data was considered separately because of differences in reference ranges, criteria defining abnormalities, and units.

7.1.6.3 Standard Analyses and Explorations of Laboratory Data

7.1.6.3.1 Analyses Focused on Measures of Central Tendency

From the above-mentioned pool of clinical trials, the sponsor conducted an analysis of mean change from baseline for all laboratory analytes, comparing sertraline to placebo. The following is a list of all the statistically significant differences found (at a 5% level of significance).

Analyte	Mean change from baseline-sertraline	Mean change from baseline-placebo
BUN	+ 0.6 mg/dl	- 0.1 mg/dl
Alk. Phos.	+2.9 U/L	-0.2 U/L
Neutrophils	+0.5%	-1.1%
SGOT	+1.4 U/L	-0.3 U/L
SGPT	+2.4 U/L	-0.3 U/L
Cholesterol	+6.7 mg/dl	-4.3 mg/dl
Uric acid	-0.3 mg/dl	-0.03 mg/dl

The uricosuric effect of sertraline and increased cholesterol levels associated with sertraline treatment have been noted previously. These findings will be discussed below.

7.1.6.3.2 Analyses Focused on Outliers

Pfizer also analyzed the data from this same pool of clinical trials with respect to patients who exceeded predetermined values for potentially clinically significant laboratory abnormalities. Generally speaking, the criteria applied were comparable to the criteria for identifying laboratory values as clinically significantly abnormal in the Division's February 1987 Supplementary Suggestions for Preparing an Integrated Summary of Safety. There were no statistically significant differences between sertraline and placebo treatment groups with respect to the proportion of patients exceeding these criteria.

7.1.6.3.3 Dropouts for Laboratory Abnormalities

There were 2 sertraline treated patients (#550 and #130) out of 430 (0.5%), and 1 placebo patient (#457) out of 275 (0.4%) who discontinued treatment with asymptomatic liver enzyme elevations; all three had subsequent decrease in liver enzyme values.

7.1.7 Vital Signs

7.1.6.1 Extent of Vital Sign Measurements in the Development Program

In all placebo controlled studies, vital signs were measured every 1-2 weeks during treatment. In protocols 326, 326A, 529 and 514 orthostatic vital signs were also obtained.

7.1.7.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

Unlike the clinical laboratory analysis, the primary pool for analysis of vital sign findings was the pool of all placebo controlled studies (protocols 629, 630, 529, 326, 326A, and 514), i.e., the primary integrated database. Here, the foreign and domestic data were deemed compatible.

7.1.7.3 Standard Analyses and Explorations of Vital Sign Data

7.1.7.3.1 Analyses Focused on Measures of Central Tendency

From the above-mentioned pool of clinical trials, the sponsor conducted an analysis of mean change from baseline for all vital signs, comparing sertraline to placebo. The following is a list of all the statistically significant differences found (at a 5% level of significance).

Parameter	Mean change from baseline-sertraline	Mean change from baseline-placebo
HR supine (/min)	-1.5	+0.9
Weight (lb)	-0.9	+0.3

7.1.7.3.2 Analyses Focused on Outliers

The sponsor defined potentially clinically significant treatment emergent vital sign changes as follows: heart rate > 120 or < 50 bpm; systolic BP >180 or < 90 mmHg; diastolic BP > 105 or < 50 mmHg. Also, the change from baseline had to exceed 15 bpm for heart rate, 20 mmHg for systolic BP and 15 mmHg for diastolic BP. For body weight, the criterion was a 7% change from baseline. Applying these criteria, there were no statistically significant differences between sertraline and placebo treated patients with respect to the numbers of patients meeting a specific criterion.

7.1.7.3.3 Dropouts for Vital Sign Abnormalities

Two sertraline treated patients dropped out for hypertension (patient 542 in study 0630 and patient 349 in study 0529); both had past histories of hypertension. Also, one sertraline patient was listed as having dropped out for tachycardia.

7.1.8 ECGs

7.1.8.1 Extent of ECG Testing in the Development Program

In the primary integrated database, a total of 408 setratline patients and 264 placebo patients had both baseline and on treatment ECGs available for analysis.

7.1.8.2 Selection of Studies and Analyses for Overall Drug-Control Comparisons

The analysis of ECG findings encompassed data from the primary integrated database studies.

7.1.8.3 Standard Analyses and Explorations of ECG Data

The sponsor merely reported that a total of 64 sertraline patients out of 408 (15.7%) had ECGs that were normal at baseline but abnormal at follow up, compared to 49 of 264 placebo patients (18.6%). None of these abnormalities were considered clinically significant, although criteria for clinical significance were not specified, apparently being left to the judgement of the investigator. No quantitative analyses were performed on the aggregate ECG data.

7.1.9 Special Studies

There were no such studies in this supplement.

7.1.10 Withdrawal Phenomena/Abuse Potential

I discovered no clinical data relevant to this topic in this supplement.

7.1.11 Human Reproduction Data

I discovered no clinical data relevant to this topic in this supplement. Sertraline patient # 35 in protocol 0629 discontinued due to pregnancy, but no follow up was provided.

7.1.12 Overdose Experience

Please refer to the current package insert. There were no overdoses reported in the panic disorder studies.

7.2 Review of Systems

7.2.1 Cardiovascular

In the current Zoloft labeling, it is noted that analysis of ECG data from 774 patients receiving sertraline in clinical trials revealed no pattern of significant ECG abnormalities.

In this database, cardiovascular adverse experiences were not important causes of discontinuation from treatment and were not among the common, drug related adverse events. A slight decrease in mean heart rate was observed, as noted above. No serious adverse events involved the cardiovascular system. One Japanese subject withdrew for palpitations; two subjects withdrew for hypertension but both had previous histories of high blood pressure, and one subject withdrew for tachycardia.

These data do not provide evidence that sertraline treatment of panic disorder patients presents any unique cardiovascular risk.

7.2.2 Gastrointestinal

Nausea, diarrhea and dyspepsia are recognized adverse reactions to sertraline treatment, as described in the current Zoloft labeling. In these clinical trials, no serious adverse events involved the gastrointestinal system. There were a total of 27 adverse gastrointestinal events associated with premature disoncontinuation in sertraline treated patients. Among these, the most common were nausea, diarrhea, and dyspepsia. Thus there did not appear to be a unique pattern of adverse drug reactions for panic disorder patients in this body system.

7.2.3 Hemic and Lymphatic

Setraline treatment has been associated with abnormal platelet function as manifested by abnormal bleeding and purpura; otherwise sertraline is not believed to exert much effect on this body system. No serious adverse events involving the hemic and lymphatic system were observed. One sertraline subject (#197) discontinued for vaginal bleeding, which could have been a manifestation of platelet dysfunction. There was no evidence for a risk specific to panic disorder patients involving this organ system.

7.2.4 Metabolic and Endocrine

Sertraline treatment has been associated with SIADH and with weight loss. In these trials sertraline treatment produced a slight decrease in mean weight (see above). There was one serious adverse endocrine event: subject #047 was hospitalized for diabetes mellitus and was treated with insulin. This seems unlikely to be drug related, however. A slight but statistically significant increase in mean serum cholesterol was observed in sertraline patients (see above), with a net difference in change from baseline of 11 mg/dl for sertraline versus placebo. Dr. Knudsen observed a similar finding in his review of the sertraline clinical trials for obsessive compulsive disorder. As Dr. Knudsen noted in his review, increase in cardiovascular mortality is a continuous function of serum cholesterol levels. For comparison, the mean decrease in serum cholesterol observed in hyperchloesterolemic patients receiving the cholesterol

lowering drug lovastatin appears to be roughly 20%. A drug which increases mean cholesterol levels could, conceivably, convey added cardiovascular risk.

7.2.5 Musculoskeletal

Serious adverse events in this database for the musculoskeletal system resulted from motor vehicle accidents. Sertraline patient #176 sustained multiple fractures in a motorcycle accident; the patient had been drinking at the time. Sertraline patient #602 sustained a leg fracture in a motorcycle accident, and sertraline patient #1071 fractured a femur and his wrist in a motor vehicle accident (it was not specified if the patient was driving). In addition, placebo patient #404 was hospitalized for observation after head trauma in a motor vehicle accident. Although it is somewhat unusual to observe this many injuries from auto accidents in a relatively small clinical trial development program, I would not conclude that sertraline us increases the risk of motor vehicle accidents, particularly since one accident occurred in the placebo group, and clinical study data shows no adverse psychomotor effects from sertraline treatment. Otherwise, there were no important adverse experiences involving the musculoskeletal system.

7.2.6 Nervous

Nervous system adverse experiences associated with sertraline treatment include agitation, insomnia, tremor, dizziness, somnolence, fatigue, headache, and activation of mania, all described in the current Zoloft package insert. In this data set, there was one seizure in a placebo patient and none in sertraline patients. No suicidal ideation was reported in sertraline treated patients. There was one patient (#398) who experienced what was described as an aggressive reaction to the first sertraline dose, and discontinued from the study. Serious adverse events in sertraline treated patients involving the nervous system included labrynthitis with discovery of a cerebral aneurysm after a neurological workup (patient #151); and syncope, twitching and tremulousness which after inpatient evaluation were deemed to be manifestations of panic attacks (patient #612). One patient whose treatment remained blinded (#2280040) was withdrawn and hospitalized for severe anxiety. I do not believe that sertraline was causally related to any of these serious events. One patient (#176) was discontinued from sertraline treatment because of agitation, and hallucinations which resolved after discontinuation.

Altogether, 51 of the 61 sertraline patients who discontinued prematurely had associated adverse psychiatric events; for the most part, these events were similar to those already described in association with sertraline as noted above. There were no instances of treatment emergent mania among sertraline patients. Paresthesia, dizziness and headache were the most common neurological events associated with premature withdrawal.

As noted above under the heading Literature, Pfizer furnished copies of two reports describing a total of three cases of treatment emergent panic attacks associated with sertraline therapy of other disorders. One of these patients had concurrent suicidal ideation. It is possible that certain individuals may be susceptible to such reactions to sertraline treatment; however, the weight of evidence presented in this supplement supports an anti-panic effect of sertraline rather than a panic-provoking effect.
On balance, these data do not suggest a unique pattern of nervous system side effects for panic disorder patients receiving sertraline.

7.2.7 Respiratory

Sertraline is not noted for effects on the respiratory tract. In this database, hyperventilation and upper respiratory tract infection accounted for one premature discontinuation each; no serious adverse events involved the respiratory system. Sertraline tretment of panic disorder does not appear to involve any particular risk to the respiratory system.

7.2.8 Dermatologic

The Division has recently requested Pfizer to amend the Zoloft labeling to describe certain severe cutaneous adverse drug reactions associated with sertraline, such as toxic epidermal necrolysis. No serious cutaneous adverse experiences were observed in these clinical trials. Two sertraline patients discontinued with urticaria. Sertraline does not seem to present unique dermatologic risks for panic disorder patients.

7.2.9 Special Senses

No serious adverse experiences involved the special senses, and no pattern of adverse experiences or adverse dropouts involving special senses was found which might signal a risk with use of sertraline.

7.2.10 Genitourinary

Sertraline patient #508 had surgery for bladder carcinoma; this was the only serious adverse event involving the genitourinary system. Ejaculation failure was a common adverse event and one of the frequent causes of premature discontinuation (see above); however, this has been noted previously in association with sertraline use and is not unique to panic disorder patients.

A slight but statistically significant effect on serum uric acid concentrations was observed (see above), with sertraline producing a slight decrease. Sertraline is known to have a weak uricosuric effect (please refer to the current package insert).

7.3 Summary of Key Adverse Findings

On balance, the pattern of adverse drug reactions observed in the sertraline panic disorder development program does not differ in any important way from that observed in other approved indications (i.e., depression and obsessive compulsive disorder). The finding of increased serum cholesterol in both the obsessive compulsive clinical trials and the panic disorder trials suggests that this might be drug related.

8.0 Labeling Review

This supplement was submitted prior to approval of the obsessive compulsive disorder indication, and consequently the draft labeling does not incorporate the OCD adverse event descriptions. Since this supplement will be the third indication for Zoloft, I recommend that Pfizer adopt a labeling format similar to what has been proposed for Prozac, using a 5% incidence cutoff for adverse events in the table and incorporating other appropriate modifications.

Under Adverse Reactions-Commonly Observed in Pfizer's draft labeling, I am uncertain as to why the event term "ejaculation failure" is qualified as "primarily ejaculatory delay."

Otherwise, I have no objection to the labeling proposed by the sponsor on clinical safety grounds.

9.0 Conclusions

Pfizer has provided adequate evidence that sertraline is safe in the treatment of panic disorder. Although not specific to this indication, the finding of increased serum cholesterol, replicating an observation in the OCD clinical studies, may warrant further investigation.

10.0 Recommendations

From a clinical safety standpoint this supplement is approvable.

11/1/96

Andrew Mosholder, M.D.
Medical Officer, Division of Neuropharmacologic Drug Products

Orig. NDA 19-839 supplement 11
Div File
HFD 120:TLaughren/PDavid/AMosholder/HLee
MM;lle

11-7-96
I agree that this supplement is approvable. See memo to file for more detailed response.
Thomas P. Laughren, MD
TL, PDP

Appendix 5.1.1 Table of all studies as of 6/30/95 (Overseas studies are indicated)

Placebo Controlled Studies	
Protocol 529*	DB, parallel group, 7 center, 12 week fixed dose trial, sertraline v. placebo, outpatients, panic disorder (n=approx. 45 in each of 4 treatment groups); sertraline 50-200 mg/d
Protocol 514*	DB, parallel group, 8 center, 12 wk fixed dose trial, sertraline v. placebo, outpatients, panic disorder (n=approx. 40 in each of 4 treatment groups); sertraline 50-200 mg/d
Protocol 629*	DB, parallel group, 10 center, 10 wk flexible dose trial, sertraline v. placebo, outpatients, panic disorder (n=approx. 80 in each of 2 treatment groups); sertraline 25-200 mg/d
Protocol 630*	DB, parallel group, 10 center, 10 wk flexible dose trial, sertraline v. placebo, outpatients, panic disorder (n=88 in each of 2 treatment groups); sertraline 25-200 mg/d
Protocol 326* (Germany)	DB, parallel group, 1 center, 12 wk flexible dose trial, sertraline v. placebo v. imipramine, outpatients, panic disorder (n=approx 15 in each of 3 treatment groups); sertraline 50-300 mg/d, imipramine 50-300 mg/d.
Protocol 326A* (U.K.)	DB, parallel group, 1 center, 12 wk flexible dose trial, sertraline v. placebo v. imipramine, outpatients, panic disorder (n=2 in each of 3 treatment groups); sertraline 50-300 mg/d, imipramine 50-300 mg/d.
Protocol 337 (U.K.)	DB, parallel group, multicenter, 12 wk flexible dose trial, sertraline v. placebo v. imipramine, outpatients, panic disorder (n=100 total in 3 treatment groups); sertraline 25-200 mg/d, imipramine 25-200 mg/d. Ongoing.
Protocol 603 (Japan)	DB, parallel group, multicenter, 12 wk flexible dose trial, panic disorder (n=108 total). Ongoing.
Protocol 646	DB, parallel group, multicenter, 10 wk, flexible dose trial, panic disorder (n=125 total); sertraline 25-100 mg/d. Ongoing.
Uncontrolled studies	
Protocol 003 (Japan)	Open label, single center 12 wk flexible dose trial, outpatients, panic disorder (n=47). Sertraline 25-100 mg/d.

* Included in integrated primary database

Appendix 8.1.5.2

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Panic Disorder* (adapted from sponsor's table)

Adverse Experience	(Percent of Patients Reporting) Sertraline (N=430)	Placebo (N=275)
Autonomic Nervous System Disorders		
Mouth Dry	15	10
Sweating Increased	5	1
Centr. & Periph. Nerv. System Disorders		
Tremor	5	1
Paresthesia	4	3
Disorders of Skin and Appendages		
Rash	4	3
Gastrointestinal Disorders		
Nausea	29	18
Diarrhea	20	9
Dyspepsia	10	8
Constipation	7	3
Anorexia	7	2
Vomiting	6	3
General		
Fatigue	11	6
Hot Flushes	3	1
Musculoskeletal System Disorders		
Arthraigia	2	1
Psychiatric Disorders		
Insomnia	25	18
Somnolence	15	9
Nervousness	9	5
Libido Decreased	7	1
Agitation	6	2
Anxiety	4	3
Concentration Impaired	3	0
Depersonalization	2	1
Special Senses		
Tinnitus	4	3
Urogenital		
Ejaculation Failure (1)	19	1
Impotence (2)	2	1

*Events reported by at least 2% of patients treated with Zoloft are included, except for the following events which had an incidence on placebo greater than or equal to Zoloft: headache, dizziness, malaise, abdominal pain, respiratory disorder, pharyngitis, flatulence, vision abnormal, pain, upper respiratory tract infection, and paroniria.
(1) - Primarily ejaculatory delay; % based on male patients only: 216 Zoloft and 134 placebo patients.
(2)- % based on male patients only: 216 Zoloft and 134 placebo patients.

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	19,839
Sponsor:	Pfizer
Drug:	Zoloft® (sertraline)
Indication:	Supplement for Panic Disorder
Date of Submission:	December 20, 1995

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy

This supplement contains the results of four placebo controlled studies which were carried out to provide evidence for the effectiveness of sertraline in panic disorder with or without agoraphobia. Two of the studies followed a flexible dose design using identical protocols numbered 93CE21-0629 (629) and 93CE21-0630 (630), and two followed a fixed dose design also with identical protocols numbered 90CE21-0529 (529) and 90CE21-0514 (5[redacted]. The two flexible dose studies (629 and 630) showed sertraline produced more improvement than placebo in panic disorder. The results of the fixed dose studies were less clear. Neither showed a dose response. In protocol 529, there was some supportive evidence for sertraline's efficacy and in protocol 514, there were no differences between the individual sertraline dose groups and placebo although the combined sertraline group was significantly different than placebo. The first two studies will be described in detail; the discussion of the results for Protocol 529 is less extensive and mainly summary information on the results will be provided Protocol 514.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Flexible Dose Studies: 90CE21-0629 (4-1-94 to 4-19-95) **and 90CE21-0630** (4-2-94 to 4-14-95)

The two flexible dose studies followed the same protocol, and hence, the common protocol will be presented first and will be followed by the conduct and outcome for each study separately.

7.2.1.1 Investigators/Location

There were ten investigators in study 629 and in study 630. All reside in the US.

Study 629

Robert J. Bielski, M.D.	Robert B. Pohl, M.D.,
Robert D. Linden, M.D.	Wayne K. Goodman, M.D.,
Carl A. Houck, M.D.	Bharat Nakra, M.D.,
Mark T. Hegel, Ph.D.	Kay Y. Ota, Ph.D.
Barry S. Baumel, M.D.	John S. Carmen, M.D.,

Study 630

Jeffrey L. Rausch M.D.	Donald O'Hair, Ph.D.
Richard Weisler, M.D.	Mark Pollack, M.D.
Jeffrey Apter, M.D.	Lynn Cunningham, M.D.
William McEntee, M.D.	William Coryell, M.D.
Anita H. Clayton, M.D.	Rege Stewart, M.D.

7.2.1.2 Study Plan

Objective. To evaluate the comparative safety and efficacy of sertraline and placebo in outpatients with panic disorder.

Subjects. A total of 160 adult outpatients with a DSM-III-R diagnosis of panic disorder with or without agoraphobia (based on the SCID) formed the subject population. Subjects were required to have a minimum of four panic attacks, at least one of which was unanticipated, in the four weeks prior to the study. During the two-week baseline, they were required to have at least 3 and less than 100 DSM-III-R-defined panic attacks. At the end of baseline, the maximum allowable total score on the 21 item Hamilton Rating Scale for Depression was 17 and the minimum allowable total score on the Hamilton Rating Scale for Anxiety was 18. Women were to be using an adequate contraceptive method.

Patients were excluded if they meet DSM-III-R criteria for major diagnoses other than panic disorder (e.g., major depression, schizophrenia etc.) or if they had a primary anxiety diagnosis other than panic disorder. They were also be excluded if they were not physically healthy or required concomitant psychoactive medication or concurrent psychotherapy or behavioral therapy. These criteria including others are detailed in the protocol.

Design. The study followed a randomized, double-blind, parallel group design comparing sertraline and placebo using flexible dosing. The study began with a two week, single blind placebo phase and was followed by a ten week, double blind treatment phase. Sertraline was provided in 25 mg tablets with identical placebo tablets for the first two week and 50 mg tablets for the duration of the trial, if needed. The dosage was to begin at one 25 mg tablet daily in the evening for the first week, followed by two tablets, for the second week. If a dosage increase was required, the third week dosage would be two 50 mg tablets daily. Further increases could be made to three tablets (150 mg) and four tablets (200 mg) which was the maximum dose allowed. Dosage decreases could be made with 50 mg tablets, or 25 mg tablets at the second lowest dose.

Procedure. Patients were seen at the beginning and end of the washout and at the end of weeks 1, 2, 3, 4, 6, 8, and 10. The efficacy assessments included a daily patient diary, the Hamilton Rating Scale for Depression (21 item scale), the Hamilton Rating Scale for Anxiety, the modified Sheehan Panic and Anticipatory Anxiety Scale (PAAS), the Multicenter Panic Anxiety Scale (MC-PAS), the Clinical Global Impressions Scale, a Patient Global Evaluation, and the Quality of Life Scale. The psychiatric rating scales were completed at the end of washout and at each patient visit. Safety assessments included a physical exam, ECG, laboratory tests, vital signs (blood pressure, pulse and weight), urine drug screen and serum alprazolam screen.

Efficacy Analysis Plan. Four variables were identified as primary: change from

baseline in number of full panic attacks, in CGI severity, in anticipatory anxiety (percent-time-worrying) and the actual scores for the CGI improvement item. Because the panic attack and anticipatory anxiety variables were not normally distributed, the sponsor log transformed these data. An analysis of variance was carried out on the ratio of the transformed weekly score to the transformed baseline score. The sponsor confirmed the endpoint results for these two variables and the other variables with non-parametric tests. For the Clinical Global Impressions Scale, the sponsor analyzed the change-from-baseline for the severity item and the actual score for the improvement item with analyses of variance

When we asked the sponsor to provide tables showing mean change-from-baseline scores and the level of significance of the drug-placebo comparisons, they provided the significance levels obtained with the ratios for the panic attack and percent of time worrying variables. These tables are included in the appendix.

The FDA biostatistics reviewer performed non-parametric tests on the change-from-baseline scores for number of panic attacks, percent time worrying, and the CGI severity item, and on the actual score for the CGI improvement item. These results are discussed in the results section below.

7.2.1.3 Flexible Dose Study 629

7.2.1.3.1 Study Conduct and Outcome

Demographics and Baseline Characteristics. One hundred seventy three subjects were randomized to treatment. Five failed to return and two had no follow-up efficacy data leaving 166 subjects (79 sertraline and 87 placebo) in the intent-to-treat (ITT) population. This group had a mean age of 37.5 years (range, 18- 79 years), a mean weight of 170 pounds, a preponderance of females over males (57 to 43 percent), and of whites over non-whites (Table 629-1 in the appendix). There were no significant differences between sertraline and placebo on any demographic variable, on the baseline score for the Hamilton Rating Scale for Depression total (mean = 11.2), and or on duration of illness (mean = 9.2 years). There was also no difference between the two groups on any of the primary or secondary efficacy variables at baseline.

Patient Disposition and Dosage Information. More placebo than sertraline patients completed the ten week trial (84% to 76%) (Table 629-2 in the appendix). The most frequent reason for dropping out in the sertraline group was adverse effects (7%) whereas the most frequent reason, in the placebo group was insufficient clinical response (7%). The mean dosage of sertraline increased from the first to the tenth week of the trial. At week 4, the mean was 105 mg; at week 6, 128 mg; at weeks 8 and 10, it was just above 140 mg (Table 629-3 - appendix).

Efficacy Results. In the following, the results of the sponsor's analyses will be presented first followed by the results of the FDA analyses. As was discussed above, in the panic and percent time worrying variables, the sponsor analyzed ratios which included the baseline score. The tables referred to are in the Appendix at the end of the text.

The first outcome measure was change from baseline in number of panic attacks. The sponsor's results for the ratios and the mean change from baseline are given in Tables 629-4 and 629-5 in the appendix. The sponsors found that the LOCF drug-placebo comparisons

for panic attacks were significant in favor of sertraline at 7 of 10 time points (weeks 3 to 10 except 8) and the OC comparisons, at 5 of 10 time points (weeks 3 to 7). The endpoint (final two week LOCF) analysis was significant. The non-parametric endpoint analysis was significant for the change-from-baseline (p=.002) but not for the ratio(0.051). The FDA non-parametric analyses on change-from-baseline were significant in favor of sertraline at 8 of 10 time points (weeks 3 - 10) and at the endpoint.

The results of the sponsor's analyses for anticipatory anxiety (Percent time spent worrying) are shown in Tables 629-6 and 629-7 These results were based on ratio scores. There was no difference at any time point between the two treatments in percent time spent worrying with the LOCF and endpoint analyses and only one significant OC analysis. The endpoint parametric test was significant. None of the FDA non-parametric analyses were significant.

The results of the analysis of the CGI Severity and improvement items are shown in tables 629-8, 629-9, 629-10 and 629-11 in the appendix. In the sponsor's analysis, the LOCF analyses for the severity change-from-baseline scores were significant in favor of sertraline at 6 of 7 assessments (weeks 2 - 10), and the OC analyses were significant at 5 assessments (weeks 2 to 10 except week 8). The global improvement score was significant for the LOCF analyses at 5 of 7 assessments (weeks 3 - 10) and for the OC analyses at 4 of 7 assessments (weeks 3, 4, 6, and 10). The FDA non-parametric analyses on change-from-baseline severity scores were significant at weeks 4, 6, 8, 10, and endpoint. The corresponding analysis for the Improvement item indicated the treatment differences were significant at weeks 1, 3, 6, 8, 10, and endpoint.

7.2.1.3.2 Conclusions

The efficacy results are summarized in the following table.

Study 629
Total Number of Significant Comparisons - Sertraline vs. Placebo

Variable	Total weeks analyzed	LOCF analyses significant	OC analyses significant	FDA analyses signficant
1. Panic Attacks	10	7	5	8
2. CGI Severity	7	6	5	4
3. CGI Improvement	7	5	4	5
4. % Time Worrying	10	0	1	0

There is evidence of sertraline's efficacy on the first three variables and the sponsor's results were confirmed by the FDA analyses. The percent-time-worrying variable did not support the claim. This study provides evidence for sertraline's efficacy in panic disorder.

7.2.1.4 Flexible dose study 630

7.2.1.4.1 Study Conduct and Outcome

Demographics and Baseline Characteristics. One hundred seventy eight subjects were randomized to treatment. Two placebo patients failed to return, leaving 176 subjects (88 sertraline and 88 placebo) in the intent-to-treat (ITT) population. This group had a mean age of approximately 36 years (range, 18- 72 years), a mean weight of 168 pounds, a preponderance of females over males (65 to 35 percent), and were primarily white (Table 630-1 in the appendix). There were no significant differences between the sertraline and placebo group on any demographic variable or on the baseline scores for the Hamilton Rating Scale for Depression total (mean = 10.7) and duration of illness (mean = 9.9 years). There were also no differences between the two groups on any of the primary or secondary efficacy variables at baseline.

Patient Disposition and Dosage Information. The proportion of sertraline and of placebo patients who completed the ten week trial was 83% (Table 630-2); the overall retention rate was acceptable. The most frequent reason for discontinuation in the sertraline group was adverse effects (8%) whereas the most frequent reasons in the placebo group were insufficient clinical response (5%) and lost to follow-up (6%). The mean dosage of sertraline increased from the first to the tenth week of the trial. At week 4, the mean was 96 mg; at week 6, 115 mg; week 8, 122 mg; and week 10, 131 mg (Table 630.3).

Efficacy Results. As in Protocol 629, the results of both the sponsor's and the FDA's analyses will be presented. As was also detailed above, the sponsor analyzed ratios which included the baseline score for the panic and percent time worrying variables. The tables are provided in the appendix.

The first outcome measure was change from baseline in number of panic attacks. The sponsor's results for the ratios and the mean change from baseline are given in Tables 630-4 and 630-5 in the appendix. The LOCF drug-placebo ratio comparisons were significant in favor of sertraline at 7 of 10 time points (weeks 3 - 10 except week 6), and the OC, at 4 of 10 time points (weeks 3 - 6 except 5). The endpoint (final two week LOCF analysis) was also significant. The sponsor's non-parametric endpoint analyses were not significant (0.058 for the ratio and 0.12 for the change-from-baseline). The FDA non-parametric analyses on change-from-baseline were significant in favor of sertraline at weeks 2 - 5. Analyses for the latter half of the study and the endpoint were not significant.

For the anticipatory anxiety item (percent time spent worrying), the sponsor's analyses of ratio's found that sertraline subjects spent less time worrying at 2 of 10 LOCF assessments (weeks 7 and 10) and at 3 of 10 OC assessments (weeks 5, 7, and 10) than did the placebo subjects (Tables 630-6 and 630-7). The endpoint analysis was not significant. The FDA analyses analyses were significant at weeks 4 and 6.

The sponsor's results for the CGI Severity and Global Improvement items are given in tables 630-8, 630-9, 630-10, and 630-11 in the appendix. The LOCF analyses for both the severity change-from-baseline score and the global improvement score were significant in favor of sertraline at 3 of 7 time points (weeks 1, 6, 10) and endpoint; the OC analyses were significant at 4 of 7 time points (weeks 1, 4, 6, and 10) for severity-change from baseline and at 5 or 7 time points (weeks 1, 4, 6, 8, and 10) for improvement. The FDA analyses of the severity change-from-baseline variable were significant at 4 of 7 time points (weeks 1, 4, 6,

10), and endpoint. The Improvement item was significant at 5 of 7 time points (weeks 1, 4, 6, 8,10), and endpoint.

7.2.1.4.2 Conclusions:

The results are summarized in the table below.

Study 630 Total Number of Significant Comparisons - Sertraline vs. Placebo				
Variable	Total weeks analyzed	LOCF analyses significant	OC analyses significant	FDA analyses significant
1. Panic Attacks	10	7	4	4
2. CGI Severity	7	3	4	4
3. CGI Improvement	7	3	3	5
4. % Time Worrying	10	2	3	2

In this study, the panic attack item and the CGI scale items showed more improvement with sertraline than with placebo. The effect on anticipatory anxiety was minimal. The FDA analyses confirmed the sponsor's findings. This study provides evidence for the effectiveness of sertraline in panic disorder.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

7.2.2 Fixed Dose Studies: 90CE21-0529 (8/21/91 - 11/3/93) **and 90CE21-0514** (9/3/91 - 11/3/93)

As with the flexible dose studies, the two fixed dose studies followed the same protocol. The common study plan will be presented first and will be followed by the conduct and outcome for each study separately.

7.2.2.1 Investigators/Locations (all US)

There were eight investigators in each of the fixed dose studies. All reside in the US.

Study 529

Charles Weise, M.D.	Charleston, WV
Eugene A. DuBoff, M.D.	Denver, CO
James M. Ferguson, M.D.	Salt Lake City, UT
Peter D. Londborg, M.D.	Seattle, WA
Murray H. Rosenthal, D.O.	San Diego, CA
Ward Smith, M.D.	Portland, OR
Donald England, M.D.	Eugene, OR
Jonathan Cole, M.D.*	Belmont, MA

*No patients were randomized by this investigator.

Study 514

Jeffrey Apter, M.D.	Princeton, NJ
Neal R.Cutler, M.D.	Beverly Hills, CA
Roberto Dominquez, M.D.	Miami, FL
Bharat Nakra, M.D.	St. Louis, MO
Robert A. Riesenberg, M.D.	Decatur, GA
Javaid Sheikh, M.D.	Stanford, CA
Angelos Halaris, M.D., Ph.D.	Cleveland, OH
Laszlo Papp, M.D.	Glen Oaks, NY

7.2.2.2 Study Plan for the Two Fixed Dose Studies

Objective. To evaluate the comparative safety and efficacy of three doses of sertraline (50, 100 and 200 mg) and placebo in outpatients with panic disorder.

Design. Both fixed dose studies had eight investigators each of whom was expected to submit data on 20 subjects. The study followed a randomized, double blind, parallel group design. There were four treatment groups: sertraline 50 mg daily, sertraline 100 mg daily, sertraline 200 mg daily and placebo. The trial began with a two-week single blind placebo washout and, if subjects continued to meet entry criteria, was followed by randomization to to one of the four conditions for the double-blind, treatment phase of 12 weeks. The dosage began at 50 mg of sertraline for the first week and was increased by 50 mg weekly until the assigned dosage was reached. The medication was administered as two capsules in the evening. The only concomitant medication allowed was chloral hydrate for sleep.

Subjects. The subject population consisted of 160 adult outpatients (males and post-

menopausal or surgically sterilized females, 18 years of age and older) who met DSM-III-R criteria for panic disorder with or without agoraphobia using the SCID. Subjects were required to have at least four panic attacks during the four weeks prior to the study and three panic attacks during the two week placebo washout. Prior to admission to the study, all subjects were given a physical exam including a battery of laboratory tests and had a medical and psychiatric history taken to ensure they were healthy. Any current psychiatric disorder other than panic disorder (e.g., affective disorder, organic brain disorder, drug abuse etc.) was cause for exclusion, as was a history of schizophrenia, paranoid disorder or psychotic disorder or any required concomitant medication with CNS effects. The specific details of these exclusions are in the protocol. The protocol also called for testing for alprazolam and other benzodiazepines at baseline, week 2 and week 4. If, after warnings, the tests were still positive, subjects were to be dropped from the trial.

Procedure. Subjects were seen at the beginning and the end of the two week baseline, and at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12. The efficacy assessments included a daily patient diary, the HAM-D - 24 item (baseline only), the HAM-A, the Sheehan Panic and Anticipatory Anxiety Scale, the CGI - Severity and Improvement items, and the Profile of Mood States (POMS). These were completed at each visit. Subjects kept a daily diary throughout the study recording panic attack variables.

The safety assessments included vital signs which were collected at each visit, a physical exam, ECGs, plasma samples, urine drug screen and serum alprazolam levels which were collected at specified visits during the trial.

Efficacy Analysis Plan. Four variables were identified as primary: change from baseline in number of full panic attacks, in CGI severity, in anticipatory anxiety (percent-time-worrying) and the actual scores for the CGI improvement item. Because the panic attack and anticipatory anxiety variables were not normally distributed, the sponsor log transformed these data. An analysis of variance was carried out on the ratio of the transformed weekly score to the transformed baseline score. The sponsor confirmed the endpoint results for these two variables and the other variables with non-parametric tests. For the Clinical Global Impressions Scale, the sponsor analyzed the change-from-baseline for the severity item and the actual score for the improvement item with analyses of variance

When we asked the sponsor to submit tables showing mean change-from-baseline scores and the level of significance of the drug-placebo comparisons, they provided the significance levels obtained with the ratios for the panic attack and the anticipatory anxiety items. These tables are included in the appendix..

The FDA biostatistics reviewer performed non-parametric tests on the change-from-baseline scores for number of panic attacks, percent time worrying, and the CGI severity item, and on the actual score for the CGI improvement item. These results are discussed in the results section below.

7.2.2.3 Fixed Dose Study #529 (90CE21-0529)

7.2.2.3.1 Study Conduct and Outcome

Demographics and Baseline Characteristics. One hundred seventy eight subjects were randomized to treatment. One patient in the sertraline 50mg group failed to return after the baseline and five patients (one each from the placebo, 50mg, and 200 mg groups, and 2

from the 100 mg group) did not have any efficacy data, leaving 172 subjects in the intent-to-treat (ITT) population (44 in two treatment groups and 42 in the other two). The ITT population had a mean age of approximately 39 years (43 years for the females and 34 years for the males with a range of 18.9 to 74.5 years), a mean weight of 176 pounds, a preponderance of females over males in the 50 and 100 mg groups and of males over females in the 200mg and placebo groups (Table 529-1). In addition, subjects were primarily white. Tests among the sertraline and placebo groups on the demographic variables were not significant except for sex which reflected the reversal of male-female proportions in two treatment groups. There were no significant differences among the groups on the baseline scores for the Hamilton Rating Scale for Depression total (mean = 12.7), duration of illness (mean = 7.75 years) and Hollingshead Classification.There were also no differences among the four groups on any of main efficacy variables at baseline (i.e., number of total panic attacks, the percent time in anticipatory anxiety, episodes of anticipatory anxiety, the POMS factors, and the HAM-A). There was no overall difference at baseline in the Clinical Global Impressions Scale severity item although the pooled sertraline group had significantly less severity than the placebo (a mean of 4.4 vs. 4.6).

Patient Disposition. The percent of sertraline and placebo patients who completed the twelve week trial were similar, i.e., 63% and 69% respectively (Table 529-2). There was no difference among the four treatment groups in rate of dropout. The most frequent reason for discontinuation overall was adverse effects (19.7% for sertraline vs. 4% for placebo) and insufficient clinical response (5.3% for sertraline vs. 11.1 for placebo). The rates of adverse effects for the 50, 100 and 200 mg groups and placebo were 19%, 14%, 27% and 4% respectively. The corresponding rates for insufficient clinical response were 14%, 0%, 2% and 11%.

Efficacy Results.The sponsor's results for each of the four efficacy variables by week are given in Tables 529-3 to 529-10 in the appendix. Because there are three treatment groups and only a modest number of significant comparisons, I have chosen to display the number of significant comparisons in a table rather than describe the outcomes in narrative. The reader is referred to the tables in the appendices for the mean scores (ratios for panic attacks and anticipatory anxiety, change from baseline for CGI severity and mean improvement score). The summary table is below and the shaded areas indicate the treatment group with the highest number of significant comparisons.

Study 529 Total Number of Significant Comparisons - Sertraline vs. Placebo				
LOCF Analyses				
Variable	Total weeks analyzed	50 mg Group	100 mg Group	200 mg group
1. Panic Attacks	**12**	**4**	**9**	**3**
2. CGI Severity	**8**	**0**	**2**	**0**
3. CGI Improvement	**8**	**0**	**3**	**0**
4. % Time Worrying	**12**	**3**	**9**	**0**

OC Analyses				
1. Panic Attacks	12	3	1	3
2. CGI Severity	8	1	2	2
3. CGI Improvement	8	1	4	4
4. % Time Worrying	12	6	8	0
FDA Non-Parametric Analyses				
1. Panic Attacks	12	0	0	0
2. CGI Severity	8	1	2	0
3. CGI Improvement	8	1	5	5
4. % Time Worrying	12	7	9	0

In the LOCF analyses, the 100 mg group had the most significant comparisons for each of the variables. The results with the OC analyses indicated the 100 and 200 mg treatment groups were similar in the number of significant comparisons. In the FDA analysis, the 100 mg group again had the highest number of significant comparisons.

7.2.2.3.2 Conclusions

This fixed dose study provides only supportive evidence for the efficacy of sertraline in panic disorder. There was no difference among the different doses using paired comparisons and hence, there was no dose effect. In addition, the Linear Dose Response test for study 0529 was not significant, confirming the paired comparisons.

7.2.2.4 Fixed Dose Study #514 (90CE21-0514)

7.2.2.4.1 Conduct of trial.

Demographics and Baseline Characteristics. One hundred fifty seven subjects were randomized to treatment. Five patients in the sertraline groups (one in the 50mg group, and two each in the 100 and 200 mg groups) failed to return after baseline and two more sertraline subjects (one each in the 100 and 200 mg groups) did not have any efficacy data, leaving 150 subjects in the intent-to-treat (ITT) population (38 in three treatment groups and 36 in one). The ITT population had a mean age of approximately 40 years with a higher mean age for females (45.5 years) than males (36.4 years), a mean weight of 179 pounds, a preponderance of males over females in all groups with from two to eight times more males than females. In addition, subjects were primarily white (ranging from 76% to 82% of each group) (Table 514-1). Tests between each sertraline group and placebo on the demographic variables were not significant except for sex where there was a wide range in the proportion of males. There were no significant differences among the groups on the baseline scores for the Hamilton Rating Scale for Depression total (12.6), duration of illness (9.4 years) and Hollingshead Classification. There were also no differences among the four groups on any of main efficacy variables at baseline (i.e., number of total panic attacks, the percent time in

anticipatory anxiety, the number of episodes of anticipatory anxiety, the Clinical Global Impressions Scale severity item, the POMS factors, and the HAM-A).

Patient Disposition and Dosage Information. The percent of sertraline and placebo patients who completed the twelve week trial was 62% and 71% respectively (Table 514-2). The placebo and 100 mg group had the lowest dropout rates (31 & 23); the 50 and 200 mg groups had the highest (44%). The most frequent reason for discontinuation in the sertraline groups was adverse effects (17.5% vs. 5.3% for placebo). The difference in the rate of adverse effects was significant for the 200 mg sertraline vs. placebo comparison (21.6% and 5.3% respectively).

Efficacy Results. The sponsor noted that the endpoint analyses among the treatment groups for the efficacy variables in Study 514 were not significant. The mean ratios for the panic attack and anticipatory anxiety variables, the change-from-baseline scores for the CGI severity item and the mean scores for the CGI global improvement item are given in the appendix (Tables 514-3 to 514-10). In the following, I have indicated the number of significant comparisons.

Study 514 Total Number of Significant Comparisons - Sertraline vs. Placebo				
LOCF Analyses				
Variable	Total weeks analyzed	50 mg Group	100 mg Group	200 mg group
1. Panic Attacks	12	0	1	0
2. CGI Severity	8	0	1	0
3. CGI Improvement	8	0	0	0
4. % Time Worrying	12	0	0	0
OC Analyses				
1. Panic Attacks	12	2	7	4
2. CGI Severity	8	2	1	3
3. CGI Improvement	8	2	0	3
4. % Time Worrying	12	0	0	0

There were very few significant comparisons and none for 'percent time worrying'.

7.2.2.4.2 Conclusions

This study, at best, is mildly supportive. The subjects in this study, as in the other fixed dose study (#529), had different demographic characteristics than the subjects in the flexible dose studies. That is, women of child bearing potential were excluded from the fixed

dose studies and, as a result, there were fewer female subjects and they were older than in the flexible dose studies.

7.2.3 Subgroup Analyses

The sponsor examined the effect of gender on panic attacks, limited symptom attacks and percent time worrying in each of the four studies. They also examined the effects of gender, age and race on panic attacks in the combined study population.

In Protocol 629, the sponsor reported a significant treatment by gender interaction (p=0.035) for panic attacks which they attributed to the "presence of larger sertraline-placebo differences in female patients as compared to male patients". The endpoint geometric means for panic attacks were as follows:

PROTOCOL 629
PANIC ATTACKS - ENDPOINT GEOMETRIC MEANS

Males (N=71)		Females (N=95)	
Sertraline	Placebo	Sertraline	Placebo
0.24	0.26	0.17	0.33

The treatment by gender interactions were not significant for the other two variables.

The same analyses were carried out in Protocol 630 and neither the interactions nor the main effects were significant for the three variables. In Protocol 529, there was a significant effect of gender for the three measures but no significant treatment by gender interactions for the same variables.

In study 514, both the sex and treatment by sex interaction effects were significant in the analysis of panic attacks when the sertraline treatment groups were combined. There was also a significant interaction on the Hamilton Rating Scale for Anxiety. The results for the panic attack variable are shown below.

PROTOCOL 514
PANIC ATTACKS - ENDPOINT GEOMETRIC MEANS

Males (N=108)		Females (N=44)	
Sertraline	Placebo	Sertraline	Placebo
0.26	0.48	0.24	0.14

In the female group, there were fewer panic attacks on placebo than sertraline.

The sponsor also evaluated the effect of gender, age, and race on the panic attack variable using the pooled study population (629, 630, 529, & 514). There were no treatment by sex, by age or by race interactions for this group. The sponsor also looked at the more severely ill subjects and determined that their response was similar to that found in the total population.

7.2.4 Overall Conclusions:

The two flexible dose studies indicate that sertraline produces more improvement than placebo in panic disorder. This was shown on the CGI variables of severity and improvement and on the panic attack variable. The anticipatory anxiety variable (percent of time worrying) was only rarely significant in these two studies. The fixed dose studies were more problematic in terms of efficacy. That is, protocol 529 may be considered supportive but protocol 514 is less than supportive. In both these studies, the test for a dose response was negative. Inspection of the results, however, suggests that the 100 mg dose produced the most significant results.

J. Hillary Lee

J. Hillary Lee, Ph.D.

cc: NDA 19,839
HFD-120 Div. File
HFD-120/TLaughren/HLee/MMille

C:\WPFILES\ZOLFPNIC.PRM
October 22, 1996

11-7-96
I agree that studies 529 & 530 provide evidence of antipsychotic activity for Zoloft. See memo to file for more detailed response.

James P. Laughren, MD
TL, PDP

APPENDIX

Table 629 - 1
Demographic Characteristics

Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Zoloft	80	37.8		34 (42.5%)	46(57.5%)	72 (90.0%)	8(10.0%)
Placebo	88	37.2		38(43.2%)	50(56.8%)	75(85.2%)	13(14.8%)

Table 629 - 2

Patient Completion Rates

Treatment Groups	Number Random-ized	Intent-to-Treat Sample	Number (%) of Patients Completing						
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10
Zoloft	85	79	79(100.0%)	75 (94.9%)	69(87.3%)	67 (84.8%)	64(81.0%)	61(77.2%)	60(75.9%)
Placebo	88	87	87(100.0%)	83 (95.4%)	82(94.3%)	82 (94.3%)	79(90.8%)	75(86.2%)	73(83.9%)

Table 629 - 3 Dosing Information							
Mean Dosage for Completers							
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10
Zoloft	24.7	46.5	82.7	105.6	128.6	141.2	143.1

Table 629 - 4 Mean Change from Baseline in Total Number of Panic Observed Cases Analysis					
	Treatment Groups				
Week	Zoloft		Placebo		p-value
	n	X	n	X	
BL Mean	79	6.38	87	5.19	
1	79	-1.22	87	-1.14	.610
2	75	-2.86	83	-1.37	.102
3	69	-4.44	81	-2.12	.009
4	67	-5.31	82	-2.32	.010
5	64	-5.26	78	-2.62	.033
6	62	-5.66	77	-2.86	.004
7	61	-5.51	74	-2.64	.037
8	61	-5.25	72	-2.76	.232
9	59	-5.92	73	-2.71	.060
10	59	-5.96	72	-2.98	.086

Table 629 - 5 Mean Change from Baseline in Total Number of Panic Last Observation Carried Forward Analysis					
	Treatment Groups				
Week	Zoloft		Placebo		
	n	X	n	X	p-value
BL Mean	79	6.38	87	5.19	
1	79	-1.22	87	-1.14	.610
2	79	-2.71	87	-1.40	.127
3	79	-4.05	87	-2.05	.012
4	79	-4.74	87	-2.24	.008
5	79	-4.49	87	-2.52	.034
6	79	-4.71	87	-2.64	.005
7	79	-4.71	87	-2.36	.033
8	79	-4.51	87	-2.64	.100
9	79	-5.01	87	-2.61	.037
10	79	-5.04	87	-2.81	.032

Table 629 - 6 Mean Change from Baseline in Time Spent Worrying Observed Cases Analysis					
	Treatment Groups				
Week	Zoloft		Placebo		
	n	X	n	X	p-value
BL Mean	79	29.78	87	32.63	
1	79	-2.97	87	-4.60	.735
2	75	-4.25	83	-5.48	.543
3	69	-8.99	81	-8.64	.456
4	67	-10.40	82	-10.60	.265
5	64	-15.98	78	-10.41	.037
6	62	-14.80	77	-12.48	.407
7	61	-14.57	74	-13.58	.350
8	61	-14.49	72	-11.29	.157
9	59	-17.98	73	-13.84	.055
10	59	-18.93	72	-15.44	.125

Table 629 - 7 Mean Change from Baseline in Time Spent Worrying Last Observation Carried Forward Analysis					
	Treatment Groups				
Week	Zoloft		Placebo		
	n	X	n	X	p-value
BL Mean	79	29.78	87	32.63	
1	79	-2.97	87	-4.60	.735
2	79	-4.15	87	-5.62	.637
3	79	-8.15	87	-8.33	.672
4	79	-9.66	87	-10.01	.182
5	79	-13.58	87	-9.59	.064
6	79	-12.32	87	-10.81	.337
7	79	-12.41	87	-11.96	.376
8	79	-12.35	87	-10.78	.212
9	79	-14.94	87	-12.67	.121
10	79	-15.65	87	-13.80	.102

Table 629 - 8
Mean Change from Baseline in CGI Severity

Observed Cases Analysis																
	Treatment Week															
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft	7	4.28	7	- .19	7	- .57	6	- .88	6	-1.36	6	-1.39	6	-1.41	6	-1.86
Placebo	8	4.30	8	- .08	8	- .27	8	- .48	8	- .77	7	- .97	7	- .97	7	-1.06
2-sided p-value comparing Zoloft and Placebo																
p-value			.319		.033		.013		.001		.048		.058		.001	

Table 629 - 9 Mean Change from Baseline in CGI Severity																
Last Observation Carried Forward Analysis																
	Treatment Week															
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft	7	4.28	7	- .19	7	- .54	7	- .79	7	-1.24	7	-1.26	7	-1.33	7	-1.64
Placebo	8	4.30	8	- .08	8	- .27	8	- .42	8	- .68	8	- .82	8	- .83	8	- .90
2-sided p-value comparing Zoloft and Placebo																
p-value			.319		.049		.026		.001		.022		.014		.001	

Table 629 - 10
CGI Improvement
Observed Cases Analysis

	Treatment Week													
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft	7	3.58	7	3.07	6	2.52	6	2.34	6	2.06	6	2.29	6	1.78
Placebo	8	3.51	8	3.27	8	3.15	8	2.75	7	2.64	7	2.56	7	2.67
2-sided p-value comparing Zoloft and Placebo														
p-value	.669		.251		.000		.032		.003		.216		< .001	

Table 629 - 11
CGI Improvement
Last Observation Carried Forward Analysis

	Treatment Week													
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft	7	3.58	7	3.11	7	2.64	7	2.45	7	2.25	7	2.33	7	2.02
Placebo	8	3.51	8	3.28	8	3.16	8	2.84	8	2.76	8	2.74	8	2.82
2-sided p-value comparing Zoloft and Placebo														
p-value	.669		.342		.002		.029		.005		.041		< .001	

Table 630 - 1
Demographic Characteristics

Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Zoloft	88	37.8		27 (30.7%)	61(69.3%)	85 (96.6%)	3(3.4%)
Placebo	88	34.9		34(38.6%)	54(61.4%)	80(90.9%)	8(9.1%)

Table 630 - 2

Patient Completion Rates

Treatment Groups	Number Random-ized	Intent-to-Treat Sample	Number (%) of Patients Completing						
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10
Zoloft	88	88	88(100.0%)	81 (92.0%)	80(90.9%)	80 (90.9%)	79(89.8%)	76(86.4%)	73(83.0%)
Placebo	90	88	88(100.0%)	87 (98.9%)	84(95.5%)	82 (93.2%)	80(90.9%)	74(84.1%)	73(83.0%)

Table 630 - 3 Dosing Information							
Mean Dosage for Completers							
	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10
Zoloft	24.8	47.1	76.6	96.3	115.1	122.0	130.8

Table 630 - 4 Mean Change from Baseline in Total Number of Panic Observed Cases Analysis					
	Treatment Groups				
Week	Zoloft		Placebo		p-value
	n	X	n	X	
BL Mean	88	6.04	88	5.59	
1	88	-1.93	87	-1.02	.247
2	81	-2.97	86	-1.74	.036
3	80	-3.89	84	- .72	.005
4	80	-4.58	82	-1.85	.001
5	79	-4.53	79	-2.19	.003
6	79	-4.69	78	-2.85	.070
7	77	-5.06	72	-3.49	.020
8	74	-5.05	73	-3.48	.110
9	74	-5.49	73	-3.71	.052
10	71	-5.02	72	-3.56	.068

Table 630 - 5
Mean Change from Baseline in Total Number of Panic
Last Observation Carried Forward Analysis

	Treatment Groups				
Week	**Zoloft**		**Placebo**		
	n	**X**	**n**	**X**	**p-value**
BL Mean	88	6.04	88	5.59	
1	88	-1.93	87	-1.02	.247
2	88	-2.79	88	-1.95	.137
3	88	-3.61	88	- .92	.033
4	88	-4.24	88	-1.10	.003
5	88	-4.17	88	-1.47	.014
6	88	-4.31	88	-1.96	.089
7	88	-4.54	88	-2.29	.021
8	88	-4.44	88	-2.30	.043
9	88	-4.81	88	-2.39	.025
10	88	-4.71	88	-2.27	.021

Table 630 - 6 Mean Change from Baseline in Time Spent Worrying Observed Cases Analysis					
	Treatment Groups				
Week	Zoloft		Placebo		
	n	X	n	X	p-value
BL Mean	88	29.94	88	25.86	
1	88	- .21	87	-3.47	.123
2	81	-4.93	86	-3.96	.807
3	80	-6.92	84	-4.65	.565
4	80	-9.49	82	-5.26	.098
5	79	-10.94	79	-5.96	.034
6	79	-11.81	78	-7.40	.220
7	77	-11.99	72	-7.87	.015
8	74	-11.48	73	-8.73	.184
9	74	-13.71	73	-11.41	.166
10	71	-13.19	72	-10.70	.028

Table 630 - 7
Mean Change from Baseline in Time Spent Worrying
Last Observation Carried Forward Analysis

	Treatment Groups				
Week	**Zoloft**		**Placebo**		
	n	**X**	**n**	**X**	**p-value**
BL Mean	88	29.94	88	25.86	
1	88	- .21	87	-3.47	.123
2	88	-3.27	88	-3.87	.861
3	88	-5.12	88	-4.46	.863
4	88	-7.47	88	-4.51	.160
5	88	-8.80	88	-5.06	.050
6	88	-9.59	88	-5.98	.191
7	88	-10.08	88	-7.04	.025
8	88	-10.38	88	-7.04	.056
9	88	-12.25	88	-9.06	.075
10	88	-11.97	88	-8.44	.010

Table 630 - 8 Mean Change from Baseline in CGI Severity																
Observed Cases Analysis																
	Treatment Week															
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft	8	4.51	8	- .06	8	- .42	7	- .83	7	-1.23	7	-1.27	7	-1.50	7	-1.75
Placebo	8	4.51	8	- .32	8	- .50	8	- .77	8	- .85	7	- .88	7	-1.13	7	-1.18
2-sided p-value comparing Zoloft and Placebo																
p-value			.027		.574		.699		.027		.026		.067		.007	

Table 630 - 9
Mean Change from Baseline in CGI Severity
Last Observation Carried Forward Analysis

	Treatment Week															
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft	8	4.51	8	- .06	8	- .35	8	- .74	8	-1.12	8	-1.18	8	-1.33	8	-1.56
Placebo	8	4.51	8	- .32	8	- .50	8	- .73	8	- .81	8	- .83	8	-1.02	8	-1.04
2-sided p-value comparing Zoloft and Placebo																
p-value			.027		.276		.974		.066		.043		.091		.009	

Table 630 - 10 CGI Improvement														
Observed Cases Analysis														
	Treatment Week													
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft	8	3.69	8	3.14	7	2.72	7	2.43	7	2.31	7	2.25	7	2.06
Placebo	8	3.41	8	3.17	8	2.96	8	2.82	7	2.74	7	2.62	7	2.56
2-sided p-value comparing Zoloft and Placebo														
p-value	.041		.870		.155		.020		.009		.048		.004	

Table 630 - 11
CGI Improvement
Last Observation Carried Forward Analysis

	Treatment Week													
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft	8	3.69	8	3.27	8	2.89	8	2.60	8	2.47	8	2.42	8	2.26
Placebo	8	3.41	8	3.17	8	3.04	8	2.93	8	2.88	8	2.78	8	2.74
2-sided p-value comparing Zoloft and Placebo														
p-value	.041		.480		.401		.071		.023		.062		.010	

Table 529 - 1
Study: 0529
Demographic Characteristics

Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Zoloft 50mg	43	37.2		16 (37.2%)	27(62.8%)	38 (88.4%)	5(11.6%)
Zoloft 100mg	44	41.8		20(45.5%)	24 (54.5%)	40(90.9%)	4(9.1%)
Zoloft 200mg	45	37.2		29(64.4%)	16(35.6%)	41(91.1%)	4(8.9%)
Placebo	45	39.1		29(64.4%)	16(35.6%)	44(97.8%)	1(2.2%)

Table 529 - 2

Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Number (%) of Patients Completing							
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	
Zoloft 50mg	44	42	42(100.0%)	38 (90.5%)	36(85.7%)	32 (76.2%)	29(69.0%)	27(64.3%)	26(61.9%)	24
Zoloft 100mg	44	42	42(100.0%)	38 (90.5%)	38(90.5%)	38 (90.5%)	37(88.1%)	35(83.3%)	35(83.3%)	34
Zoloft 200mg	45	44	44(100.0%)	39 (88.6%)	34(77.3%)	32 (72.7%)	31(70.5%)	27(61.4%)	27(61.4%)	26
Placebo	45	44	44(100.0%)	43 (97.7%)	42(95.5%)	41 (93.2%)	38(86.4%)	34(77.3%)	32(72.7%)	31

Table 529 - 3
Mean Change from Baseline in Total Number of Panic Attacks
Observed Cases Analysis

Week	Treatment Groups								2-sided p-values for pairwise comparisons		
	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	42	10.15	42	10.65	44	5.75	44	13.74			
1	42	-4.80	41	- .78	44	- .91	44	-4.33	.905	.759	.870
2	37	-7.78	38	-3.84	38	-1.68	43	-3.76	.009	.009	.199
3	36	-7.96	38	-3.63	33	-3.41	42	-6.69	.630	.241	.169
4	32	-9.27	38	-4.92	32	-4.00	41	-6.27	.012	.120	.021
5	29	-8.76	38	-5.00	31	-3.77	39	-6.72	.523	.053	.009
6	29	-9.38	36	-5.04	31	-2.16	37	-5.97	.167	.067	.062
7	27	-10.02	35	-4.26	27	-3.00	35	-3.14	.204	.097	.083
8	27	-9.98	35	-4.89	27	-3.78	34	-4.37	.025	.070	.047
9	26	-8.73	34	-5.44	26	-3.88	32	-5.30	.977	.456	.724
10	26	-8.23	34	-5.82	26	-3.65	32	-4.67	.412	.122	.387
11	24	-9.33	34	-7.46	25	-3.66	31	-5.13	.116	.131	.237
12	24	-9.33	34	-6.87	25	-3.74	31	-6.48	.110	.184	.100

Table 529 - 4
Mean Change from Baseline in Total Number of Panic Attacks
Last Observation Carried Forward Analysis

Week	Treatment Groups								2-sided p-values for comparisons		
	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	42	10.15	42	10.65	44	5.75	44	13.74			
1	42	-4.80	41	- .78	44	- .91	44	-4.33	.905	.759	.870
2	42	-6.75	41	-3.90	44	-2.30	44	-3.94	.040	.004	.186
3	42	-6.99	41	-3.71	44	-3.07	44	-6.35	.641	.132	.349
4	42	-8.11	41	-4.90	44	-3.48	44	-5.81	.030	.050	.106
5	42	-7.89	41	-4.98	44	-3.45	44	-5.88	.264	.009	.043
6	42	-8.32	41	-6.66	44	-2.32	44	-6.42	.146	.007	.154
7	42	-8.58	41	-5.98	44	-3.07	44	-4.13	.092	.005	.102
8	42	-8.56	41	-6.51	44	-3.55	44	-5.19	.019	.001	.042
9	42	-8.73	41	-7.22	44	-3.75	44	-5.15	.244	.004	.271
10	42	-8.42	41	-7.54	44	-3.61	44	-4.69	.134	.001	.128
11	42	-8.73	41	-8.73	44	-3.61	44	-4.99	.051	< .001	.083
12	42	-8.73	41	-8.24	44	-3.66	44	-5.94	.040	.001	.044

Table 529 - 5
Mean Change from Baseline in Time Spent Worrying
Observed Cases Analysis

Week	Treatment Groups								2-sided p-values for comparisons		
	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	42	21.71	42	23.94	44	18.89	44	19.45			
1	42	.68	41	-6.02	44	.28	44	-4.65	.289	.990	.342
2	37	-8.21	38	-10.63	38	.72	43	-3.54	.058	.037	.954
3	36	-8.19	38	-9.75	33	-4.96	42	-5.31	.077	.114	.294
4	32	-6.69	38	-10.11	32	-7.50	41	-8.05	.248	.411	.524
5	29	-12.63	38	-13.13	31	-8.80	39	-6.46	.003	.055	.237
6	29	-13.18	36	-11.97	31	-5.96	37	-6.66	.003	.042	.308
7	27	-14.36	35	-14.33	27	-10.44	35	-5.52	.012	.015	.210
8	27	-13.85	35	-14.83	27	-7.76	34	-4.84	.001	.002	.194
9	26	-12.28	34	-15.45	26	-9.82	32	-6.46	.050	.039	.392
10	26	-11.42	34	-15.83	26	-11.33	32	-6.02	.061	.015	.158
11	24	-12.98	34	-15.25	25	-11.72	31	-4.47	.036	.017	.107
12	24	-12.18	34	-15.40	25	-9.32	31	-4.12	.034	.012	.125

Table 529 - 6
Mean Change from Baseline in Time Spent Worrying
Last Observation Carried Forward Analysis

	Treatment Groups								2-sided p-values for comparisons		
Week	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	42	21.71	42	23.94	44	18.89	44	19.45			
1	42	.68	41	-6.02	44	.28	44	-4.65	.289	.990	.342
2	42	-5.71	41	-10.11	44	.08	44	-3.51	.206	.026	.871
3	42	-6.10	41	-9.29	44	-2.71	44	-4.82	.237	.072	.376
4	42	-5.33	41	-9.63	44	-4.52	44	-7.35	.970	.188	.609
5	42	-9.39	41	-12.43	44	-6.52	44	-5.58	.059	.017	.386
6	42	-9.76	41	-11.77	44	-4.52	44	-5.90	.037	.010	.356
7	42	-10.84	41	-13.61	44	-6.80	44	-4.80	.052	.005	.450
8	42	-10.51	41	-14.04	44	-5.16	44	-4.93	.010	.001	.432
9	42	-11.12	41	-14.55	44	-6.40	44	-6.28	.059	.009	.573
10	42	-10.58	41	-14.86	44	-7.29	44	-5.96	.073	.003	.265
11	42	-11.47	41	-14.94	44	-7.30	44	-4.61	.020	.001	.181
12	42	-11.02	41	-15.06	44	-5.94	44	-4.36	.020	.001	.231

Table 529 - 7
Mean Change from Baseline in CGI Severity
Observed Cases Analysis

	Treatment Week															
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	42	4.38	42	- .25	37	- .93	36	- .92	32	-1.43	29	-1.62	27	-1.74	26	-1.83	24	-1.77
Zoloft 100mg	42	4.50	42	- .33	37	- .97	38	-1.28	38	-1.52	37	-1.64	35	-1.95	35	-1.83	33	-1.95
Zoloft 200mg	43	4.28	43	- .27	35	- .96	33	-1.30	31	-1.49	30	-1.57	26	-1.88	26	-1.98	25	-2.02
Placebo	44	4.64	44	- .40	42	- .61	41	- .91	41	-1.08	38	-1.07	34	-1.24	32	-1.48	31	-1.48
2-sided p-values for pairwise comparisons																		
50mg vs P			.387		.151		.956		.173		.027		.105		.269		.352	
100mg vs P			.696		.102		.103		.057		.009		.009		.207		.088	
200mg vs P			.472		.123		.104		.093		.031		.032		.101		.078	

Table 529 - 8

Mean Change from Baseline in CGI Severity

Last Observation Carried Forward Analysis

	Treatment Week																	
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	42	4.38	42	- .25	42	- .82	42	- .82	42	-1.15	42	-1.30	42	-1.36	42	-1.45	42	-1.42
Zoloft 100mg	42	4.50	42	- .33	42	- .91	42	-1.17	42	-1.39	42	-1.48	42	-1.69	42	-1.64	42	-1.73
Zoloft 200mg	43	4.28	43	- .27	43	- .77	43	-1.06	43	-1.19	43	-1.28	43	-1.44	43	-1.48	43	-1.54
Placebo	44	4.64	44	- .40	44	- .56	44	- .80	44	- .97	44	-1.00	44	-1.12	44	-1.23	44	-1.24
2-sided p-values for pairwise comparisons																		
50mg vs P				.387		.230		.932		.442		.200		.372		.404		.489
100mg vs P				.696		.110		.112		.080		.041		.031		.122		.064
200mg vs P				.472		.339		.271		.361		.237		.233		.350		.265

Table 529 - 9 CGI Improvement																
Observed Cases Analysis																
	Treatment Week															
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	42	3.50	37	2.69	36	2.80	32	2.24	29	1.98	27	2.03	26	2.12	24	2.12
Zoloft 100mg	42	3.14	37	2.52	38	2.24	38	2.24	37	2.11	35	1.88	35	1.86	33	1.90
Zoloft 200mg	44	3.52	36	2.70	34	2.18	32	2.01	31	1.95	27	1.80	27	1.78	26	1.84
Placebo	44	3.28	42	3.05	41	2.83	41	2.70	38	2.72	33	2.32	32	2.29	31	2.23
2-sided p-values for pairwise comparisons																
50mg vs P	.274		.096		.909		.065		.004		.290		.568		.707	
100mg vs P	.526		.013		.006		.036		.007		.076		.104		.202	
200mg vs P	.238		.102		.003		.003		.001		.045		.069		.162	

Table 529 - 10 CGI Improvement																
Last Observation Carried Forward Analysis																
	Treatment Week															
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	42	3.50	42	2.90	42	2.94	42	2.64	42	2.46	42	2.47	42	2.51	42	2.48
Zoloft 100mg	42	3.14	42	2.60	42	2.34	42	2.34	42	2.27	42	2.13	42	2.11	42	2.13
Zoloft 200mg	44	3.52	44	2.88	44	2.49	44	2.42	44	2.36	44	2.28	44	2.29	44	2.31
Placebo	44	3.28	44	3.10	44	2.91	44	2.78	44	2.81	43	2.58	43	2.57	43	2.51
2-sided p-values for pairwise comparisons																
50mg vs P	.274		.329		.908		.554		.155		.671		.842		.898	
100mg vs P	.526		.018		.010		.070		.029		.081		.089		.151	
200mg vs P	.238		.285		.055		.128		.070		.242		.291		.444	

Table 514 - 1
Demographic Characteristics

Treatment Groups	n	Age (years)		Sex [n(%)]		Race [n(%)]	
		Mean	Range	Male	Female	White	Non-White
Zoloft 50mg	38	37.3		34 (89.5%)	4(10.5%)	31 (81.6%)	7(18.4%)
Zoloft 100mg	39	42.8		23(59.0%)	16 (41.0%)	31(79.5%)	8(20.5%)
Zoloft 200mg	37	41.3		25(67.6%)	12(32.4%)	28(75.7%)	9(24.3%)
Placebo	38	37.5		26(68.4%)	12(31.6%)	29(76.3%)	9(23.7%)

Table 514 - 2
Patient Completion Rates

Treatment Groups	Number Randomized	Intent-to-Treat Sample	Number (%) of Patients Completing							
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 1
Zoloft 50mg	39	38	38(100.0%	31 (81.6%)	27(71.1%)	26 (68.4%)	25(65.8%)	24(63.2%)	24(63.2%)	24(63.
Z. 100mg	41	38	38(100.0%	32 (84.2%)	32(84.2%)	30 (78.9%)	29(76.3%)	28(73.7%)	26(68.4%)	24(63.
Z. 200mg	39	36	36(100.0%	32 (88.9%)	31(86.1%)	30 (83.3%)	28(77.8%)	26(72.2%)	25(69.4%)	23(63.
Placebo	38	38	38(100.0%	36 (94.7%)	33(86.8%)	33 (86.8%)	32(84.2%)	29(76.3%)	28(73.7%)	27(71.

Table 514 - 3
Mean Change from Baseline in Total Number of Panic Attacks
Observed Cases Analysis

	Treatment Groups								2-sided p-values for comparisons		
Week	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	38	7.03	38	17.28	36	7.71	38	9.59			
1	37	-1.26	38	-4.88	36	- .49	38	- .93	.496	.274	.969
2	31	-1.84	32	-12.80	32	- .59	36	-2.60	.715	.051	.660
3	26	-3.37	32	-14.33	31	-3.06	33	-3.30	.263	.265	.296
4	26	-4.00	30	-16.87	30	-4.12	33	-3.12	.079	.007	.056
5	25	-2.48	29	-16.00	28	-5.30	31	-3.92	.035	.007	.004
6	25	-4.08	29	-15.07	28	-5.77	32	-4.36	.012	.015	.036
7	24	-4.69	28	-16.55	26	-6.48	29	-4.52	.034	.023	.103
8	24	-4.85	27	-16.96	26	-6.40	29	-5.76	.192	.049	.110
9	24	-4.65	25	-16.16	25	-7.70	28	-5.95	.386	.212	.037
10	24	-4.27	25	-16.08	25	-7.90	28	-5.80	.582	.353	.074
11	23	-4.74	24	-19.02	23	-7.41	27	-6.11	.413	.042	.129
12	24	-4.94	24	-19.06	23	-7.67	27	-5.81	.104	.019	.027

Table 514 - 4
Mean Change from Baseline in Total Number of Panic Attacks
Last Observation Carried Forward Analysis

Week	Treatment Groups								2-sided p-values for comparisons		
	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	38	7.03	38	17.28	36	7.71	38	9.59			
1	37	-1.26	38	-4.88	36	- .49	38	- .93	.496	.274	.969
2	38	-1.58	38	-11.01	36	- .57	38	-2.64	.952	.179	.995
3	38	-2.24	38	-12.30	36	-2.24	38	-3.43	.979	.383	.451
4	38	-2.66	38	-13.93	36	-3.07	38	-3.28	.499	.034	.146
5	38	-1.61	38	-14.04	36	-3.29	38	-3.96	.822	.073	.205
6	38	-2.66	38	-13.33	36	-3.65	38	-4.28	.416	.146	.398
7	38	-3.00	38	-14.09	36	-3.93	38	-3.83	.241	.075	.205
8	38	-3.11	38	-14.01	36	-3.88	38	-4.78	.624	.186	.444
9	38	-2.97	38	-13.67	36	-4.82	38	-4.70	.773	.287	.205
10	38	-2.74	38	-13.62	36	-4.96	38	-4.59	.940	.465	.241
11	38	-2.92	38	-14.59	36	-4.49	38	-4.86	.935	.229	.319
12	38	-3.16	38	-14.62	36	-4.65	38	-4.64	.523	.081	.224

Table 514 - 5
Mean Change from Baseline in Time Spent Worrying
Observed Cases Analysis

Week	Treatment Groups								2-sided p-values for comparisons		
	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	38	23.82	38	20.10	36	28.27	37	21.98			
1	35	-3.10	37	.27	36	-1.67	36	-3.14	.946	.250	.359
2	30	-8.10	31	-6.10	32	-4.37	34	-6.64	.914	.317	.146
3	25	-7.06	32	-9.33	31	-9.60	32	-8.41	.347	.726	.589
4	25	-9.76	30	-10.00	30	-12.75	32	-8.32	.972	.622	.336
5	24	-12.21	29	-11.88	28	-13.61	30	-9.15	.397	.772	.755
6	24	-11.73	29	-11.35	28	-14.93	29	-9.38	.894	.870	.432
7	24	-12.58	28	-6.26	26	-17.97	28	-9.56	.205	.735	.698
8	24	-10.40	27	-14.77	26	-17.92	28	-8.94	.490	.187	.511
9	24	-12.85	24	-13.19	25	-20.02	27	-10.87	.379	.882	.605
10	24	-11.95	24	-14.16	25	-19.47	27	-10.39	.465	.267	.913
11	23	-11.91	24	-17.38	23	-20.49	26	-9.91	.534	.067	.407
12	23	-12.24	23	-16.46	23	-21.27	26	-10.01	.377	.134	.326

Table 514 - 6
Mean Change from Baseline in Time Spent Worrying
Last Observation Carried Forward Analysis

	Treatment Groups								2-sided p-values for comparisons		
Week	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	38	23.82	38	20.10	36	28.27	37	21.98			
1	35	-3.10	37	.27	36	-1.67	36	-3.14	.946	.250	.359
2	36	-7.27	38	-2.71	36	-4.75	36	-6.13	.730	.222	.280
3	36	-9.03	38	-5.61	36	-8.51	37	-7.38	.270	.745	.304
4	36	-9.93	38	-6.21	36	-11.00	37	-7.30	.483	.568	.351
5	36	-11.78	38	-7.76	36	-11.32	37	-7.29	.986	.741	.872
6	36	-11.46	38	-7.36	36	-12.35	37	-7.86	.715	.653	.567
7	37	-12.70	38	-3.03	36	-13.77	37	-7.64	.539	.970	.668
8	37	-11.28	38	-9.04	36	-13.73	37	-7.18	.819	.294	.685
9	37	-12.88	38	-7.80	36	-15.34	37	-8.33	.857	.778	.613
10	37	-12.29	38	-8.41	36	-14.96	37	-7.97	.966	.274	.722
11	37	-12.17	38	-9.79	36	-15.32	37	-7.27	.821	.087	.240
12	37	-12.21	38	-9.31	36	-15.83	37	-7.33	.464	.187	.321

Table 514 - 7

Mean Change from Baseline in CGI Severity

Observed Cases Analysis

	Treatment Week																	
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	38	4.38	37	- .50	29	- .89	26	-1.26	26	-1.39	25	-1.84	24	-1.91	24	-2.04	24	-1.99
Z. 100mg	38	4.53	38	- .08	32	- .40	30	- .82	29	-1.01	29	-1.20	28	-1.34	26	-1.71	24	-1.84
Z. 200mg	36	4.42	36	- .26	32	- .70	31	-1.23	30	-1.44	27	-1.78	26	-1.81	25	-2.16	23	-2.20
Placebo	38	4.42	38	- .47	36	- .63	33	- .95	32	- .95	32	- .85	29	-1.38	28	-1.44	27	-1.61
2-sided p-values for pairwise comparisons																		
50mg vs P			.888		.213		.224		.137		.001		.059		.035		.183	
100mg vs P			.037		.229		.572		.805		.193		.862		.315		.426	
200mg vs P			.256		.747		.244		.078		.002		.122		.012		.042	

Table 514 - 8
Mean Change from Baseline in CGI Severity
Last Observation Carried Forward Analysis

	Treatment Week															
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	38	4.38	37	- .50	37	- .72	37	- .93	37	-1.00	37	-1.30	37	-1.47	37	-1.51	37	-1.50
Zoloft 100mg	38	4.53	38	- .08	38	- .34	38	- .74	38	- .83	38	- .98	38	- .99	38	-1.12	38	-1.14
Zoloft 200mg	36	4.42	36	- .26	36	- .58	36	- .99	36	-1.15	36	-1.36	36	-1.37	36	-1.56	36	-1.63
Placebo	38	4.42	38	- .47	38	- .69	38	- .89	38	- .89	38	- .85	38	-1.10	38	-1.11	38	-1.13
2-sided p-values for pairwise comparisons																		
50mg vs P				.888		.891		.880		.662		.109		.215		.198		.227
100mg vs P				.037		.075		.527		.829		.631		.695		.978		.976
200mg vs P				.256		.575		.672		.320		.069		.357		.141		.104

Table 514 - 9
CGI Improvement
Observed Cases Analysis

	Treatment Week															
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	37	3.72	29	2.75	26	2.49	26	2.14	25	1.93	24	1.82	24	1.74	24	1.73
Zoloft 100mg	38	3.52	32	3.14	30	2.64	29	2.49	29	2.30	28	2.18	26	1.83	24	1.79
Zoloft 200mg	36	3.46	32	2.97	31	2.39	30	2.19	27	2.03	26	1.93	25	1.61	23	1.66
Placebo	38	3.47	36	3.04	33	2.78	32	2.71	32	2.80	29	2.33	28	2.12	27	2.19
2-sided p-values for pairwise comparisons																
50mg vs P	.321		.265		.280		.063		.004		.033		.074		.051	
100mg vs P	.821		.695		.579		.411		.057		.526		.164		.090	
200mg vs P	.978		.770		.143		.069		.009		.091		.016		.028	

Table 514 - 10 CGI Improvement																
Last Observation Carried Forward Analysis																
	Treatment Week															
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	37	3.72	37	3.29	37	3.21	37	3.03	37	2.84	37	2.70	37	2.68	37	2.63
Zoloft 100mg	38	3.52	38	3.26	38	2.85	38	2.76	38	2.59	38	2.63	38	2.55	38	2.51
Zoloft 200mg	36	3.46	36	3.23	36	2.86	36	2.68	36	2.67	36	2.58	36	2.40	36	2.43
Placebo	38	3.47	38	3.01	38	2.84	38	2.80	38	2.81	38	2.65	38	2.61	38	2.66
2-sided p-values for pairwise comparisons																
50mg vs P	.321		.308		.224		.485		.914		.881		.822		.945	
100mg vs P	.821		.358		.990		.893		.506		.959		.867		.676	
200mg vs P	.978		.429		.955		.690		.682		.833		.533		.511	

DETIRN

Date: SEP 12 1996

Statistical Review and Evaluation

SEP 9 1996

NDA #: 19-839/SE1-011

Applicant: Pfizer, Inc.

Name of the Drug: Zoloft® (sertraline hydrochloride) Tablets

Indication: Panic Disorder

Documents Reviewed: Volumes 1.1, 1.3 to 1.29, amendments dated 2-16-96, 3-6-96, 3-21-96, 3-29-96, 5-28-96, 6-28-96, 7-24-96, 8-12-96, and 8-20-96

Clinical Reviewer: Hillary Lee, Ph.D. (HFD-120)

The issues in this review have been discussed with the reviewing Medical Officer, Hillary Lee, Ph.D. (HFD-120).

Various Sections of this review are:

I. **Background/Introduction**

This efficacy supplement for the treatment of Panic Disorder comprises two flexible dose and two fixed multiple-dose principal studies (double-blind, randomized, parallel group) conducted in the U.S. in 673 outpatients with panic disorder: 414 received sertraline and 259 received placebo. Actual enrollments in the studies were slightly more than those mentioned in the protocols, except for Protocol 0514. Summary design aspects of these

studies are attached as Table 0.1.1.[1]

Protocol 0514 was identical in design to Protocol 0529. For Study 0514, the sponsor stated, "The reduction in panic attack frequency was greater in the pooled sertraline group than in the placebo group, but the difference was not statistically significant. ... Like panic attacks, all of the other efficacy variables (except HAM-A) exhibited a nonsignificant trend toward greater improvement in the pooled sertraline group at endpoint." This reviewer has not reviewed this study.

II. Clinical Studies

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned to be done by this reviewer.

By discussion with Dr. Lee (HFD-120) and from other meetings, this reviewer has the idea that "Change from Baseline in Number of Full Panic Attacks" and "Change from Baseline in CGI Severity of Illness" are the two most important efficacy variables; "Phobic Avoidance" ,"Percent of Time Worrying", and "CGI Improvement" are also important.

1. Study Based on Protocol 93CE21-0629

Essential features of the study, including Objectives, Design, (Patient) Population, Results, and Summary and Conclusions may be seen in the synopsis provided by the sponsor in the NDA pages 8-40 to 8-42. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

1A. Objectives

This was a randomized, multicenter, double-blind, parallel group, flexible dose study to evaluate the comparative safety and efficacy of sertraline and of placebo in outpatients with panic disorder.

---

[1] In the Table (or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

1B. Disposition of Patients

Attached Figure 1.2.1 compares the two treatment arms with respect to the Percent of Patients in Study (continuing over time). After Week 2, withdrawal from the placebo group was less than that from the sertraline group. The overall discontinuation rate for the sertraline group was 26% and that for the placebo group was 17% (not significantly different).

The most frequent reasons for discontinuation in the sertraline group was adverse experience (9% vs 1% in the placebo group, p=.028). In the placebo group the most common reason for discontinuation was insufficient clinical response (7% vs 1% in the sertraline group). This difference between groups was not statistically significant.

Discontinuations due to protocol violation were 5% from the sertraline group and 1.1% from the placebo group, and due to "Other" were 5% from the sertraline group and 0.0% from the placebo group.

The Mean Duration on study (NDA p.8 68) was 58.2 days for sertraline and 64.2 days for placebo.

1C. Efficacy Results (Sponsor's Analyses)

The protocol mentioned "The number of panic attacks per week" as the primary efficacy variable. The protocol was unsatisfactory with respect to some other specifics. For example, analysis methods and primary datasets were not mentioned in the protocol; there were opportunities for post-hoc choices. This is noteworthy, especially because, instead of analyzing the original data, the sponsor transformed the data to log([endpoint attacks + 0.5]/[baseline attacks + 0.5])for analyses. On the other hand, the tests for normality were highly significant showing the non-normality of data. Also, a log transformation is not unusual under such circumstances.

Above transformation was employed only for the analyses of the ratios (not for the differences) and not for any descriptive statistics.

The nonparametric Wilcoxon rank sum tests provided by the sponsor or done by the reviewer should be depended upon heavily.

On request, the sponsor supplied the Analysis Plan later. The Analysis Plan issue date was April 25, 1995 and the Study Unblinding Approval date was July 18, 1995. The log

transformation performed was mentioned in that Plan.

This reviewer's comparison of LOCF and OC results is based on the relative superiority of sertraline results to placebo results.

The sponsor stated, "End-point is the Last Observation Carried Forward (LOCF). For the analyses of the PAAS endpoints, data based on the averages for the last 2 weeks were used; if Week 1 data only were collected, those data were used." Time-specific results in the attached Tables are from the observed cases (OC).

The patients set considered is the intent-to-treat one, as stated by the sponsor,"Patients who took at least one dose of double-blind medication and provided any follow-up data were included in the analysis for safety; patients included in the safety analysis who had baseline and post-randomization efficacy data were included in the analysis for efficacy."

The alternative analysis based on the average number of full panic attacks per week considered the whole period the patient was on the study, instead of considering time intervals separately.

Number of Panic Attacks (Primary Efficacy Variable)

Mean Ratio to Baseline at each week and Endpoint is attached as Table 1.3.1a and the p-values are in Table 1.3.1b. Median Number of Panic Attacks at Baseline, other weeks, and Endpoint is attached as Table 1.3.1c.

By the p-values provided by the sponsor, the Endpoint result is clearly significant. The OC results are statistically significant over the five weeks, Weeks 3 to 7, out of the 10 Weeks (1 to 10). The LOCF results (p.16 of submission dated 3-29-96) are statistically significant except at Weeks 1,2, and 8. Sertraline group showed, relatively (to placebo), better Mean Change (difference) from Baseline in the OC analysis than in the LOCF analysis.

At Endpoint, the (geometric) mean (adjusted) of the ratio to Baseline Number of Panic Attacks was .30 for placebo and .20 for sertraline.

The non-parametric p-value for endpoint values of Panic Attacks (p.45 of 3-29-96 submission) is .051 for Ratio and .002 for the difference.

Results by an alternative analysis based on the average number of panic attacks per week, considering the whole period a patient is in the study, are in the attached Table 0.4.1 (weighted by the time on Study). The 95% confidence interval for the ratio (to baseline) was (.509, .876), which does not include 1, shows the efficacy of sertraline. [The Zoloft/placebo ratio was based again on the mean ratio, for each drug, of panic attacks per week on drug to panic attacks per week at baseline.] However, the one for the difference (with baseline) was (-2.71, .191), which includes 0, does not show the efficacy of sertraline.

Among the patients who dropped during Weeks 1-3, the placebo patients showed exceptionally bad responses and the sertraline patients showed exceptionally good responses (Figure 1.3.2). Inclusion of this group of patients in the analysis should show better efficacy of sertraline. [The sponsor provided uneven (with respect to time intervals) dropout groups than desired by the reviewer, and stated, "A finer breakdown provides little further information since few patients discontinued late in the studies. Moreover, these categories gave roughly equal number of patients in the two non-completer subgroups."]

CGI Severity of Illness Item

Mean Change (difference) from Baseline is attached as Table 1.4.1.

The Endpoint result is statistically highly significant. The weekly OC results also are statistically, overall, significant. The LOCF results (p.20, submission dated 3-29-96) are stronger. Thus, the efficacy of sertraline has been shown statistically with respect to (wrt) the change from baseline in CGI Severity of Illness.

By the Endpoint Data Set, the mean (adjusted) reduction (difference) in CGI Severity of Illness Item from baseline is 0.90 and 1.64 respectively for placebo and sertraline groups.

CGI Improvement

Results on CGI Improvement (Mean Ratings at Each Visit and at Endpoint) are in the attached Table 1.6.1.

The Endpoint result is statistically highly significant. The weekly OC results also are statistically significant at weeks 3, 4, 6, and 10. The LOCF results (p.22, submission dated 3-29-96) are significant at all weeks except Weeks 1 and 2. Thus, the efficacy of sertraline has been shown statistically with respect

to (wrt) the CGI Improvement.

By the Endpoint Data Set, the mean (adjusted) CGI Improvement score was 2.82 and 2.02 respectively for placebo and sertraline groups.

Anticipatory Anxiety: Percent of Time Worrying

For Percent Time Worrying, Mean Ratio to Baseline at each week and Endpoint, together with p-values, is attached as Table 1.5.1a. Median Percent Time Worrying at Baseline, other weeks, and Endpoint is attached as Table 1.5.1b.

These results were statistically non-significant except only for Week 5 (OC). None of the LOCF results (p.18 of submission dated 3-29-96) was statistically significant. Thus, efficacy of sertraline has not been shown statistically with respect to the Ratio to baseline in Percentage of Time Worrying.

By the Endpoint Data Set, the (geometric) mean of the Ratio to Baseline in "Anticipatiry Anxiety: Percent of Time Worrying" were .40 and .30, respectively, for placebo and sertraline groups.

The non-parametric p-value at Endpoint for % Time Worrying, Ratio to Baseline, (p.43, submission of 3-29-96) is .036.

Phobic Avoidance

The "Phobic Avoidance" subscale of CGI Improvement has been analyzed by the sponsor only at Endpoint. The adjusted mean score was 2.72 for sertraline and 3.16 for placebo. Efficacy of sertraline was shown statistically wrt phobic avoidance (2-sided p-value = .036 from analysis of variance with treatment, site, and treatment-by-site as effects). [Page 8 94 of the NDA]

1D. Reviewer's Analyses

As a cross-check with the sponsor's model based analyses, this reviewer performed non-parametric 1-way analyses (Wilcoxon's 2-sample test) by SAS PROC NPAR1WAY on the change (difference) from baseline, corresponding to those time points and data sets submitted in the original NDA by the sponsor (Weekly OC and Endpoint), using data supplied by the sponsor on diskettes.

In the single case, for Number of Panic Attacks at Endpoint, where the sponsor submitted in an amendment the same analysis (p-

value) as the reviewer's, the result is matching.

P-values from Wilcoxon's 2-Sample Test

	Change From Baseline in Number of Panic Attacks	CGI Sev.	%Time Worrying	CGI Improvement
Week 1	1.000	.707	.474	.040
Week 2	.067	.232	.478	.609
Week 3	.007	.112	.489	.017
Week 4	.007	.028	.406	.064
Week 5	.009	-	.338	-
Week 6	.0002	.048	.778	.002
Week 7	.003	-	.765	-
Week 8	.007	.031	.542	.012
Week 9	.001	-	.320	-
Week 10	.001	.001	.362	.0001
Endpoint	.002	.002	.734	.0002

Except for Percent Time Worrying, these analyses provide evidence in favor of the efficacy of sertraline. This is the same conclusion as from the sponsor's analyses.

1E. **Comments and Conclusions on Study Based on Protocol 0629**

There was statistical evidence in favor of the efficacy of sertraline with respect to "Number of Panic Attacks", "CGI Severity of Illness", "CGI Improvement," "Phobic Avoidance" item of CGI Improvement but not wrt "Percent of Time Worrying". Provided the data supplied by the sponsor on the diskette is reliable, this reviewer's analyses support this conclusion based on the sponsor's analyses.

On the treatment by sex interaction, the sponsor stated,"..., the interaction between sex and treatment was significant for panic attacks (p-value = .035). ... this interaction may be attributable to the presence of larger sertraline-placebo differences in female patients as compared to male patients."

Eight patients withdrew from the sertraline group due to "protocol violation" and "other" reasons, compared with only one from the placebo group. Seven patients withdrew from the

sertraline group due to adverse experience compared with only one from the placebo group (p-value for the comparrison is .028). On the other hand, 6 patients withdrew from the placebo group due to insufficient clinical response compared with only one from the sertraline group (this difference was not statistically significant).

2. Study Based on Protocol 93CE21-0630

Essential features of the study, including Objectives, Design, (Patient) Population, Results, and Summary and Conclusions may be seen in the synopsis provided by the sponsor in the NDA pages 8-1345 to 8-1347. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

2A. Objectives

This was a randomized, multicenter, double-blind, parallel group, flexible dose study designed to evaluate the comparative safety and efficacy of sertraline and of placebo in outpatients panic disorder.

2B. Disposition of Patients

Attached Figure 2.2.1 compares the two treatment arms with respect to Percent of Patients in Study (continuing over time). The largest difference between the continuation rates occured at Week 2 with 92.0% for sertraline and 98.9% for placebo. At Week 10 there were 83% patients in each group.

Attached Table 2.2.2 of the distribution of Duration on Study shows some imbalance at Week 1 and after Week 8.

2C. Efficacy Results (Sponsor's Analyses)

The protocol mentioned "The number of panic attacks per week" as the primary efficacy variable. The protocol was unsatisfactory with respect to some other specifics. For example, analysis methods and primary datasets were not mentioned in the protocol; there were opportunities for post-hoc choices. This is noteworthy, especially because, instead of analyzing the original

data, the sponsor transformed the data to log([endpoint attacks + 0.5]/[baseline attacks + 0.5])for analyses.

Above transformation was employed only for the analyses of the ratios (not for the differences) and not for any descriptive statistics.

The nonparametric Wilcoxon rank sum tests provided by the sponsor or done by the reviewer should be depended upon heavily.

On request, the sponsor supplied the Analysis Plan later. The Analysis Plan issue date was April 25, 1995 and the Study Unblinding Approval date was July 18, 1995. The log transformation performed was mentioned in that Plan.

The sponsor stated, "End-point is the Last Observation Carried Forward (LOCF). For the analyses of the PAAS endpoints, data based on the averages for the last 2 weeks were used; if Week 1 data only were collected, those data were used." Weekly or other results in the original NDA were based on observed cases (OC).

The patients set considered is the intent-to-treat one, as stated by the sponsor,"Patients who took at least one dose of double-blind medication and provided any follow-up data were included in the analysis for safety; patients included in the safety analysis who had baseline and post-randomization efficacy data were included in the analysis for efficacy."

Number of Panic Attacks (Primary Efficacy Variable)

Mean Ratio to Baseline at each week and Endpoint is attached as Table 2.3.1a and the p-values are in Table 2.3.1b. Median Number of Panic Attacks at Baseline, other weeks, and Endpoint is attached as Table 2.3.1c.

By the p-values provided by the sponsor, the Endpoint result is clearly significant. The OC results are reasonably statistically significant over most of the weeks. The LOCF results (p.5 of amendment dated 3-29-96) were better and statistically significant from Week 3, except at Week 6.

By the Endpoint Data Set, the (geometric) mean (adjusted) of the Ratio to Baseline Number of Panic Attacks was .21 for sertraline and .31 for placebo.

Results by an alternative analysis based on the average number of

panic attacks per week, considering the whole period a patient is in the study, are in the attached Table 0.4.1 (weighted by the time on Study). The 95% confidence interval for the ratio was (.553, .823), which does not include 1, shows the efficacy of sertraline. [The Zoloft/placebo ratio was based again on the mean ratio, for each drug, of panic attacks per week on drug to panic attacks per week at baseline.] The one for the difference was (-2.71, -.630), which does not include 0, also shows the efficacy of sertraline.

The non-parametric p-value supplied by the sponsor at Endpoint on Number of Panic Attacks (p.45, submission of 3-29-96) is.058 for ratio and .12 for the difference.

CGI Severity of Illness Item

Mean Change (difference) from Baseline is attached as Table 2.4.1.

The Endpoint result is statistically highly significant. The weekly OC results also were statistically significant in favor of sertraline, except at Weeks 2, 3, and 8. At Week 1, sertraline was statistically significantly inferior to placebo. However, the results were statistically significant or nearly significant after Week 3. By LOCF results (p.9 of amendment dated 3-29-96) sertraline was statistically significantly superior to placebo only at Weeks 6 and 10 (2 out of 7), and inferior to placebo at Week 1. Thus the statistical superiority of sertraline to placebo has been shown only marginally.

By the Endpoint Data Set, the mean (adjusted) reduction (difference) in CGI Severity of Illness Item from baseline is 1.04 and 1.56 respectively for placebo and sertraline groups.

Anticipatory Anxiety: Percent of Time Worrying

Table of Mean Ratio to Baseline at each week and Endpoint, together with p-values, is attached as Table 2.5.1a. Median Number of Panic Attacks at Baseline, other weeks, and Endpoint is attached as Table 2.5.1b.

These results were statistically non-significant except only for Week 5, 7, and 10 (3 out of 10, endpoint p-value= .055). Sertraline was numerically inferior at Week 1. Thus, efficacy of sertraline has been shown statistically marginally with respect to the Ratio to baseline in Percentage of Time Worrying. With respect to statistical significance, the LOCF results (p.7 0f amendment dated 3-29-96) were similar.

By the Endpoint Data Set, the (geometric) mean of the Ratio to Baseline in "Anticipatory Anxiety: Percent of Time Worrying" were .53 and .38, respectively, for placebo and sertraline groups.

The non-parametric p-value, supplied by the sponsor for Endpoint Ratio to Baseline, on %Time Worrying (p.43, submission of 3-29-96) is.675.

CGI Improvement

Results on CGI Improvement (Mean Ratings at Each Visit and at Endpoint) are in the attached Table 2.6.1.

The Endpoint result was statistically significant. The weekly OC results also were statistically significant in favor of sertraline, except at Weeks 2 and 3. At Week 1, sertraline was statistically significantly inferior to placebo, by both OC and LOCF data sets. Statistical superiority of sertraline to placebo was shown only at Weeks 6 and 10, by the LOCF results (p.11 of 3-29-96 submission). Thus the efficacy of sertraline may be claimed to have been shown statistically only moderately with respect to (wrt) the CGI Improvement.

By the Endpoint Data Set, the mean (adjusted) CGI Improvement score was 2.74 and 2.26 respectively for placebo and sertraline groups.

Phobic Avoidance

The "Phobic Avoidance" subscale of CGI Improvement has been analyzed by the sponsor only at Endpoint (p. 8 1397 of NDA). The adjusted mean score was 2.65 for sertraline and 3.03 for placebo. Superiority of sertraline over placebo was shown numerically but not quite by statistical significance wrt phobic avoidance (2-sided p-value = .064, which is nearly significant, from analysis of variance with treatment, site, and treatment-by-site as effects).

2D. Reviewer's Analyses

As a cross-check with the sponsor's model based analyses, this reviewer performed non-parametric 1-way analyses (Wilcoxon's 2-sample test) by SAS PROC NPAR1WAY on the change from baseline, corresponding to those time points and data sets submitted in the original NDA by the sponsor (Weekly OC and Endpoint), using data supplied by the sponsor on diskettes.

In the single case, for Number of Panic Attacks at Endpoint, where the sponsor submitted in an amendment the same analysis (p-value) as the reviewer's, the result is matching.

P-values from Wilcoxon's 2-Sample Test

	Change From Baseline in Number of Panic Attacks	CGI Sev.	%Time Worrying	CGI Improvement
Week 1	.254	.003	.130	.004
Week 2	.021	.693	.941	.760
Week 3	.001	.550	.278	.250
Week 4	.022	.011	.026	.016
Week 5	.029	-	.088	-
Week 6	.104	.004	.047	.004
Week 7	.189	-	.158	-
Week 8	.240	.056	.287	.033
Week 9	.162	-	.240	-
Week 10	.141	.004	.230	.003
Endpoint	.120	.003	.116	.002

These analyses show the evidence in favor of the efficacy of sertraline wrt CGI Severity of Illness and CGI Improvement, although placebo was favored at Week 1. The evidence provided by the Number of Panic attacks is not quite acceptable. Decreasing sample sizes over the latter weeks may have influenced to some extent the non-significance of p-values over Weeks 6 to 10. The numerical differences between sertraline and placebo over the latter weeks were no less than that at Week 2. However, even the Endpoint p-value which should be based on all patients was not significant.

2E. **Comments and Conclusions on Study Based on Protocol 0630**

There was moderate statistical evidence in favor of the efficacy of sertraline with respect to Number of Panic Attacks, CGI Severity of Illness, CGI Improvement, marginal statistical evidence wrt Phobic Avoidance, but no statistical evidence wrt Percent of Time Worrying.

The evidence wrt Number of Panic Attacks was stronger by the sponsor's model-based analysis but unacceptable by the reviewer's

non-parametric analysis. On the other hand, the evidence wrt CGI Severity and CGI Improvement were stronger by the reviewer's non-parametric analysis.

Seven patients withdrew from the sertraline group due to "Adverse Events" compared with three from the placebo group. Also, three patients withdrew from the sertraline group due to "protocol voilation" compared with one from the placebo group.

3. Study Based on Protocol 90CE21-0529

Essential features of the study, including Objectives, Design, Study Population, Results, and Summary and Conclusions may be seen in the Study Synopsis provided by the sponsor in the NDA pages 8 2701 to 8 2703. In addition, the Clinical Reviewer's report contains essential features of the study.

This reviewer will discuss only the efficacy results and a few other items as needed below and provide all other criticisms under the "Reviewer's Comments".

3A. Objectives

This was a multicenter, double-blind, parallel study designed to evaluate the comparative safety and efficacy of 3 doses of sertraline and placebo in outpatients with panic disorder.

3B. Disposition of Patients

Attached Figure 3.2.1 compares the treatment arms with respect to Percent of Patients in Study (continuing over time). Before Week 4, withdrawal from the placebo group was the minimum; after that 100 mg group was the best in retaining patients.

The two most frequent reasons for discontinuation overall were adverse experience and insufficient clinical response. There was a significantly higher rate of discontinuation due to adverse experiences in the 50 mg (18.6%), 200 mg (26.7%), and pooled sertraline group (19.7%) than in the placebo group (4.4). There was a significantly lower rate of discontinuation due to insufficient clinical response in the 100 mg sertraline group(0.0%) than in the 50 mg group (14.0%); there was a marginally significant difference between the 100 mg and placebo (11.1%) groups.

The Mean Duration on study in days was (NDA p. 8 2736) 70.1, 58.7, 70.5, and 57.9 respectively for placebo, and setraline 50,100, and 200 mg.

3C. Efficacy Results (Sponsor's Analyses)

The protocol was totally silent on statistical aspects. The NDA reports, "End-point is the Last Observation Carried Forward (LOCF). For the analyses of the PAAS endpoints, data based on the averages for the last 2 weeks were used; if Week 1 data only were collected, those data were used." Weekly or other results in the original NDA were based on observed cases (OC).

The patients set considered is the intent-to-treat one, as stated by the sponsor,"Patients who took at least one dose of double-blind medication and had any follow-up data were included in the analysis for safety; patients included in the safety analysis who had baseline and post-randomization efficacy data were included in the analysis for efficacy. Patients discontinued before titration to their assigned dose were analyzed on the basis of their assigned randomization groups; ..."

Two sets of p-values have been provided in the original NDA. One is for comparing all the four treatment groups simultaneously (overall) by the F-test. Another is from the analysis done after pooling all three sertraline groups together and then comparing with the placebo group.

On request, the sponsor has provided the "Analysis Plan". As stated by the sponsor, the Analysis Plan issue date was May 9, 1994 and the Study Unblinding Approval Date was May 16, 1994.

This Analysis Plan stated, "Adjustments will be made for multiple comparisons using Fisher's protected least significance method." The sponsor did not even supply (though stated that those had been done) the pairwise comparison p-values in the original NDA. On request, the sponsor provided some pairwise comparison p-values without any discussion of statistical significance. This reviewer will discuss the sponsor's pairwise comparison results by applying the Hochberg's method, which seems to be more accepted here than the Fisher's LSD method.

The Analysis Plan mentioned "adding 1" before logarithmic transformation of some efficacy measures; however, in reality ½ was added.

Above transformation was employed only for the analyses of the

ratios (not for the differences) and not for any descriptive statistics.

The Analysis Plan stated,"For percentage of time spent worrying 10% will be added; ... ." The report stated,"For percent time in anticipatory anxiety (percent time worrying), 1% was added to each baseline and endpoint measurement, instead of 0.5."

Number of Panic Attacks (Primary Efficacy Variable)

Mean Ratio to Baseline at each week and Endpoint is attached as Table 3.3.1a. Median Number of Panic Attacks at Baseline, other weeks, and Endpoint is attached as Table 3.3.1b. Mean Change From Baseline is in Table 3.3.1c for weekly OC, in Table 3.3.1d for weekly LOCF, and in Table 3.3.1e for Endpoint; however, the p-values are based on "Ratios" and not on Change From Baseline measured by difference.

From the Endpoint analyses of Table 3.3.1e, we see some evidence in favor of the efficacy of sertraline wrt Number of Panic Attacks.

From the weekly OC analyses of Table 3.3.1c, we see only 3 significant p-values out of 36 p-values. This is not an acceptable evidence in favor of the efficacy of sertraline.

From the weekly LOCF analyses of Table 3.3.1d, we see some reasonable evidence in favor of the efficacy of 100 mg sertraline. Week 8 and Week 12 p-values are significant for all three doses.

By the p-values provided by the sponsor on p.8 2749, the Endpoint result is clearly significant by "overall" and "pooled" analyses. The OC results are statistically significant at most of the weeks by the "pooled" analysis and not by the "overall" analysis. By pairwise comparisons at Endpoint, the 100 mg vs placebo comparison p-value (Table 1 of June 28,1996 submission) is highly significant.

By the Endpoint (LOCF) Data Set, the (geometric) mean (adjusted)of the Ratio to Baseline Number of Panic Attacks was .21, .14, .20, and .35 respectively for 200, 100, and 50 mg sertraline and placebo.

Regarding the better results for the 100 mg group, we should note the sponsor's statement, "In general, the treatment groups were comparable at baseline in efficacy parameters. However, noting the formally significant results which were obtained at baseline

and ranking the results in Tables 5.1-5.4 by treatment suggests a trend toward more severe symptomatology in the sertraline 100 mg group, and less severe symptomatology in the sertraline 200 mg group."

There was really a more serious imbalance between the 200 mg (5.75) and placebo (13.74) groups than between 200 mg and 100 mg (10.65), in Baseline Mean Number of Panic Attacks. The sponsor reported that the baseline value was used as a covariate.

Results by an alternative analysis based on the average number of panic attacks per week, considering the whole period a patient is in the study, are in the attached Table 0.4.1 (weighted by the time on Study). The 95% confidence interval for the ratio was (.439, .956) when 100mg sertraline is considered, which does not include 1, shows the efficacy of 100 mg sertraline (multiple comparison adjustment was not considered for these intervals). [The Zoloft/placebo ratio was based again on the mean ratio, for each drug, of panic attacks per week on drug to panic attacks per week at baseline.] When the confidence interval was recomputed applying Dunnett's method (p.8 of 6-28-96 submission), it was (.406, 1.03), which includes 1 and, therefore, does not show the efficacy of sertraline.

Also, the 95% confidence intervals for the difference, which include 0, does not show the efficacy of sertraline, even when the three sertraline groups are pooled together.

The non-parametric p-value for endpoint values of Panic Attacks (p.45 of 3-29-96 submission) is .003 for Ratio and .061 for the difference (100mg vs placebo).

Summary: The Endpoint (as well as Weeks 8 and 12 LOCF) p-values based on ratios are clearly significant. Weekly LOCF results (based on ratios) are reasonably acceptable for 100 mg sertraline.

CGI Severity of Illness Item

Mean Change (difference) from Baseline is attached as Tables 3.4.1, 3.4.2, and 3.4.3.

The Endpoint result (Table 3.4.1) is not statistically significant.

The weekly OC results also are statistically significant only for a few weeks around the middle of the 12-week treatment period, by

the "pooled" or "overall" analyses (Table 3.4.1) and not by pairwise comparisons (except for 100 mg at Weeks 6 and 8, Table 3.4.2). None of the weekly LOCF pairwise comparison p-values (Table 3.4.3) are significant. Thus, the efficacy of sertraline has not been shown statistically with respect to the change (difference) from baseline in CGI Severity of Illness.

By the Endpoint Data Set, the mean (adjusted) reduction (difference) in CGI Severity of Illness Item from baseline is 1.5, 1.8, 1.4, and 1.2 respectively for 200, 100, and 50 mg sertraline and placebo groups.

The non-parametric p-value for endpoint change (difference) from baseline (p.43 of 3-29-96 submission) is .063 (100mg vs placebo).

CGI Improvement

Results on CGI Improvement (Mean Ratings at Each Visit and at Endpoint) are in the attached Table 3.5.1, 3.5.2, and 3.5.3.

The Endpoint result (Table 3.5.1) is not statistically significant.

The weekly OC results are statistically significant at Weeks 3, 4, and 5 by the "Overall" analysis and at Weeks 2, 3, 4, 6, and 8 by the "pooled analysis" (Table 3.5.1) but only sporadically significant by pairwise analyses (Table 3.5.2). The weekly LOCF p-values (Table 3.5.3) are significant only for 100 mg at Weeks 2 and 3. Thus, the efficacy of sertraline has not been shown statistically satisfactorily with respect to (wrt) the CGI Improvement.

By the Endpoint Data Set, the mean (adjusted) CGI Improvement score was 2.5, 2.5, 2.1,and 2.3 respectively for placebo and sertraline 50, 100, 200 mg groups.

The non-parametric p-value at endpoint (p.43 of 3-29-96 submission) is .056 (100mg vs placebo).

Anticipatory Anxiety: Percent of Time Worrying

Mean Ratio to Baseline at each week and Endpoint is attached as Table 3.6.1a (with p-values for "Overall" and "Pooled" analyses). Median Number of Panic Attacks at Baseline, other weeks, and Endpoint is attached as Table 3.6.1b.

Endpoint results were statistically significant. Weekly (OC)

results were statistically significant for weeks 4 to 12 by the pooled analysis and only for Weeks 4 to 7 by the overall analysis.

By pairwise comparisons, the 100 mg vs placebo comparison p-value at Endpoint (page 44 of 3-29-96 submission) is highly significant.

Mean Change (difference) From Baseline with p-values for pairwise comparisons are in Tables 3.6.2 (LOCF) and 3.6.3 (OC). Considering multiple comparison adjustments, only the LOCF p-values for 100 mg are reasonably consistently siginificant. OC p-values for 50 mg are significant at Weeks 5 to 8 and for 100 mg are significant at Weeks 7, 8, 10, 11, and 12.

Thus, the efficacy of sertraline has been shown statistically moderately with respect to the Ratio to baseline in Percentage of Time Worrying, at least, for 100 mg.

By the Endpoint Data Set, the (geometric) mean of the Ratio to Baseline in "Anticipatiry Anxiety: Percent of Time Worrying" were .43, .25, .36, and .63, respectively, for 200, 100, and 50 mg sertraline and placebo groups.

The non-parametric p-value at endpoint (p.43 of 3-29-96 submission) is .015 (for Ratio to baseline, 100mg vs placebo).

3D. Reviewer's Analyses

As a cross-check with the sponsor's model based analyses, this reviewer performed non-parametric 1-way analyses (Wilcoxon's 2-sample test) by SAS PROC NPAR1WAY on the change (difference) from baseline, corresponding to those time points and data sets submitted in the original NDA by the sponsor (Weekly OC and Endpoint), using data supplied by the sponsor on diskettes.

In the single case, for Number of Panic Attacks at Endpoint, where the sponsor submitted in an amendment the same analysis (p-value) as the reviewer's, the result is matching.

Hochberg's method will be applied for multiple comparison adjustments.

P-values for 50 mg Vs Placebo Comparisons from Wilcoxon's 2-Sample Test

	Change From Baseline in Number of Panic Attacks	CGI Sev.	%Time Worrying	CGI Improvement
Week 1	.525	.331	.337	.594
Week 2	.110	.438	.011	.170
Week 3	.648	.703	.103	.750
Week 4	.426	.341	.863	.067
Week 5	.852	-	.075	-
Week 6	.726	.049	.024	.002
Week 7	.202	-	.031	-
Week 8	.154	.240	.017	.091
Week 9	.654	-	.038	-
Week 10	.457	.311	.085	.190
Week 11	.354	-	.006	-
Week 12	.400	.340	.004	.324
Endpoint	.283	.596	.006	.439

P-values for 100 mg Vs Placebo Comparisons from Wilcoxon's 2-Sample Test

	Change From Baseline in Number of Panic Attacks	CGI Sev.	%Time Worrying	CGI Improvement
Week 1	.518	.776	.441	.372
Week 2	.216	.156	.002	.017
Week 3	.828	.130	.037	.003
Week 4	.750	.093	.177	.047
Week 5	.676	-	.010	-
Week 6	.838	.021	.037	.007
Week 7	.332	-	.023	-
Week 8	.162	.031	.022	.037
Week 9	.471	-	.037	-
Week 10	.215	.216	.056	.050
Week 11	.155	-	.004	-
Week 12	.296	.084	.005	.122
Endpoint	.062	.063	.001	.056

P-values for 200 mg Vs Placebo Comparisons from Wilcoxon's 2-Sample Test

	Change From Baseline in Number of Panic Attacks	CGI Sev.	%Time Worrying	CGI Improvement
Week 1	.061	.240	.167	.443
Week 2	.966	.431	.678	.141
Week 3	.201	.434	.433	.001
Week 4	.730	.350	.872	.006
Week 5	.758	-	.329	-
Week 6	.478	.087	.554	.002
Week 7	.675	-	.211	-
Week 8	.716	.226	.744	.026
Week 9	.621	-	.348	-
Week 10	.963	.347	.152	.024
Week 11	.798	-	.023	-
Week 12	.836	.167	.152	.098
Endpoint	.619	.531	.208	.343

Only wrt %Time worrying there were some significant p-values for 100 mg and 50 mg groups. With respect to CGI Improvement, the significance of p-values (3 for 200 mg, 2 for 100 mg and 1 for 50 mg) occurred sporadically only , after multiple comparison adjustments.

3E. **Comments and Conclusions on Study Based on Protocol 0529**

We see some evidence in favor of the efficacy of 100 mg sertraline wrt Panic Attacks and %Time Worrying, from Endpoint analyses of Table 3.3.1e and other LOCF analyses, and also from the alternative analysis (for Number of Panic Attacks), based on Ratios. Non-parametric analysis based on Change (difference) From Baseline shows the efficacy of 100 mg sertraline only wrt %Time worrying. Therefore, the evidence provided by this study in favor of the efficacy of 100 mg sertraline is at most marginal.

As mentioned under "Efficacy Results," the sponsor's analysis methods did not match exactly what was mentioned in the "Analysis Plan".

On the effect of sex, the sponsor stated, "When sex and its interaction with treatment was added to the statistical model, there was a significant sex effect for all three measures;

treament effects were more pronounced in females than in males in all treatment groups. However, the interaction of sex and treatment was not significant in any analysis, indicating that differences between males and females were consistent across treatments. ... Differences in baseline severity between males and females did not account for the differences observed at endpoint; only percent time worrying in the placebo group differed substantially between females and males at baseline, the medians being 16.0% for males and 6.5% for females. The analyses of variance controlled for baseline severity."

III. **Reviewer's Overall Comments**

Statistically, Study 629 showed reasonable statistical evidence, Study 630 showed moderate statistical evidence, Study 529 showed minimal statistical evidence (based on ratios to baseline) for 100 mg, and Study 514 (not reviewed) showed almost no statistical evidence for the efficacy of sertraline. The overall statistical and numerical superiority of sertraline over placebo is marginally acceptable as providing some evidence, though not strong, in favor of the efficacy of sertraline in the treatment of panic disorder. The sponsor stated, "With a single exception in the 0514 study, all of these variables in all of the studies reveal numerically greater improvement at endpoint in the sertraline group relative to the placebo group, ..."

Side-by-side graphical comparison of all four studies based on 95% confidence intervals (multiple comparison adjustment not considered) for Average Number of Panic Attacks (considering the total time the patient is in the study) is presented in Figures 0.4.2 (Ratio to Baseline), 0.4.3 (Difference From Baseline), 0.4.4 (Ratio to Baseline, weighted by the time on study), 0.4.5 (Difference From Baseline, weighted by the time on study).

We have a good example, here, how non-significant results can be turned into significant results even by acceptable analyses. The sponsor did not claim any statistically significant results for Study 514, based on analyses specified in the Analysis Plan. However, Figure 0.4.4 (without multiple comparison adjustment) shows marginal evidence (better than in Study 529) in favor of sertraline.

These graphs provide some idea about the probable margin of errors. In that respect, the statistical evidence is not consistently strong. However, sertraline is always numerically superior to placebo.

Figure 0.4.6 presents 95% confidence intervals for Panic Attack Endpoint to Baseline Ratios, using 2-week Endpoint. A reasonably acceptable picture of the statistical evidence in favor of sertraline is provided by studies 629, 630, and 529, by this analysis.

When the Mean Number of Baseline Panic Attacks varies considerably among treatment groups (as in Study 529) and study to study (including those for other drugs), Mean Change from Baseline may not be a good instrument for comparison; geometric mean of ratios to Baseline may be a better instrument.

On the statistically non-significant results of the study based on Protocol 0514, the sponsor stated, "Among study completers, however, the pooled sertraline group exhibited a significantly greater reduction in panic attack frequency than the placebo group (p=.016). The discrepancy between the results of the completer analysis and the endpoint analysis, as well as between this study and other studies, may be related to the high rate of discontinuations for adverse experiences that occurred during the first week of the study in the sertraline group (10.5%) but not the placebo group (0%). Efficacy data from such patients are included in the endpoint analysis (but not the completer analysis) even though the patients are unlikely to demonstrate a therapeutic response during only a few days of active treatment."

There is some truth in the above statement. However, even the weekly OC results were not that strong; only a few of them were statistically significant.

The sponsor provided a particular analysis with OC patients but last observation carried backward to the week under consideration. By this analysis, almost all p-values in all four studies became significant.

Endpoint results on secondary efficacy variables are summarized in the attached Table 0.3.2. Excluding Study 0514, we see that at least two of the three studies provided statistical evidence in favor of the efficacy of sertraline wrt each secondary efficacy variable.

The Mean Daily Dose by visit week, for the flexible dose studies, is presented in attached Tables 0.3.1a and 0.3.1b. For visit week 10, the mean daily dose of sertraline was 143.9 mg and 131.4 mg respectively for study 0629 (positive) and study 0630 (moderately positive). At Endpoint, the corresponding mean doses were 126 mg and 118 mg. The mean daily dose increased monotonically from Week 1 to week 10. The mean number of tablets used was, generally, more in the placebo group than in the

sertraline group. The sponsor has mentioned that the fixed dose Study 0529 showed efficacy of 50 mg (statistically) and has suggested,"If a satisfactory response is not observed with the 50 mg dose, the daily dose should be increased in 50 mg increments to a maximum dose of 200 mg daily (based on clinical response and dose-limiting side effects)."

The sponsor stated that, "Although trough plasma concentrations of sertraline are proportional to dose, there is no clear relationship between plasma sertraline levels and clinical response."

Discontinuation Due to Lack of Efficacy, Zero Full Panic Attacks, and Full Remission: Combining the four studies 0629, 0630, 0529,and 0514 by the Mantel-Haenszel method, there were highly significant differences between the sertraline and placebo groups with respect to the above three clinically relevant (claimed by the sponsor) measures, with the p-values .016, .009, and .009 respectively.

The sponsor stated, "The rates of discontinuation were greater in the pooled sertraline group than in the placebo group in each study. Overall, 31.4% of the sertraline patients versus 21.2% of the placebo patients discontinued. ... Among all studies, the rates of discontinuation associated with adverse events were 14.5% for sertraline-treated patients versus 3.1% for placebo-treated patients (statistically significant difference for protocols 0629 and 0529). ... Discontinuation due to insufficient clinical response did not differ significantly among treatment groups in any individual study, but the rates were greater in placebo treated patients than in sertraline-treated patients in every study. Overall, 3.6% of the sertraline-treated patients discontinued due to insufficient clinical response, compared to 6.6% of the placebo-treated patients, a significant difference."

At baseline, sertraline and placebo groups differed significantly on only one important outcome measure: in study 0529 wrt CGI severity (pooled sertraline group mean = 4.4, placebo mean = 4.6, p-value = .036, p.8 6635 of NDA).

The tests for normality were highly significant for some efficacy variables, showing the non-normality of those variables. A log transformation is not unusual under such circumstances. Also, the sponsor mentioned this transformation (perhaps, from prior experiences) in the Analysis Plan issued before unblinding of data (stated by the sponsor).

Through discussion with the Safety Reviewer, this reviewer did

not receive any safety statistical issues to consider.

There were some instances of sloppiness in the submission. These are not considered serious enough to invalidate the findings. Some were corrected by the sponsor.

Dose Response

The Linear Dose Response Test for Study 0529 was non-significant. Numerically, there was slight curvilinear (better response at 100 mg than at 50 mg but worse response at 200 mg than at 50 mg) dose response. [Attached Figure 3.3.1f.]

Subgroup Analyses

Some discussion of subgroup analyses (**pooled across studies**) were provided in the Integrated Efficacy Summary.

Race

There were 88% Caucasian patients. The sponsor stated, "Neither race (p-value= .383) nor the race-by-treatment interaction (p-value= .137) was significant in this analysis." However, when the "White" and "Non-white" categorization was made instead of "White", "Black", and "Other" categorization, the Race by Treatment interaction approached statistical significance (p = .057, p.48 of 3-29-96 submission).

Gender

The p-values for the gender and gender-by-treatment terms were respectively .017 and .516. The sponsor stated, "The significant gender effect resulted from lower ratios of endpoint to baseline attacks for females than males, regardless of treatment group. However, the lack of a significant treatment-by-gender interaction indicates that sertraline-placebo differences were similar in males and females. There was no significant relationship between body weight and response to treatment."

Since, the percentage of females in the placebo group was less than that in the sertraline group in studies 529 and 630 there is some concern in view of the fact that treatment effects were more pronounced in females.

This reviewer requested p-values after adjusting for the effect of Gender differences. After some delay, the sponsor provided

only for the primary efficacy variable at Endpoint, pooling the doses in fixed dose studies (and reproduced sex and sex by treatment interaction p-values which the reviewer did not request). From the attached Table 0.5.1, we see that the Endpoint p-values based on the primary analysis (based on the log transformation of ratios) changed substantially; for Study 629, it changed from significance (.029) to non-significance (.058). Therefore, this reviewer's conjecture that the imbalances wrt Gender might have favored the test drug is true.

This reviewer would like to remind also that there was a significant treatment by sex interaction in Study 0629 for panic attacks, where the sponsor stated,"..., the interaction between sex and treatment was significant for panic attacks (p-value = .035). ... this interaction may be attributable to the presence of larger sertraline-placebo differences in female patients as compared to male patients.". The corresponding p-value for the treatment by sex interaction in Study 514 was also significant (.031).

Therefore, there is some concern in the fact that the majority of patients in Studies 629 and 630 were females, which might have slightly inflated the results in favor of sertraline.

From Table 0.5.2, we see that in studies 629 and 630 combined, the females showed better treatment effect (a highly statistically significant difference of .11 with placebo in ratio to baseline vs a statistically nonsignificant difference of .06 for the males). Although the sample size for the male group was 132 (vs 210 for the female group), a nearly half numerical difference is noteworthy.

In studies 514 and 529 combined, the non-response of the male placebo patients is noteworthy (.44 for the ratio to baseline). As a result, the male group produced a highly significant p-value.

Also noteworthy is the fact that the number of patients was always smaller in the Gender group (Male in studies 629 and 630, and Female in studies 514 and 529) which showed poorer effect of sertraline. This favored the test drug.

Conclusion on Gender Effect: Since the male patients in studies 514 and 529 combined produced a highly significant p-value, this reviewer does not see any basis to conclude that sertraline is ineffective in males. However, the results in the studies are poorer, after adjusting for the effect of Gender, than what have been provided in the NDA.

The efficacy results are inconsistent across Gender groups; females showed better efficacy in flexible dose studies and males showed better efficacy in fixed dose studies.

Age

The sponsor stated, "The age cohorts were grouped as follows: (1)≤30; (2) >30 - 40; (3)>40 - 50 and (4) >50. Neither age (p=.352) nor its interaction with treatment (p=.932) was significant."

Baseline Severity of Illness

In studies with another drug for the same indication, there were some significant p-values for Treatment by baseline Severity of illness interaction. However, for this drug the sponsor claimed non-existence of this interaction. The sponsor stated, "The sertraline effect in this subgroup of moderate-to-severe panic disorder patients was generally similar to that which was observed in the entire sample, supporting the efficacy of sertraline in patients with more severe panic disorder."

IV. Overall Conclusion

The overall statistical and numerical superiority of sertraline to placebo is statistically marginally acceptable as providing some evidence, though not strong in view of the lack of robustness, in favor of the efficacy of sertraline in the treatment of panic disorder. The 100 mg dose showed overall better results than those shown by 50 mg and 200 mg.

The number of patients was always smaller in the Gender group (Male in flexible dose studies 629 and 630, and Female in fixed dose studies 514 and 529) which showed poorer efficacy of sertraline. Therefore, the efficacy results in these studies are really poorer, after adjusting for the effect of Gender, than what have been provided in the NDA. The efficacy results are inconsistent across Gender groups; females showed better efficacy in flexible dose studies and males showed better efficacy in fixed dose studies.

In all four studies, the overall dropout rate and dropout due to adverse experiences were more in the sertraline groups than in the placebo groups.

Japo Choudhury 8-30-96

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot JTS 8-30-96

Dr. Chi Chi 9/4/96

CC:
Archival NDA 19-839/SEI-011

HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Lee
HFD-120/Mr. Purvis
HFD-120/Mr. Mille
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Dr. Choudhury
HFD-710/Chron
J.Choudhury:x71518:DB I: August 29, 1996

This review consists of 27 pages of text and 48 pages of Tables, Figures, etc.

Table 3.1.1
LIST OF CONTROLLED U.S. STUDIES

PRINCIPAL INVESTIGATORS	STUDY NO.	SERTRALINE FORMULATION AND DOSAGE	CONTROL AGENT	NUMBER OF PATIENTS				MEAN AGE * (YRS)	SEX*		STUDY DESIGN	DURATION OF STUDY	STUDY OBJECTIVE
				TOTAL	EFFICACY EVALUABLE	SAFETY EVALUABLE	COMPLETED STUDY		M	F			
Protocol 629 Baumel Bielski Carman Goodman Hegel Houck Linden Nakra Ota Pohl	93-N-0153 93-N-0149 93-N-0188 93-N-0161 93-N-0152 93-N-0151 93-N-0150 93-N-0163 93-N-0187 93-N-0154	25 and 50 mg tabs 25 mg QD titration dose 50 mg QD to 200 mg QD	Placebo	173	166	168	132	37.5	72	96	double-blind parallel multicenter randomized flexible dose	10 wks (70 days) (mean duration of therapy=61.4 days)*	To compare the safety & efficacy of sertraline 50-200 mg QD with placebo in the treatment of panic disorder
Protocol 630 Apter Clayton Coryell Cunningham McEntee O'Hair Pollack Rausch Stewart Weisler	93-N-0159 93-N-0189 93-N-0164 93-N-0160 93-N-0162 93-N-0156 93-N-0158 93-N-0155 93-N-0190 93-N-0157	25 and 50 mg tabs 25 mg QD titration dose 50 mg QD to 200 mg QD	Placebo	178	176	176	144	36.3	61	115	double-blind parallel multicenter randomized flexible dose	10 wks (70 days) (mean duration of therapy=63.6 days)*	To compare the safety & efficacy of sertraline 50-200 mg QD with placebo in the treatment of panic disorder
Protocol 529 England DuBoff Ferguson Londborg Rosenthal Smith Weise Cole+	91-N-0025 91-N-0020 91-N-0021 91-N-0022 91-N-0023 91-N-0024 91-N-0018 91-N-0019	50 and 100 mg caps 50 mg QD 100 mg QD 200 mg QD	Placebo	178	172	177	114	38.8	94	83	double-blind parallel multicenter randomized fixed dose	12 wks (84 days) (mean duration of therapy=64.3 days)*	To compare the efficacy and safety of 50 mg QD, 100 mg QD, and 200 mg QD of sertraline with placebo in the treatment of panic disorder

* Based on safety evaluable patients
+ 0 patients entered

Continued

Table 0.1.1 Continued

LIST OF CONTROLLED U.S. STUDIES

PRINCIPAL INVESTIGATORS	STUDY NO.	SERTRALINE FORMULATION AND DOSAGE	CONTROL AGENT	NUMBER OF PATIENTS				MEAN AGE * (YRS)	SEX*		STUDY DESIGN	DURATION OF STUDY	STUDY OBJECTIV
				TOTAL	EFFICACY EVALUABLE	SAFETY EVALUABLE	COMPLETED STUDY		M	F			
Protocol 514		50 and 100 mg caps	Placebo	157	150	152	98	39.7	108	44	double-blind parallel multicenter randomized fixed dose	12 wks (84 days) (mean duration of therapy=63.6 days)*	To compare the efficacy and safety of 50 mg QD, 100 mg QD, and 200 mg QD of sertraline with placebo in the treatment of panic disorder
Apter	91-N-0010												
Cutler	91-N-0011												
Dominguez	91-N-0012	50 mg QD											
Halaris	91-N-0017	100 mg QD											
Nakra	91-N-0014	200 mg QD											
Papp	92-N-0029												
Riesenberg	91-N-0015												
Sheikh	91-N-0016												
Greist+	91-N-0013												
Dupont+	92-N-0009												

* Based on safety evaluable patients
+ 0 patients entered

Table 0.3.1a

PROTOCOL: 93CE21-0629
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORI

MEAN DAILY DOSE BY VISIT WEEK

Week	Sertraline		Placebo	
	N	Mean ± Std	N	Mean ± Std
1	80	24.7 ± 1.6	88	24.6 ± 1.3
2	75	46.5 ± 7.8	84	46.0 ± 8.7
3	69	82.7 ± 25.6	81	84.3 ± 28.5
4	67	105.6 ± 37.4	81	113.7 ± 40.4
5	63	129.5 ± 53.4	79	139.9 ± 54.6
6	64	127.8 ± 52.5	77	140.8 ± 54.5
7	61	141.7 ± 54.5	75	149.9 ± 56.7
8	61	140.6 ± 54.1	75	148.9 ± 58.5
9	59	142.3 ± 54.1	73	157.6 ± 51.9
10	59	143.9 ± 54.9	72	158.6 ± 53.3
Endpoint	80	126.1 ± 61.9	88	147.4 ± 62.6

Table 0.3.1b

PROTOCOL: 93CE21-0630
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

MEAN DAILY DOSE BY VISIT WEEK

Week	Sertraline		Placebo	
	N	Mean ± Std	N	Mean ± Std
1	88	24.8 ± 0.9	88	24.1 ± 3.1
2	81	47.1 ± 6.6	87	46.2 ± 8.0
3	80	76.6 ± 26.1	85	78.1 ± 24.4
4	80	96.3 ± 39.3	81	99.8 ± 40.1
5	80	115.6 ± 52.8	80	127.1 ± 47.6
6	79	114.6 ± 54.6	77	131.5 ± 50.3
7	76	122.0 ± 56.1	75	151.8 ± 48.0
8	74	121.8 ± 54.2	74	149.5 ± 49.4
9	74	130.3 ± 58.6	73	160.9 ± 47.5
10	71	131.4 ± 58.1	72	156.7 ± 47.3
Endpoint	88	118.1 ± 62.9	88	147.5 ± 55.5

Table 0.3.2

COMPARISON OF SECONDARY EFFICACY VARIABLES AT ENDPOINT												
	Protocol 0629			Protocol 0630			Protocol 0529			Protocol 0514		
VARIABLE	SERT	PBO	P=	SERT	PBO	P=	SERT	PBO	P=	SERT	PBO	P=
LIMITED SX. ATTACKS[1]	0.32	0.50	.015	0.43	0.48	.520	0.31	0.56	.006	.33	0.49	.055
% TIME WORRYING[1]	0.30	0.40	.143	0.38	0.53	.055	0.33	0.63	.003	0.29	0.43	.187
HAM-A[2]	-12.1	-9.4	.032	-9.5	-8.3	.356	-10.0	-7.1	.033	-9.2	-9.4	.703
CGI SEVERITY[2]	-1.64	-0.90	01	-1.56	-1.04	.009	-1.6	-1.2	.120	-1.4	-1.1	.220
CGI IMPROVEMENT[3]	2.02	2.82	.001	2.26	2.74	.011	2.3	2.5	.266	2.5	2.7	.597
MC-PAS[2]	-6.61	-4.88	.040	-6.16	-4.50	.027	NOT DONE			NOT DONE		
PT. GLOBAL EVALUATION[2]	1.98	2.93	.001	2.23	2.75	.014	NOT DONE			NOT DONE		
QUALITY OF LIFE[2]	7.52	1.64	.006	6.66	0.93	.001	NOT DONE			NOT DONE		

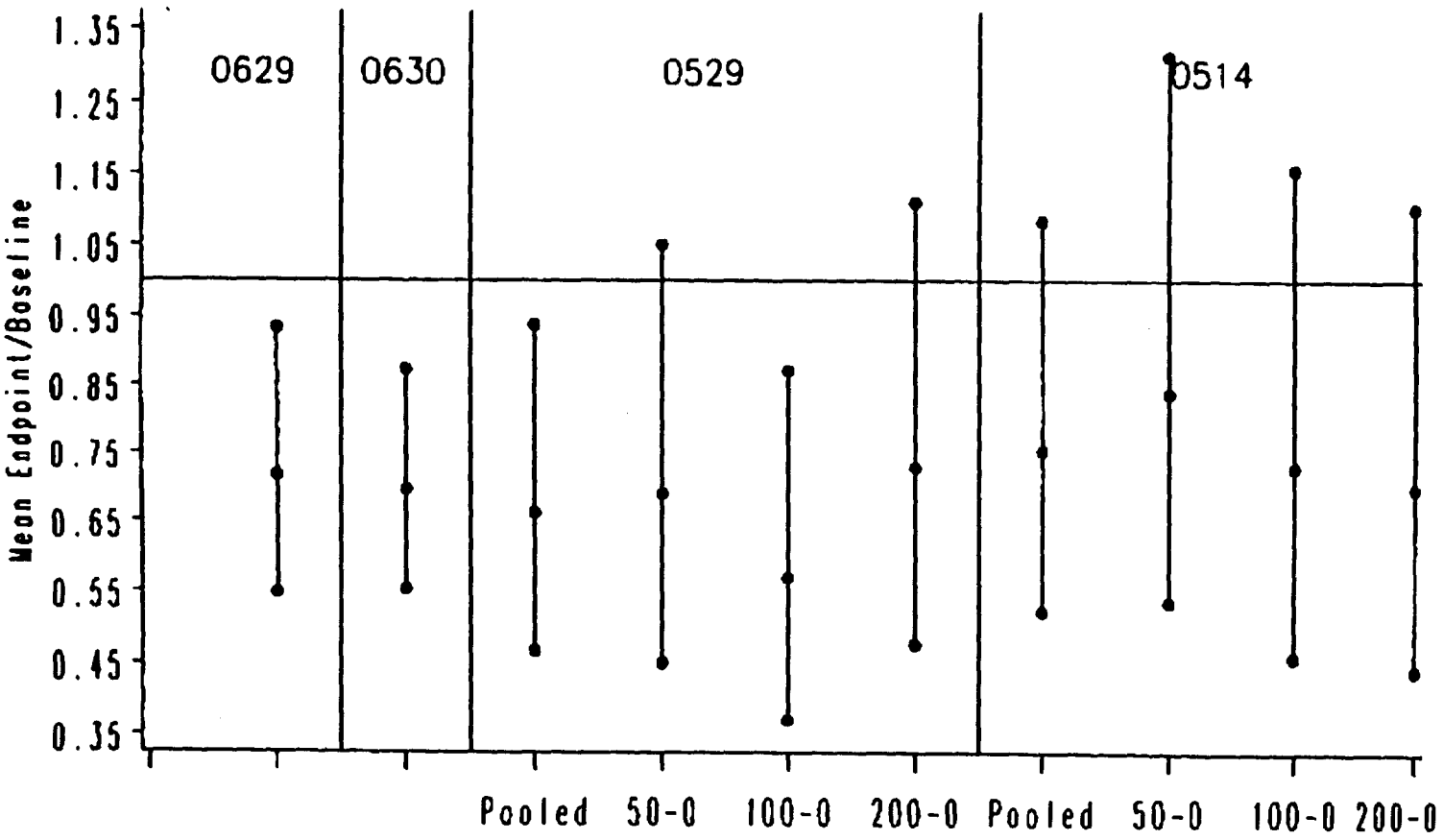
[1] Geometric mean ratio
[2] Mean change from baseline
[3] Mean value

Table 0.4.1

Average Numbers of Panic Attacks over Study Weighted by Time on Study							
Protocol	**Comparison**	**Mean Ratios (Endpoint/Baseline)**		**Ratio (95% Conf. Int.)**	**Arithmetic Means**		**Difference (95% Conf. Int.)**
		Zoloft	**Placebo**	**Zoloft/Placebo**	**Zoloft**	**Placebo**	**Zoloft - Placebo**
0629	**Zoloft vs Placebo**	.307	.460	.668(.509 , .876)	-3.92	-2.66	-1.26 (-2.71 , .191)
0630	**Zoloft vs Placebo**	.325	.482	.675 (.553 , .823)	-4.19	-2.52	-1.67(-2.70 , - .630)
0529	**Zoloft vs Placebo**	.285	.428	.666(.485 , .915)	-6.28	-3.95	-2.33(-5.26 , .601)
	50mg vs Placebo	.289		.676 (.442 , 1.034)	-7.58		-3.57 (-7.45 , .315)
	100mg vs Placebo	.277		.648(.439 , .956)	-5.23		-1.22(-4.78 , 2.337)
	200mg vs Placebo	.287		.672(.446 , 1.012)	-6.15		-2.14(-5.91 , 1.620)
0514	**Zoloft vs Placebo**	.314	.515	.610(.445 , .835)	-7.03	-5.09	-1.95(-3.90 , .013)
	50mg vs Placebo	.305		.593(.401 , .878)	-6.22		-1.16(-3.67 , 1.349)
	100mg vs Placebo	.333		.647(.444 , .944)	-8.25		-3.20(-5.67 , - .730)
	200mg vs Placebo	.287		.557(.380 , .817)	-6.75		-1.69 (-4.14 , .755)

Figure 0.4.2

Protocols 0629, 0630, 0529, 0514
95% Confidence Intervals for Panic Attack On-drug Average to Baseline Ratios



No multiple comparison adjustment

Figure 0.4.3

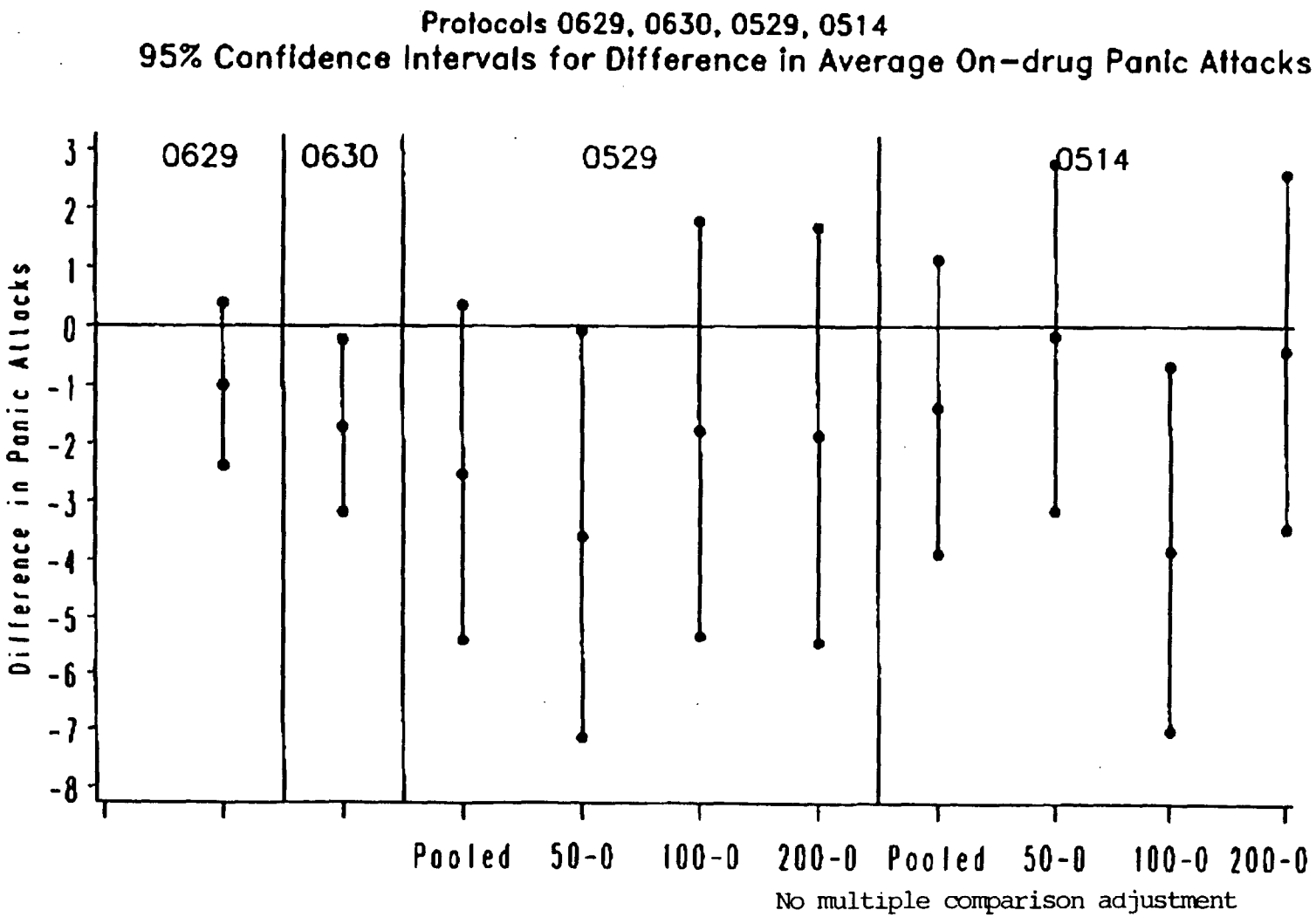
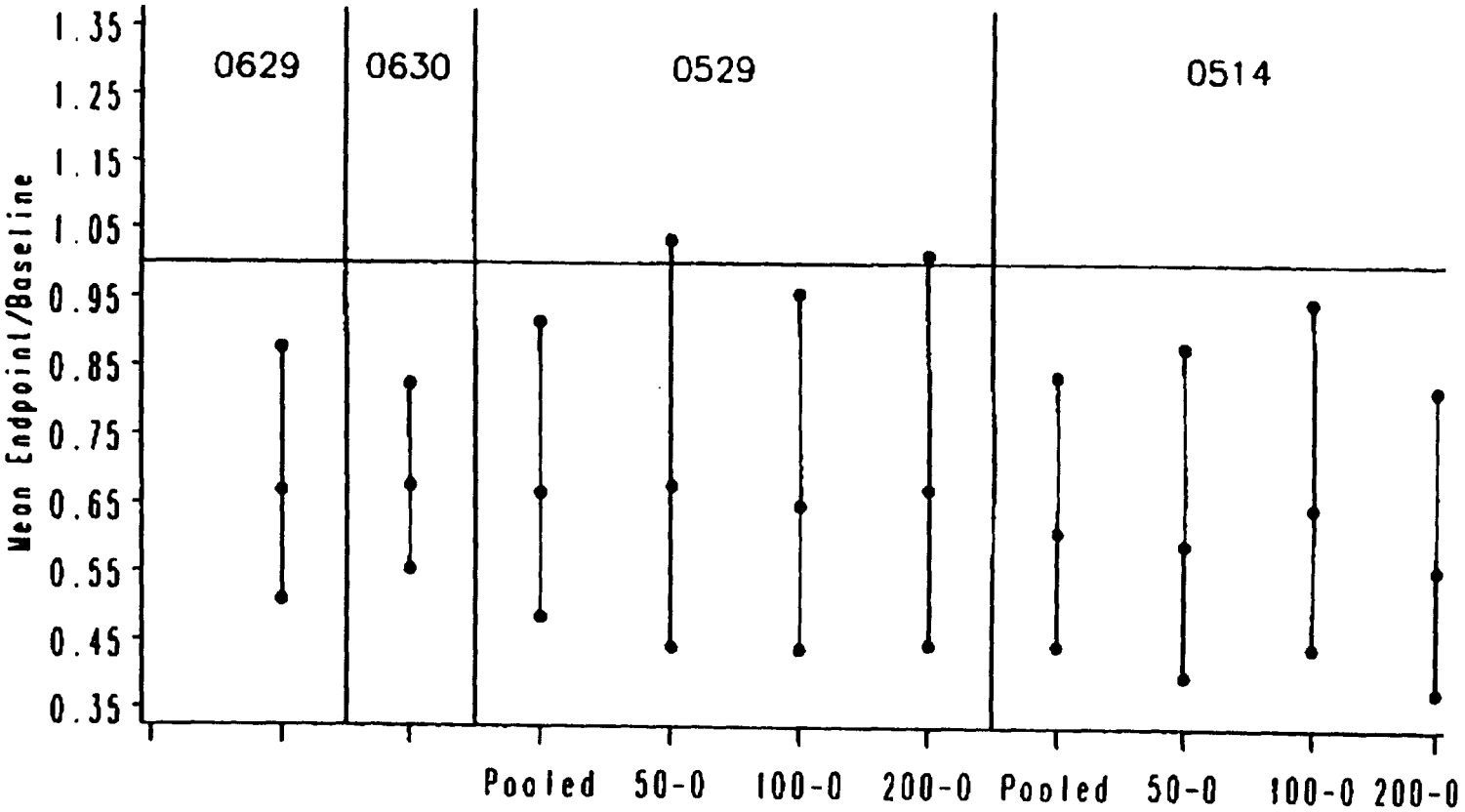

Protocols 0629, 0630, 0529, 0514
95% Confidence Intervals for Difference in Average On-drug Panic Attacks
0629
0630
0529
0514
Difference in Panic Attacks
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
Pooled
50-0
100-0
200-0
Pooled
50-0
100-0
200-0
No multiple comparison adjustment

Figure 0.4.4

Protocols 0629, 0630, 0529, 0514
95% Confidence Intervals for Panic Attack On-drug Average to Baseline Ratios
Weighted by Time on Study



No multiple comparison adjustment

Figure 0.4.5

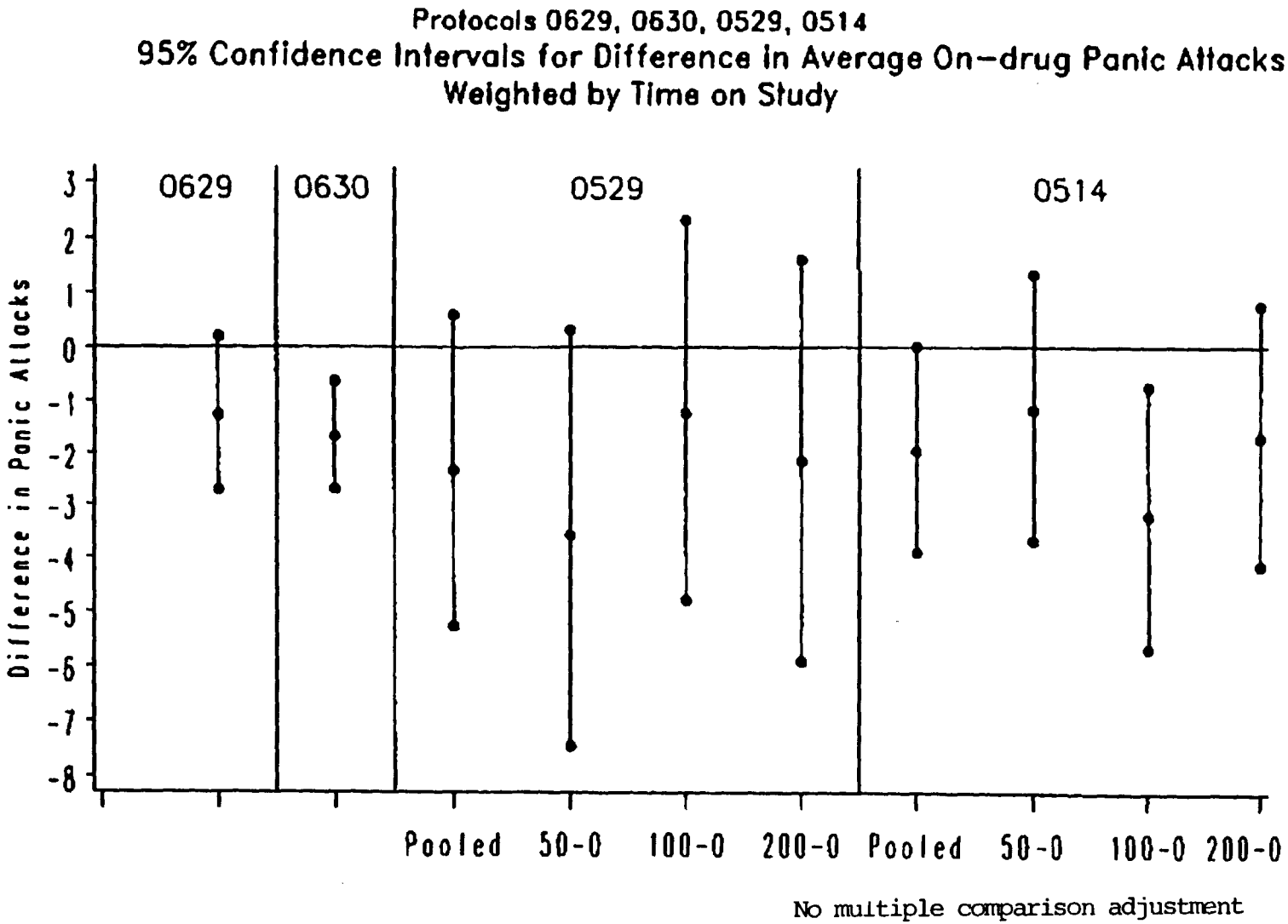
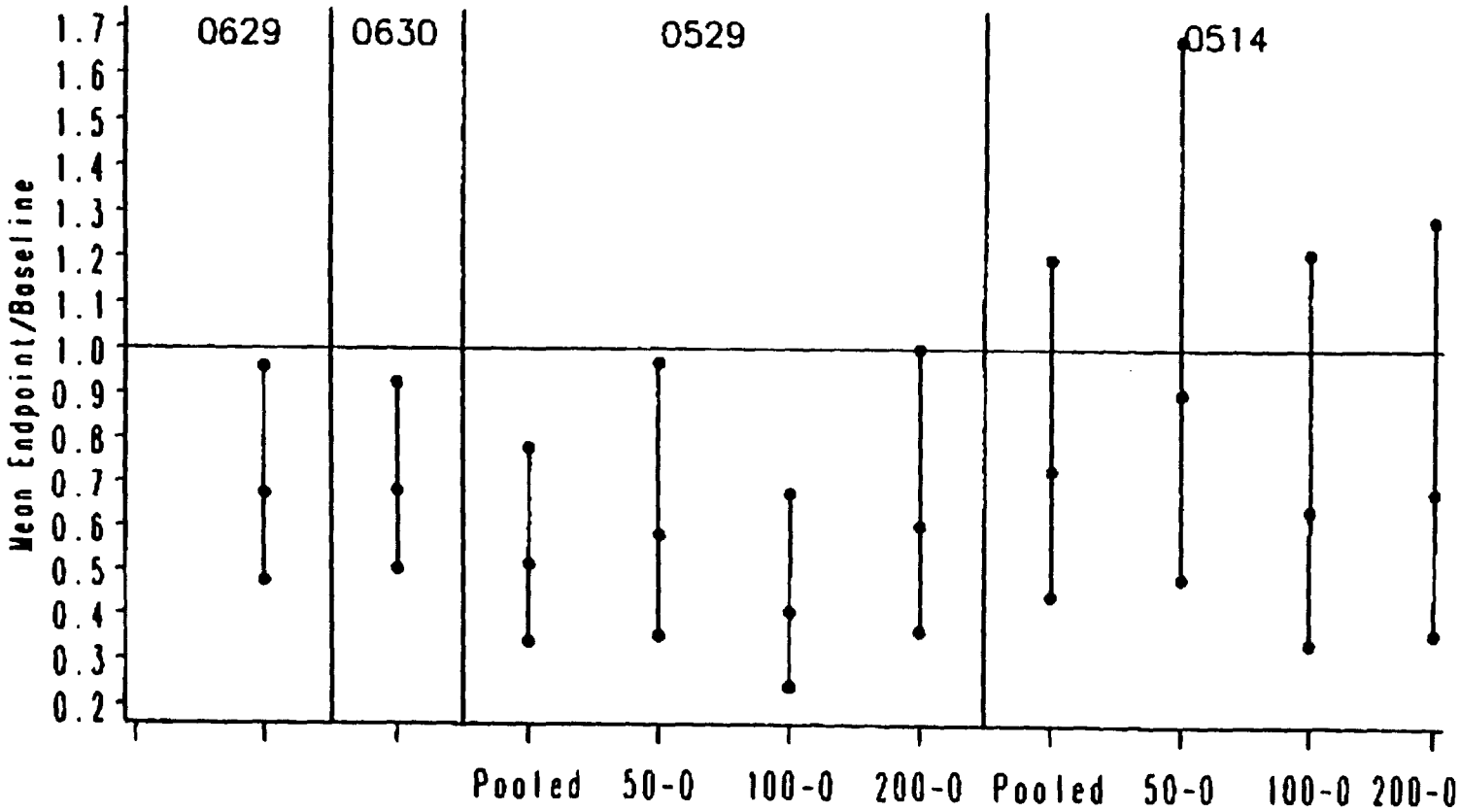

Protocols 0629, 0630, 0529, 0514
95% Confidence Intervals for Difference in Average On-drug Panic Attacks
Weighted by Time on Study
0629
0630
0529
0514
Difference in Panic Attacks
3
2
1
0
-1
-2
-3
-4
-5
-6
-7
-8
Pooled
50-0
100-0
200-0
Pooled
50-0
100-0
200-0
No multiple comparison adjustment

Figure 0.4.6

Protocols 0629, 0630, 0529, 0514

95% Confidence Intervals for Panic Attack Endpoint to Baseline Ratios

Using 2-Week Endpoint



No multiple comparison adjustment

Table 0.5.1

P-values for treatment with and without sex and sex-by-treatment in the ANOVA model by protocol

	Standard Model Without Sex Effects	Model With Sex Effects
0629	.029	.058
0630	.014	.038
0529	.002	.008
0514	.212	.836
Overall	<.001	<.001

Table 0.5.2

Table 4: Results grouped by flexible (0629 and 0630) and fixed dose (0514 and 0529) studies

	Males				Females				p-values	
	Sertraline		Placebo		Sertraline		Placebo		Sex	Sex by Treatment
	n	Mean	n	Mean	n	Mean	n	Mean		
0629 and 0630	61	.23	71	.28	106	.19	104	.31	.556	.192
0514 and 0529	143	.24	55	.44	96	.17	27	.22	.002	.222

Table 5: Results of separate analyses for males and females by flexible (0629 and 0630) and fixed dose (0514 and 0529) studies

	Males					Females				
	Sertraline		Placebo		p-value	Sertraline		Placebo		p-value
	n	Mean	n	Mean		n	Mean	n	Mean	
0629 and 0630	61	.23	71	.29	.163	106	.19	104	.30	<.001
0514 and 0529	143	.24	55	.44	.002	96	.18	27	.20	.646

Figure 1.2.1
Protocol 0629
Percent of Patients in Study

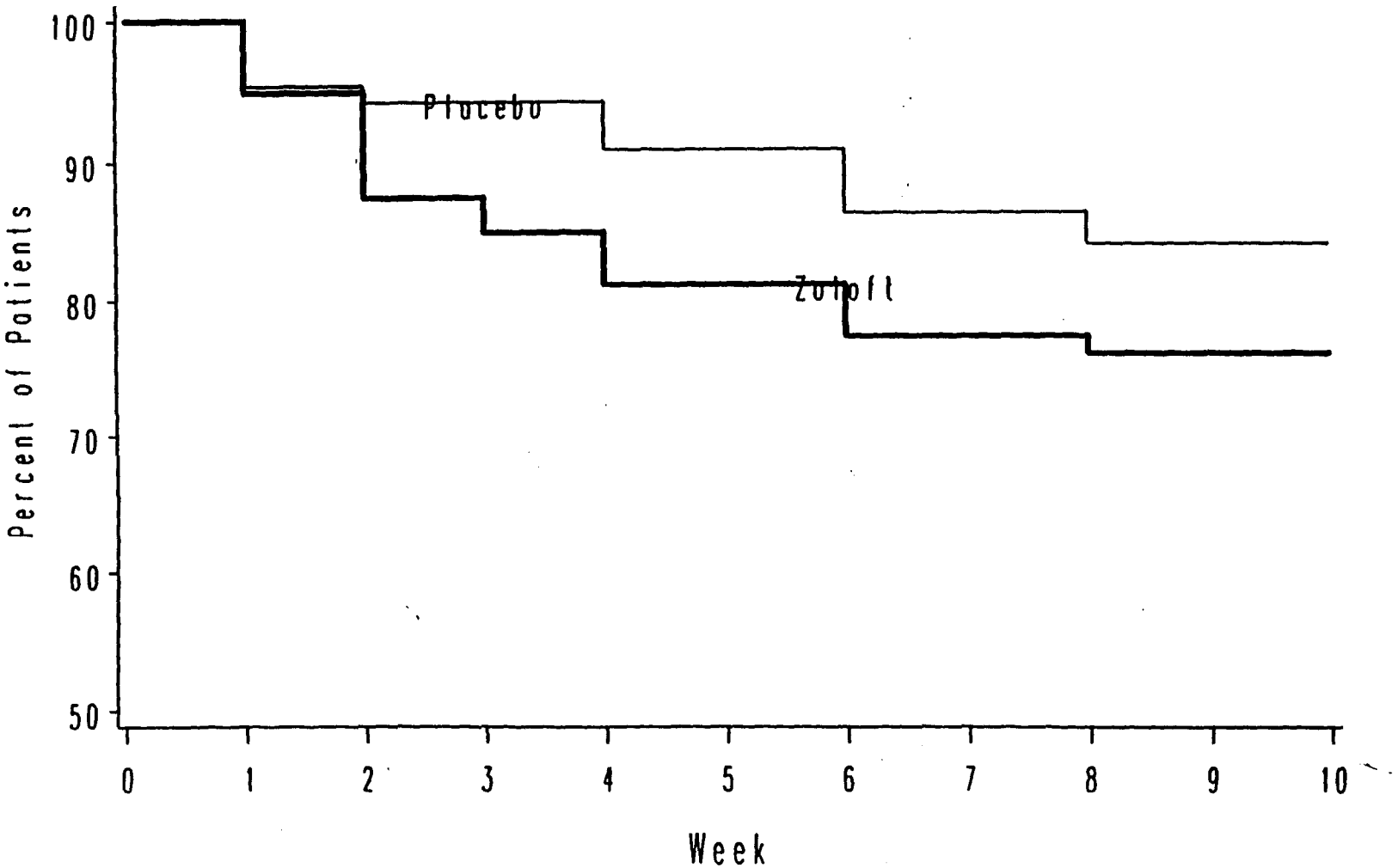


Table 1.3.1a

PROTOCOL: 93CE21-0629
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

PANIC ATTACKS - MEAN RATIO TO BASELINE AT EACH WEEK AND AT ENDPOINT

	SERTRALINE		PLACEBO	
	N	MEAN ± SD.	N	MEAN ± SD.
Week 1	79	0.77 ± 0.78	87	0.90 ± 2.30
Week 2	75	0.55 ± 0.69	83	0.73 ± 0.99
Week 3	69	0.34 ± 0.50	81	0.84 ± 3.32
Week 4	67	0.23 ± 0.40	82	0.74 ± 2.78
Week 5	64	0.18 ± 0.35	78	0.68 ± 2.42
Week 6	62	0.16 ± 0.32	77	0.58 ± 1.87
Week 7	61	0.24 ± 0.84	74	0.59 ± 2.01
Week 8	61	0.31 ± 1.00	72	0.50 ± 1.88
Week 9	59	0.11 ± 0.23	73	0.45 ± 1.09
Week 10	59	0.12 ± 0.34	72	0.47 ± 1.01
Endpoint	79	0.23 ± 0.44	87	0.49 ± 0.93

Table 1.3.1b

PROTOCOL: 93CE21-0629
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

PANIC ATTACKS - RATIO TO BASELINE AT EACH WEEK AND AT ENDPOINT (GEOMETRIC MEAN)

	SERTRALINE		PLACEBO		
	N	ADJ. MEAN	N	ADJ. MEAN	P-VALUE[1]
Week 1	79	0.54	87	0.59	.610
Week 2	75	0.38	83	0.50	.102
Week 3	69	0.27	81	0.44	.009
Week 4	67	0.21	82	0.35	.010
Week 5	64	0.17	78	0.27	.033
Week 6	62	0.17	77	0.32	.004
Week 7	61	0.17	74	0.28	.037
Week 8	61	0.19	72	0.24	.232
Week 9	59	0.16	73	0.24	.060
Week 10	59	0.16	72	0.23	.086
Endpoint	79	0.20	87	0.30	.029

1: The p-values are obtained from the analyses of variance with treatment, site and treatment-by-site as effects.

Table 1.3.1c

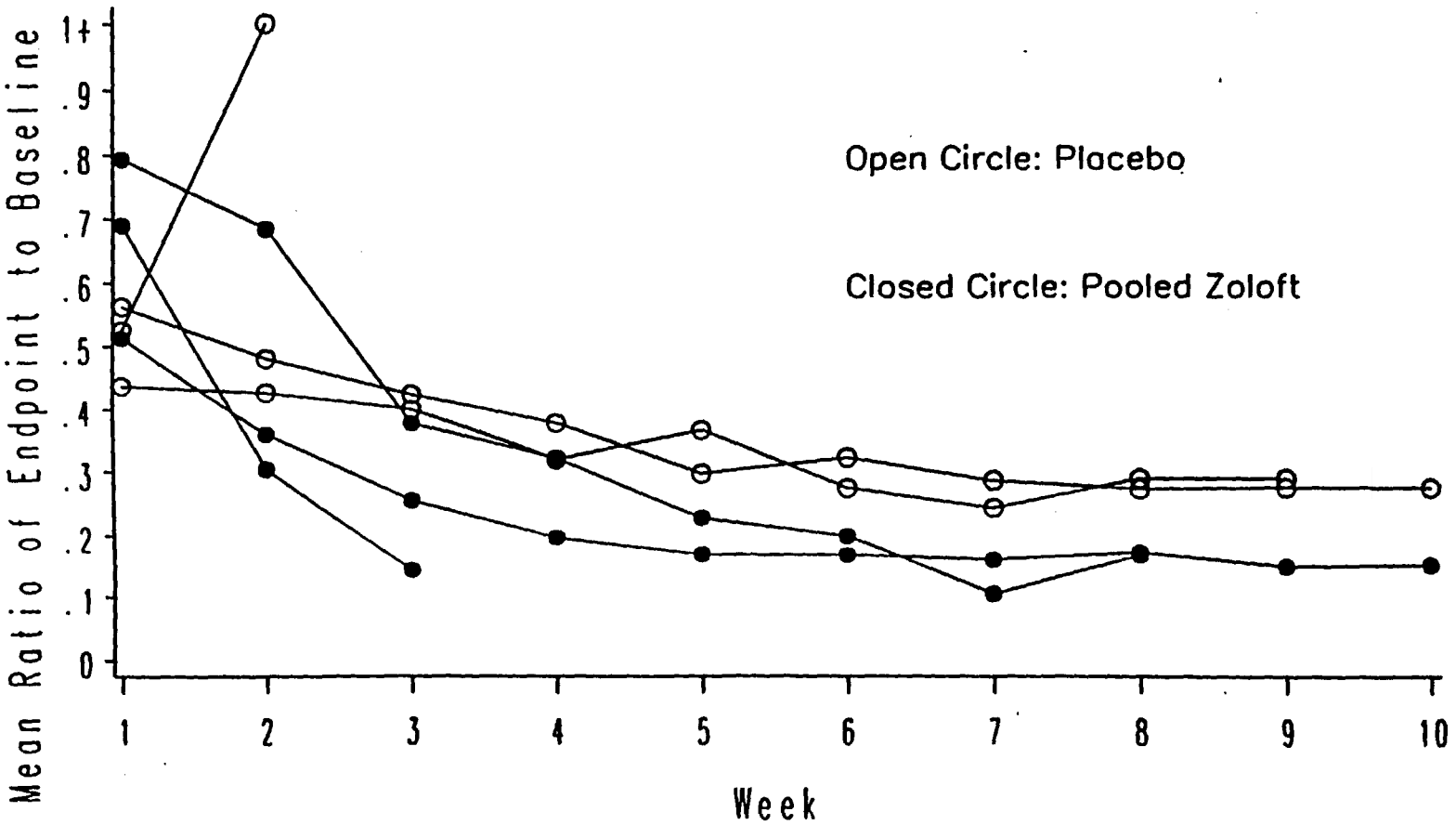
PROTOCOL: 93CE21-0629
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

MEDIAN NUMBER OF PANIC ATTACKS AT EACH WEEK AND AT ENDPOINT

	SERTRALINE		PLACEBO	
	N	MED.(IQR[1])	N	MED.(IQR)
Week 0	79	4.0(2.0- 7.5)	87	2.9(1.6- 6.4)
Week 1	79	2.1(0.9- 6.0)	87	1.6(0.0- 4.0)
Week 2	75	1.2(0.0- 5.0)	83	1.2(0.0- 5.0)
Week 3	69	0.8(0.0- 2.0)	81	1.0(0.0- 3.5)
Week 4	67	0.0(0.0- 2.0)	82	0.9(0.0- 3.0)
Week 5	64	0.0(0.0- 1.0)	78	0.0(0.0- 3.5)
Week 6	62	0.0(0.0- 1.0)	77	0.0(0.0- 3.0)
Week 7	61	0.0(0.0- 0.0)	74	0.0(0.0- 2.0)
Week 8	61	0.0(0.0- 0.9)	72	0.0(0.0- 1.8)
Week 9	59	0.0(0.0- 0.0)	73	0.0(0.0- 2.0)
Week 10	59	0.0(0.0- 0.7)	72	0.0(0.0- 2.0)
Endpoint	79	0.0(0.0- 1.0)	87	0.5(0.0- 2.0)

1: IQR is the interquartile range: (25th percentile - 75th percentile).

Figure 1.3.2
Protocol 0629
Mean Ratios of Endpoint to Baseline Panic Attacks by Completion Category(1)
Pooled Zoloft and Placebo



1: Categories: patients discontinuing in weeks 1-3, 4-9, and completers.

Table 1.4.1

PROTOCOL: 93CE21-0629
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

CLINICAL GLOBAL IMPRESSIONS (SEVERITY) - MEAN CHANGE FROM BASELINE AT EACH VISIT AND AT ENDPOINT

	SERTRALINE		PLACEBO		
	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR	P-VALUE[1]
Week 1	79	-0.19 ± 0.08	87	-0.08 ± 0.07	0.319
Week 2	75	-0.57 ± 0.10	83	-0.27 ± 0.09	0.033
Week 3	69	-0.88 ± 0.12	80	-0.48 ± 0.11	0.013
Week 4	66	-1.36 ± 0.13	82	-0.77 ± 0.11	<0.001
Week 6	62	-1.39 ± 0.16	78	-0.97 ± 0.14	0.048
Week 8	61	-1.41 ± 0.17	74	-0.97 ± 0.15	0.058
Week 10	60	-1.86 ± 0.17	73	-1.06 ± 0.16	<0.001
Endpoint	79	-1.64 ± 0.15	87	-0.90 ± 0.14	<0.001

1: The p-values are obtained from analysis of variance with treatment, site and treatment-by-site as effects.

Table 1.5.1a

PROTOCOL: 93CE21-0629
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

TABLE 8.2: PERCENT TIME WORRYING - RATIO TO BASELINE AT EACH WEEK AND AT ENDPOINT (GEOMETRIC MEAN)

	SERTRALINE		PLACEBO		
	N	MEAN	N	MEAN	P-VALUE[1]
Week 1	79	0.71	87	0.75	.735
Week 2	75	0.67	83	0.75	.543
Week 3	69	0.48	81	0.56	.456
Week 4	67	0.44	82	0.55	.265
Week 5	64	0.30	78	0.49	.037
Week 6	62	0.32	77	0.40	.407
Week 7	61	0.32	74	0.41	.350
Week 8	61	0.30	72	0.45	.157
Week 9	59	0.25	73	0.40	.055
Week 10	59	0.25	72	0.37	.125
Endpoint	79	0.30	87	0.40	.143

1: The p-values are obtained from the analyses of variance with treatment, site and treatment-by-site as effects.

Table 1.5.1b

PROTOCOL: 93CE21-0629
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

TABLE 8.1: MEDIAN PERCENT TIME WORRYING AT EACH WEEK AND AT ENDPOINT

	SERTRALINE		PLACEBO	
	N	MED.(IQR[1])	N	MED.(IQR)
Week 0	79	20.9(10.0- 42.9)	87	24.6(13.4-49.3)
Week 1	79	14.3(3.1- 44.3)	87	20.0(6.0-43.3)
Week 2	75	10.7(4.3- 46.4)	83	17.5(5.7-40.6)
Week 3	69	9.3(1.1- 36.4)	81	17.1(3.4-36.4)
Week 4	67	7.0(1.0- 28.0)	82	15.0(3.9-29.3)
Week 5	64	5.0(0.0- 22.4)	78	13.4(2.7-32.9)
Week 6	62	6.0(0.4- 25.0)	77	8.6(2.4-28.6)
Week 7	61	5.0(0.0- 25.0)	74	10.0(2.0-31.4)
Week 8	61	3.7(0.0- 25.0)	72	9.6(1.8-34.6)
Week 9	59	4.4(0.0- 20.0)	73	10.0(1.0-22.9)
Week 10	59	1.4(0.0- 18.8)	72	9.3(1.0-25.0)
Endpoint	79	4.4(0.0- 20.3)	87	10.3(1.3-26.8)

1: IQR is the interquartile range: (25th percentile - 75th percentile).

Table 1.6.1

PROTOCOL: 93CE21-0629
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

TABLE 14: CLINICAL GLOBAL IMPRESSIONS (IMPROVEMENT) - MEAN RATINGS AT EACH VISIT AND AT ENDPOINT

	SERTRALINE		PLACEBO		
	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR	P-VALUE[1]
Week 1	79	3.58 ± 0.11	87	3.51 ± 0.10	0.669
Week 2	75	3.07 ± 0.13	85	3.27 ± 0.12	0.251
Week 3	69	2.52 ± 0.12	80	3.15 ± 0.11	<0.001
Week 4	66	2.34 ± 0.15	82	2.75 ± 0.12	0.032
Week 6	62	2.06 ± 0.15	79	2.64 ± 0.12	0.003
Week 8	61	2.29 ± 0.16	74	2.56 ± 0.15	0.216
Week 10	60	1.78 ± 0.16	73	2.67 ± 0.15	<0.001
Endpoint	79	2.02 ± 0.15	87	2.82 ± 0.13	<0.001

1: The p-values are obtained from analysis of variance with treatment, site and treatment-by-site as effects.

Figure 2.2.1
Protocol 0630
Percent of Patients in Study

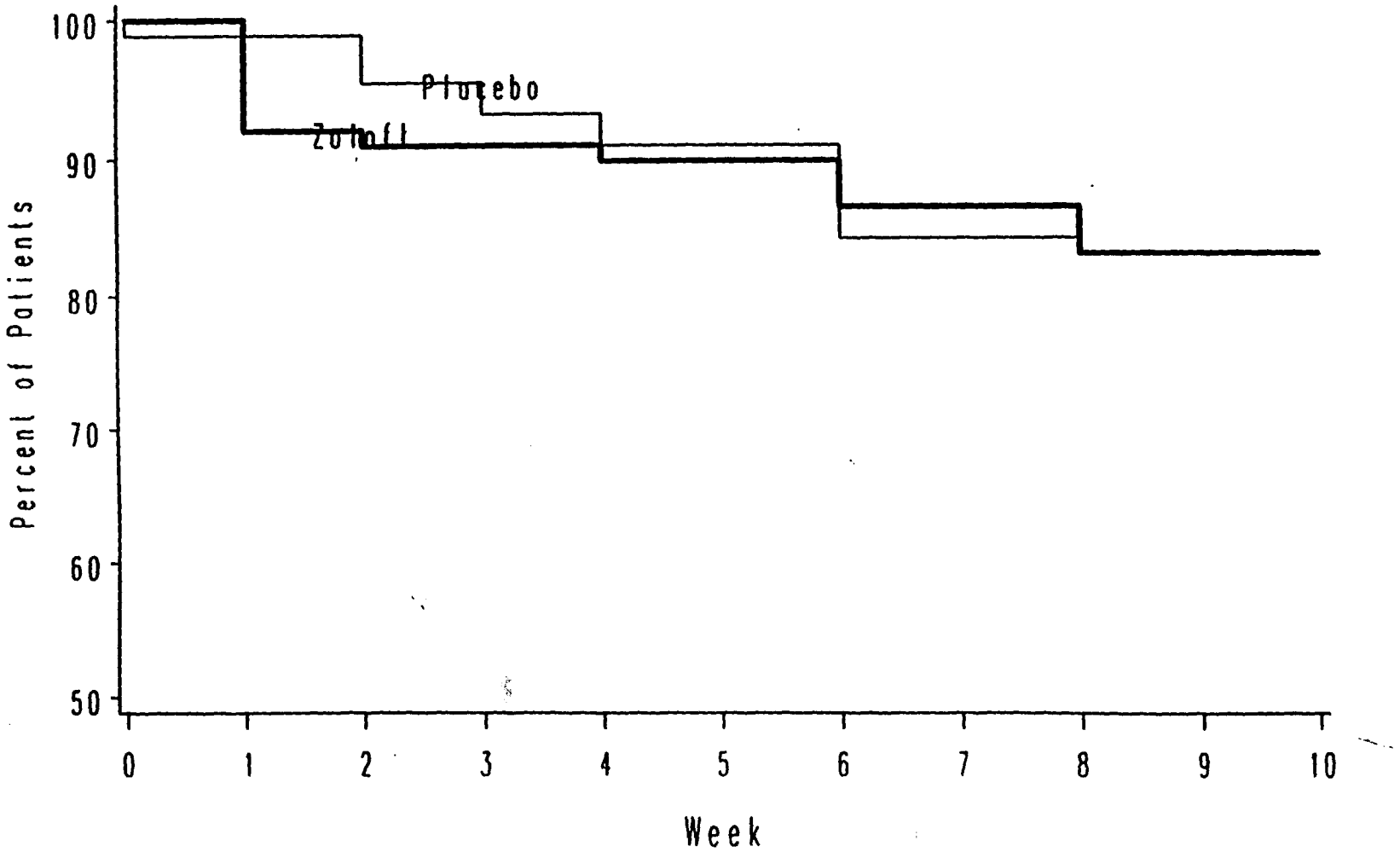


Table 2.2.2

PROTOCOL: 93CE21-0630
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

TOTAL DURATION OF THERAPY (DAYS)

	SERTRALINE	PLACEBO
NUMBER OF PATIENTS	88	88
DURATION CATEGORY (DAYS)		
1 - 7	5	1
8 - 14	2	1
15 - 21	1	3
22 - 28	0	2
29 - 42	4	3
43 - 56	2	4
57 - 70	39	50
>= 71	35	24
MEAN DURATION (DAYS)	63.1	63.9
RANGE (DAYS)	2 - 77	1 - 77

Table 2.3.1a

PROTOCOL: 93CE21-0630
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

PANIC ATTACKS - MEAN RATIO TO BASELINE AT EACH WEEK AND AT ENDPOINT

	SERTRALINE		PLACEBO	
	N	MEAN ± SD.	N	MEAN ± SD.
Week 1	87	0.73 ± 0.77	87	0.91 ± 1.01
Week 2	80	0.38 ± 0.47	86	0.67 ± 0.71
Week 3	79	0.27 ± 0.33	84	0.60 ± 0.83
Week 4	79	0.18 ± 0.27	82	0.60 ± 1.29
Week 5	78	0.19 ± 0.33	79	0.55 ± 0.87
Week 6	78	0.16 ± 0.27	78	0.38 ± 0.67
Week 7	77	0.15 ± 0.42	72	0.31 ± 0.57
Week 8	74	0.23 ± 0.65	73	0.33 ± 0.57
Week 9	74	0.10 ± 0.27	73	0.23 ± 0.48
Week 10	71	0.11 ± 0.24	72	0.23 ± 0.44
Endpoint	87	0.21 ± 0.57	88	0.41 ± 0.73

Table 2.3.1b

PROTOCOL: 93CE21-0630
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

PANIC ATTACKS - RATIO TO BASELINE AT EACH WEEK AND AT ENDPOINT (GEOMETRIC MEAN)

	SERTRALINE		PLACEBO		
	N	ADJ. MEAN	N	ADJ. MEAN	P-VALUE[1]
Week 1	88	0.58	87	0.69	.247
Week 2	81	0.38	86	0.52	.036
Week 3	80	0.30	84	0.45	.005
Week 4	80	0.24	82	0.41	.001
Week 5	79	0.24	79	0.39	.003
Week 6	79	0.22	78	0.30	.070
Week 7	77	0.19	72	0.27	.020
Week 8	74	0.21	73	0.27	.110
Week 9	74	0.17	73	0.22	.052
Week 10	71	0.18	72	0.24	.068
Endpoint	88	0.21	88	0.31	.014

1: The p-values are obtained from the analyses of variance with treatment, site and treatment-by-site as effects.

Table 2.3.1c

PROTOCOL: 93CE21-0630
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

MEDIAN NUMBER OF PANIC ATTACKS AT EACH WEEK AND AT ENDPOINT

	SERTRALINE		PLACEBO	
	N	MED.(IQR[1])	N	MED.(IQR)
Week 0	88	3.5(2.2- 6.2)	88	3.2(2.0- 6.1)
Week 1	88	2.2(0.9- 4.1)	87	2.0(1.0- 5.0)
Week 2	81	1.0(0.0- 3.0)	86	2.0(0.0- 5.0)
Week 3	80	0.0(0.0- 2.6)	84	1.1(0.0- 3.5)
Week 4	80	0.0(0.0- 2.0)	82	1.0(0.0- 3.0)
Week 5	79	0.0(0.0- 1.2)	79	1.0(0.0- 2.3)
Week 6	79	0.0(0.0- 1.2)	78	0.0(0.0- 2.0)
Week 7	77	0.0(0.0- 1.0)	72	0.0(0.0- 1.9)
Week 8	74	0.0(0.0- 1.0)	73	0.9(0.0- 1.4)
Week 9	74	0.0(0.0- 1.0)	73	0.0(0.0- 1.4)
Week 10	71	0.0(0.0- 0.8)	72	0.0(0.0- 1.1)
Endpoint	88	0.0(0.0- 0.8)	88	0.5(0.0- 1.9)

1: IQR is the interquartile range: (25th percentile - 75th percentile).

Table 2.4.1

PROTOCOL: 93CE21-0650
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

CLINICAL GLOBAL IMPRESSIONS (SEVERITY) - MEAN CHANGE FROM BASELINE AT EACH VISIT AND AT ENDPOINT

	SERTRALINE		PLACEBO		
	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR	P-VALUE[1]
Week 1	88	-0.06 ± 0.08	82	-0.32 ± 0.09	0.027
Week 2	80	-0.42 ± 0.10	87	-0.50 ± 0.10	0.574
Week 3	77	-0.83 ± 0.12	81	-0.77 ± 0.12	0.699
Week 4	79	-1.23 ± 0.12	80	-0.85 ± 0.12	0.027
Week 6	78	-1.27 ± 0.12	79	-0.88 ± 0.12	0.026
Week 8	74	-1.50 ± 0.14	74	-1.13 ± 0.14	0.067
Week 10	73	-1.75 ± 0.14	72	-1.18 ± 0.15	0.007
Endpoint	88	-1.56 ± 0.14	87	-1.04 ± 0.14	0.009

1: The p-values are obtained from analysis of variance with treatment, site and treatment-by-site as effects.

Table 2.5.1a

PROTOCOL: 93CE21-0630
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

PERCENT TIME WORRYING - RATIO TO BASELINE AT EACH WEEK AND AT ENDPOINT (GEOMETRIC MEAN)

	SERTRALINE		PLACEBO		
	N	MEAN	N	MEAN	P-VALUE[1]
Week 1	88	0.89	87	0.74	.123
Week 2	81	0.75	86	0.77	.807
Week 3	80	0.61	84	0.66	.565
Week 4	80	0.46	82	0.61	.098
Week 5	79	0.44	79	0.65	.035
Week 6	79	0.43	78	0.54	.220
Week 7	77	0.34	72	0.53	.016
Week 8	74	0.36	73	0.46	.184
Week 9	74	0.32	73	0.42	.166
Week 10	71	0.28	72	0.45	.028
Endpoint	88	0.38	88	0.53	.055

1: The p-values are obtained from the analyses of variance with treatment, site and treatment-by-site as effects.

Table 2.5.1b

PROTOCOL: 93CE21-0630
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

MEDIAN PERCENT TIME WORRYING AT EACH WEEK AND AT ENDPOINT

	SERTRALINE		PLACEBO	
	N	MED.(IQR[1])	N	MED.(IQR)
Week 0	88	24.4(9.5- 46.3)	88	21.2(6.2-40.6)
Week 1	88	22.5(5.7- 45.5)	87	16.7(2.4-37.1)
Week 2	81	20.0(4.0- 34.3)	86	16.6(2.6-33.8)
Week 3	80	14.3(2.1- 37.7)	84	11.8(2.0-34.8)
Week 4	80	10.4(0.0- 31.7)	82	11.1(1.4-31.7)
Week 5	79	13.0(0.3- 32.5)	79	10.0(2.0-28.3)
Week 6	79	9.3(0.9- 28.6)	78	9.3(0.0-28.6)
Week 7	77	10.0(0.0- 27.1)	72	7.7(0.2-25.0)
Week 8	74	8.0(0.0- 27.1)	73	6.4(0.0-23.8)
Week 9	74	5.0(0.0- 21.4)	73	6.0(0.0-22.5)
Week 10	71	5.0(0.0- 23.8)	72	7.9(0.2-20.4)
Endpoint	88	7.8(0.2- 29.7)	88	9.1(0.7-25.7)

1: IQR is the interquartile range: (25th percentile - 75th percentile).

Table 2.6.1

PROTOCOL: 93CE21-0630
STUDY: DOUBLE-BLIND FLEXIBLE DOSE PARALLEL COMPARISON OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

CLINICAL GLOBAL IMPRESSIONS (IMPROVEMENT) - MEAN RATINGS AT EACH VISIT AND AT ENDPOINT

	SERTRALINE		PLACEBO		
	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR	P-VALUE[1]
Week 1	88	3.69 ± 0.09	82	3.41 ± 0.10	0.041
Week 2	80	3.14 ± 0.11	87	3.17 ± 0.10	0.870
Week 3	77	2.72 ± 0.12	81	2.96 ± 0.12	0.155
Week 4	79	2.43 ± 0.12	80	2.82 ± 0.12	0.020
Week 6	78	2.31 ± 0.11	79	2.74 ± 0.11	0.009
Week 8	74	2.25 ± 0.13	74	2.62 ± 0.13	0.048
Week 10	73	2.06 ± 0.12	72	2.56 ± 0.12	0.004
Endpoint	88	2.26 ± 0.13	87	2.74 ± 0.13	0.011

1: The p-values are obtained from analysis of variance with treatment, site and treatment-by-site as effects.

Figure 3.2.1
Protocol 0529
Percent of Patients in Study

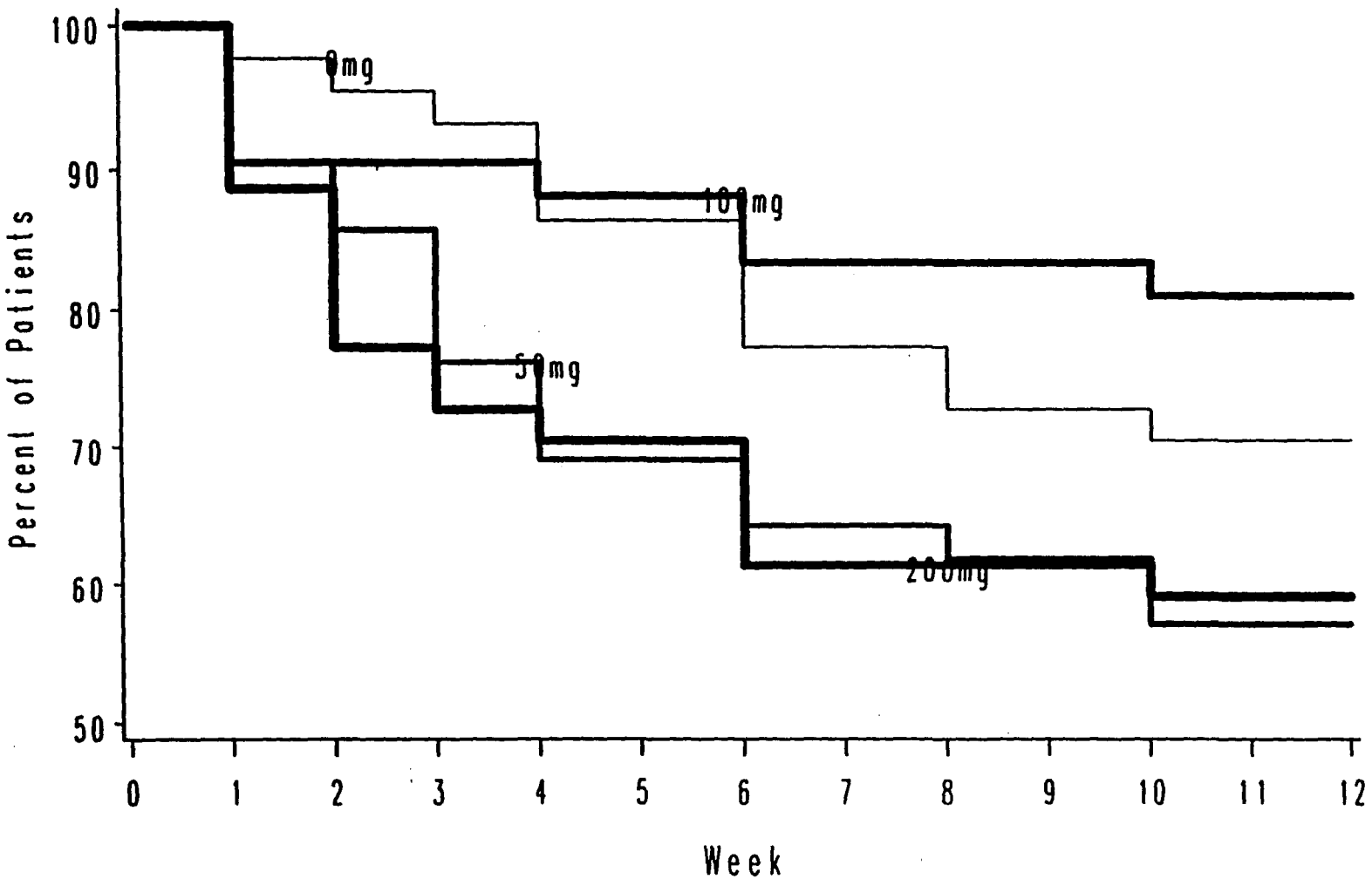


Table 3.3.1a

PROTOCOL: 90CE21-0529
STUDY: DOUBLE-BLIND PARALLEL COMPARISON OF 3 DOSES OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

PANIC ATTACKS - MEAN RATIO TO BASELINE AT EACH WEEK AND AT ENDPOINT

	SERTRALINE								PLACEBO	
	50 MG		100 MG		200 MG		POOLED			
	N	MEAN ± SD.	N	MEAN ± SD.	N	MEAN ± SD.	N	MEAN ± SD.	N	MEAN ± SD.
Week 1	41	0.80 ± 0.84	41	0.92 ± 1.24	44	1.05 ± 1.28	126	0.93 ± 1.14	43	0.74 ± 0.75
Week 2	36	0.28 ± 0.36	38	0.53 ± 1.03	38	0.95 ± 2.17	112	0.59 ± 1.43	42	0.77 ± 0.91
Week 3	35	0.38 ± 0.52	38	0.64 ± 1.26	33	0.27 ± 0.46	106	0.44 ± 0.86	41	0.38 ± 0.47
Week 4	31	0.17 ± 0.31	38	0.50 ± 1.05	32	0.19 ± 0.37	101	0.30 ± 0.71	40	0.54 ± 0.85
Week 5	28	0.31 ± 0.39	38	0.45 ± 1.13	31	0.06 ± 0.22	97	0.29 ± 0.76	38	0.56 ± 1.14
Week 6	28	0.14 ± 0.28	36	0.42 ± 0.99	31	0.24 ± 0.76	95	0.28 ± 0.76	36	0.53 ± 1.26
Week 7	26	0.10 ± 0.18	35	0.36 ± 0.81	27	0.70 ± 3.07	88	0.39 ± 1.77	34	0.54 ± 0.81
Week 8	26	0.11 ± 0.20	35	0.44 ± 1.03	27	0.15 ± 0.31	88	0.25 ± 0.69	33	0.50 ± 0.75
Week 9	25	0.11 ± 0.20	34	0.23 ± 0.66	26	0.18 ± 0.42	85	0.18 ± 0.49	31	0.45 ± 1.34
Week 10	25	0.14 ± 0.23	34	0.19 ± 0.50	26	0.14 ± 0.28	85	0.16 ± 0.37	31	0.54 ± 1.23
Week 11	23	0.10 ± 0.30	34	0.16 ± 0.46	25	0.25 ± 0.81	82	0.17 ± 0.55	30	0.55 ± 1.02
Week 12	23	0.07 ± 0.15	34	0.23 ± 0.59	25	0.26 ± 1.06	82	0.19 ± 0.70	30	0.55 ± 1.18
Endpoint	41	0.29 ± 0.59	41	0.17 ± 0.47	44	0.58 ± 1.59	126	0.35 ± 1.04	43	0.61 ± 0.94

Table 3.3.1b

PROTOCOL: 90CE21-0529
STUDY: DOUBLE-BLIND PARALLEL COMPARISON OF 3 DOSES OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

MEDIAN NUMBER OF PANIC ATTACKS AT EACH WEEK AND AT ENDPOINT

	SERTRALINE										PLACEBO	
	50 MG		100 MG		200 MG		POOLED					
	N	MED.(IQR)	N	MED.(IQR)	N	MED.(IQR)	N	MED.(IQR)	N	MED.(IQR)
Week 0	42	5.5(3.0- 10.5)	41	6.5(4.0- 11.5)	44	3.5(2.5- 5.5)	127	4.5(2.5- 9.0)	44	6.5(3.0-18.0)
Week 1	42	3.5(1.0- 7.0)	41	3.0(1.0- 13.0)	44	3.0(1.0- 7.0)	127	3.0(1.0- 7.0)	44	4.0(1.0-11.0)
Week 2	37	1.0(0.0- 3.0)	38	1.0(0.0- 6.0)	38	1.0(0.0- 5.0)	113	1.0(0.0- 4.0)	43	3.0(1.0- 9.0)
Week 3	36	1.0(0.0- 4.0)	38	1.0(0.0- 4.0)	33	0.0(0.0- 1.0)	107	1.0(0.0- 3.0)	42	1.0(0.0- 4.0)
Week 4	32	0.0(0.0- 2.5)	38	0.0(0.0- 6.0)	32	0.0(0.0- 1.0)	102	0.0(0.0- 2.0)	41	2.0(0.0- 7.0)
Week 5	29	0.0(0.0- 3.0)	38	0.0(0.0- 2.0)	31	0.0(0.0- 0.0)	98	0.0(0.0- 1.0)	39	1.0(0.0- 5.0)
Week 6	29	0.0(0.0- 2.0)	36	0.0(0.0- 1.0)	31	0.0(0.0- 1.0)	96	0.0(0.0- 1.0)	37	1.0(0.0- 4.0)
Week 7	27	0.0(0.0- 1.0)	35	0.0(0.0- 2.0)	27	0.0(0.0- 0.0)	89	0.0(0.0- 1.0)	35	1.0(0.0- 4.0)
Week 8	27	0.0(0.0- 1.0)	35	0.0(0.0- 2.0)	27	0.0(0.0- 1.0)	89	0.0(0.0- 1.0)	34	1.0(0.0- 3.0)
Week 9	26	0.0(0.0- 1.0)	34	0.0(0.0- 0.0)	26	0.0(0.0- 1.0)	86	0.0(0.0- 1.0)	32	0.0(0.0- 1.0)
Week 10	26	0.0(0.0- 1.0)	34	0.0(0.0- 0.0)	26	0.0(0.0- 0.0)	86	0.0(0.0- 1.0)	32	0.0(0.0- 4.0)
Week 11	24	0.0(0.0- 0.0)	34	0.0(0.0- 1.0)	25	0.0(0.0- 1.0)	83	0.0(0.0- 1.0)	31	0.0(0.0- 2.0)
Week 12	24	0.0(0.0- 0.0)	34	0.0(0.0- 1.0)	25	0.0(0.0- 0.0)	83	0.0(0.0- 0.0)	31	0.0(0.0- 5.0)
Endpoint	42	0.3(0.0- 2.0)	41	0.0(0.0- 1.0)	44	0.0(0.0- 1.8)	127	0.0(0.0- 1.5)	44	1.0(0.0- 5.5)

1: IQR is the interquartile range: (25th percentile - 75th percentile).

Table 3.3.1c

Study: 0529

Mean Change from Baseline in Total Number of Panic Attacks

Observed Cases Analysis

	Treatment Groups								2-sided p-values for pairwise comparisons		
Week	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	42	10.15	42	10.65	44	5.75	44	13.74			
1	42	-4.80	41	- .78	44	- .91	44	-4.33	.905	.759	.870
2	37	-7.78	38	-3.84	38	-1.68	43	-3.76	.009	.009	.199
3	36	-7.96	38	-3.63	33	-3.41	42	-6.69	.630	.241	.169
4	32	-9.27	38	-4.92	32	-4.00	41	-6.27	.012	.120	.021
5	29	-8.76	38	-5.00	31	-3.77	39	-6.72	.523	.053	.009
6	29	-9.38	36	-5.04	31	-2.16	37	-5.97	.167	.067	.062
7	27	-10.02	35	-4.26	27	-3.00	35	-3.14	.204	.097	.083
8	27	-9.98	35	-4.89	27	-3.78	34	-4.37	.025	.070	.047
9	26	-8.73	34	-5.44	26	-3.88	32	-5.30	.977	.456	.724
10	26	-8.23	34	-5.82	26	-3.65	32	-4.67	.412	.122	.387
11	24	-9.33	34	-7.46	25	-3.66	31	-5.13	.116	.131	.237
12	24	-9.33	34	-6.87	25	-3.74	31	-6.48	.110	.184	.100

Table 3.3.1d

Study: 0529

Mean Change from Baseline in Total Number of Panic Attacks

Last Observation Carried Forward Analysis

	Treatment Groups								2-sided p-values for pairwise comparisons		
Week	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	42	10.15	42	10.65	44	5.75	44	13.74			
1	42	-4.80	41	- .78	44	- .91	44	-4.33	.905	.759	.870
2	42	-6.75	41	-3.90	44	-2.30	44	-3.94	.040	.004	.186
3	42	-6.99	41	-3.71	44	-3.07	44	-6.35	.641	.132	.349
4	42	-8.11	41	-4.90	44	-3.48	44	-5.81	.030	.050	.106
5	42	-7.89	41	-4.98	44	-3.45	44	-5.88	.264	.009	.043
6	42	-8.32	41	-6.66	44	-2.32	44	-6.42	.146	.007	.154
7	42	-8.58	41	-5.98	44	-3.07	44	-4.13	.092	.005	.102
8	42	-8.56	41	-6.51	44	-3.55	44	-5.19	.019	.001	.042
9	42	-8.73	41	-7.22	44	-3.75	44	-5.15	.244	.004	.271
10	42	-8.42	41	-7.54	44	-3.61	44	-4.69	.134	.001	.128
11	42	-8.73	41	-8.73	44	-3.61	44	-4.99	.051	< .001	.083
12	42	-8.73	41	-8.24	44	-3.66	44	-5.94	.040	.001	.044

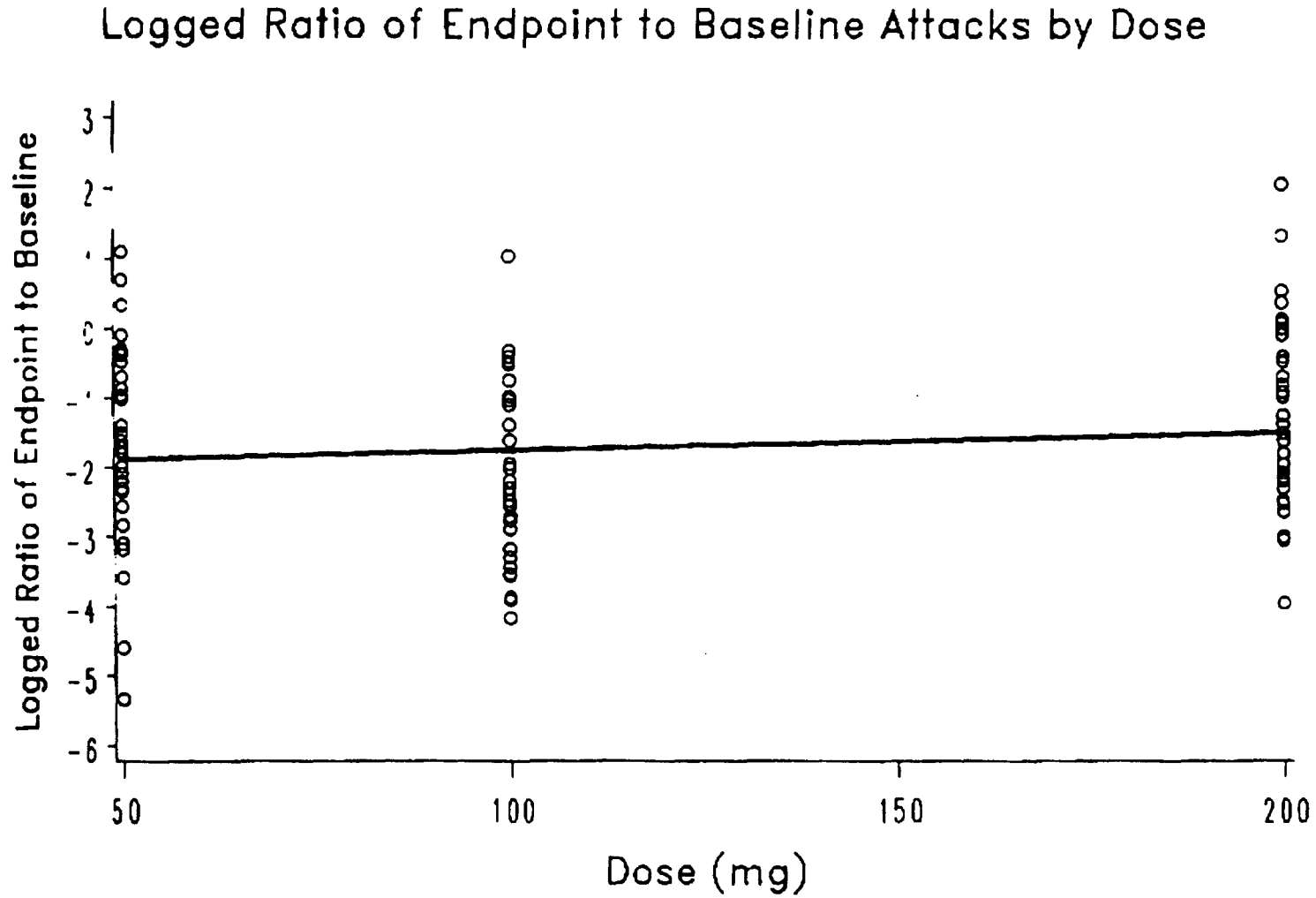
Table 3.3.1e Protocol 0529

Endpoint Analyses

	Panic Attacks		% Time Worrying		CGI Severity		CGI Improvement	
	Parametric	Wilcoxon	Parametric	Wilcoxon	Parametric	Wilcoxon	Parametric	Wilcoxon
Four-group	.007	.020	.004	.077	.256	.326	.370	.301
Zoloft vs Placebo	.002	.006	.003	.044	.120	.215	.226	.134
50mg vs Placebo	.037	.052	.027	.105	.476	.593	.852	.436
100mg vs Placebo	.001	.003	<.001	.015	.050	.063	.108	.056
200mg vs Placebo	.050	.072	.132	.379	.252	.528	.403	.341

Figure 3.3.1f

Protocol: 90CE21-0529
Study: Double Blind Parallel Study of 3 Doses of Sertraline and Placebo in Outpatients with Panic Disorder



Lower ratios indicate greater improvement.

Table 3.4.1

PROTOCOL : 90CE21-0529
STUDY: DOUBLE-BLIND PARALLEL COMPARISON OF 3 DOSES OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

CLINICAL GLOBAL IMPRESSIONS (SEVERITY) - MEAN CHANGE FROM BASELINE AT EACH VISIT AND AT ENDPOINT

	SERTRALINE								PLACEBO		P-VALUE[1]	
	50 MG		100 MG		200 MG		POOLED					
	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR.	OVER-ALL	POOLED
Week 1	42	-0.3 ± 0.13	42	-0.3 ± 0.13	43	-0.3 ± 0.13	127	-0.3 ± 0.07	44	-0.4 ± 0.13	.829	.415
Week 2	37	-0.9 ± 0.17	37	-1.0 ± 0.16	35	-1.0 ± 0.17	109	-1.0 ± 0.10	42	-0.6 ± 0.15	.283	.051
Week 3	36	-0.9 ± 0.17	38	-1.3 ± 0.16	33	-1.3 ± 0.17	107	-1.2 ± 0.10	41	-0.9 ± 0.16	.175	.184
Week 4	32	-1.4 ± 0.21	38	-1.5 ± 0.17	31	-1.5 ± 0.18	101	-1.5 ± 0.10	41	-1.1 ± 0.16	.199	.039
Week 6	29	-1.6 ± 0.19	37	-1.6 ± 0.15	30	-1.6 ± 0.17	96	-1.6 ± 0.10	38	-1.1 ± 0.15	.032	.005
Week 8	27	-1.7 ± 0.24	35	-2.0 ± 0.19	26	-1.9 ± 0.22	88	-1.8 ± 0.11	34	-1.2 ± 0.19	.047	.006
Week 10	26	-1.8 ± 0.24	35	-1.8 ± 0.19	26	-2.0 ± 0.22	87	-1.9 ± 0.12	32	-1.5 ± 0.20	.376	.091
Week 12	24	-1.8 ± 0.25	33	-2.0 ± 0.19	25	-2.0 ± 0.23	82	-1.9 ± 0.12	31	-1.5 ± 0.20	.245	.056
Endpoint	42	-1.4 ± 0.19	42	-1.8 ± 0.19	43	-1.5 ± 0.19	127	-1.6 ± 0.11	44	-1.2 ± 0.18	.256	.120

1: The p-values compare the treatment groups and are obtained from analyses of variance with treatment and center as effects. The pooled analysis compares the pooled sertraline group to placebo.

Table 3.4.2
Study: 0529
Mean Change from Baseline in CGI Severity

Observed Cases Analysis

	Treatment Week															
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	42	4.38	42	- .25	37	- .93	36	- .92	32	-1.43	29	-1.62	27	-1.74	26	-1.83	24	-1.77
Zoloft 100mg	42	4.50	42	- .33	37	- .97	38	-1.28	38	-1.52	37	-1.64	35	-1.95	35	-1.83	33	-1.95
Zoloft 200mg	43	4.28	43	- .27	35	- .96	33	-1.30	31	-1.49	30	-1.57	26	-1.88	26	-1.98	25	-2.02
Placebo	44	4.64	44	- .40	42	- .61	41	- .91	41	-1.08	38	-1.07	34	-1.24	32	-1.48	31	-1.48
2-sided p-values for pairwise comparisons																		
50mg vs P			.387		.151		.956		.173		.027		.105		.269		.352	
100mg vs P			.696		.102		.103		.057		.009		.009		.207		.088	
200mg vs P			.472		.123		.104		.093		.031		.032		.101		.078	

Table 3.4.3
Study: 0529
Mean Change from Baseline in CGI Severity

Last Observation Carried Forward Analysis

	Treatment Week															
	BL Mean		Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	42	4.38	42	- .25	42	- .82	42	- .82	42	-1.15	42	-1.30	42	-1.36	42	-1.45	42	-1.42
Zoloft 100mg	42	4.50	42	- .33	42	- .91	42	-1.17	42	-1.39	42	-1.48	42	-1.69	42	-1.64	42	-1.73
Zoloft 200mg	43	4.28	43	- .27	43	- .77	43	-1.06	43	-1.19	43	-1.28	43	-1.44	43	-1.48	43	-1.54
Placebo	44	4.64	44	- .40	44	- .56	44	- .80	44	- .97	44	-1.00	44	-1.12	44	-1.23	44	-1.24
2-sided p-values for pairwise comparisons																		
50mg vs P			.387		.230		.932		.442		.200		.372		.404		.489	
100mg vs P			.696		.110		.112		.080		.041		.031		.122		.064	
200mg vs P			.472		.339		.271		.361		.237		.233		.350		.265	

Table 3.5.1

PROTOCOLS: 90CE21-0529
STUDY: DOUBLE-BLIND PARALLEL COMPARISON OF 3 DOSES OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

CLINICAL GLOBAL IMPRESSIONS (IMPROVEMENT) - MEAN RATING AT EACH VISIT AND AT ENDPOINT

	SERTRALINE								PLACEBO		P-VALUE[1]	
	50 MG		100 MG		200 MG		POOLED					
	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR.	N	ADJ. MEAN ± STD. ERR.	OVER-ALL	POOLED
Week 1	42	3.5 ± 0.15	42	3.1 ± 0.15	44	3.5 ± 0.14	128	3.4 ± 0.09	44	3.3 ± 0.14	.213	.492
Week 2	37	2.7 ± 0.16	37	2.5 ± 0.15	36	2.7 ± 0.16	110	2.6 ± 0.09	42	3.1 ± 0.14	.078	.014
Week 3	36	2.8 ± 0.16	38	2.2 ± 0.15	34	2.2 ± 0.16	108	2.4 ± 0.09	41	2.8 ± 0.14	.002	.014
Week 4	32	2.2 ± 0.20	38	2.2 ± 0.16	32	2.0 ± 0.17	102	2.2 ± 0.10	41	2.7 ± 0.15	.022	.004
Week 6	29	2.0 ± 0.20	37	2.1 ± 0.16	31	2.0 ± 0.17	97	2.0 ± 0.09	38	2.7 ± 0.15	.003	.000
Week 8	27	2.0 ± 0.22	35	1.9 ± 0.17	27	1.8 ± 0.19	89	1.9 ± 0.10	33	2.3 ± 0.17	.180	.030
Week 10	26	2.1 ± 0.23	35	1.9 ± 0.18	27	1.8 ± 0.20	88	1.9 ± 0.11	32	2.3 ± 0.19	.229	.078
Week 12	24	2.1 ± 0.23	33	1.9 ± 0.18	26	1.8 ± 0.21	83	1.9 ± 0.11	31	2.2 ± 0.18	.447	.146
Endpoint	42	2.5 ± 0.18	42	2.1 ± 0.18	44	2.3 ± 0.18	128	2.3 ± 0.11	44	2.5 ± 0.18	.370	.266

1: The p-values compare the treatment groups and are obtained from analyses of variance with treatment and center as effects.
The pooled analysis compares the pooled sertraline group to placebo.
S529T7F - CJEF2 - 21AUG95 10:55

Table 3.5.2
Study: 0529
CGI Improvement

Observed Cases Analysis

	Treatment Week															
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	42	3.50	37	2.69	36	2.80	32	2.24	29	1.98	27	2.03	26	2.12	24	2.12
Zoloft 100mg	42	3.14	37	2.52	38	2.24	38	2.24	37	2.11	35	1.88	35	1.86	33	1.90
Zoloft 200mg	44	3.52	36	2.70	34	2.18	32	2.01	31	1.95	27	1.80	27	1.78	26	1.84
Placebo	44	3.28	42	3.05	41	2.83	41	2.70	38	2.72	33	2.32	32	2.29	31	2.23
2-sided p-values for pairwise comparisons																
50mg vs P	.274		.096		.909		.065		.004		.290		.568		.707	
100mg vs P	.526		.013		.006		.036		.007		.076		.104		.202	
200mg vs P	.238		.102		.003		.003		.001		.045		.069		.162	

Table 3.5.3
Study: 0529
CGI Improvement

Last Observation Carried Forward Analysis

	Treatment Week															
	Wk 1		Wk 2		Wk 3		Wk 4		Wk 6		Wk 8		Wk 10		Wk 12	
	n	X	n	X	n	X	n	X	n	X	n	X	n	X	n	X
Zoloft 50mg	42	3.50	42	2.90	42	2.94	42	2.64	42	2.46	42	2.47	42	2.51	42	2.48
Zoloft 100mg	42	3.14	42	2.60	42	2.34	42	2.34	42	2.27	42	2.13	42	2.11	42	2.13
Zoloft 200mg	44	3.52	44	2.88	44	2.49	44	2.42	44	2.36	44	2.28	44	2.29	44	2.31
Placebo	44	3.28	44	3.10	44	2.91	44	2.78	44	2.81	43	2.58	43	2.57	43	2.51
2-sided p-values for pairwise comparisons																
50mg vs P	.274		.329		.908		.554		.155		.671		.842		.898	
100mg vs P	.526		.018		.010		.070		.029		.081		.089		.151	
200mg vs P	.238		.285		.055		.128		.070		.242		.291		.444	

Table 3.6.1a

PROTOCOL: 90CE21-0529
STUDY: DOUBLE-BLIND PARALLEL COMPARISON OF 3 DOSES OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

PERCENT TIME WORRYING - RATIO TO BASELINE AT EACH WEEK AND AT ENDPOINT (GEOMETRIC MEAN)

	SERTRALINE								PLACEBO		P-VALUES[1]	
	50 MG		100 MG		200 MG		POOLED					
	N	ADJ. MEAN	N	ADJ. MEAN	N	ADJ. MEAN	N	ADJ. MEAN	N	ADJ. MEAN	OVER-ALL	POOLED
Week 1	42	0.81	41	0.65	44	0.79	127	0.75	44	0.65	.579	.402
Week 2	37	0.47	38	0.46	38	0.75	113	0.53	43	0.71	.050	.074
Week 3	36	0.42	38	0.44	33	0.50	107	0.45	42	0.66	.271	.055
Week 4	32	0.35	38	0.40	32	0.42	102	0.40	41	0.49	.685	.341
Week 5	29	0.21	38	0.31	31	0.37	98	0.30	39	0.51	.026	.014
Week 6	29	0.20	36	0.30	31	0.39	96	0.29	37	0.51	.020	.014
Week 7	27	0.21	35	0.24	27	0.33	89	0.26	35	0.48	.035	.009
Week 8	27	0.19	35	0.22	27	0.38	89	0.26	34	0.50	.002	.001
Week 9	26	0.20	34	0.21	26	0.30	86	0.24	32	0.49	.121	.046
Week 10	26	0.23	34	0.21	26	0.28	86	0.24	32	0.48	.082	.015
Week 11	24	0.22	34	0.22	25	0.27	83	0.23	31	0.46	.069	.007
Week 12	24	0.23	34	0.23	25	0.29	83	0.24	31	0.48	.055	.008
Endpoint	42	0.36	41	0.25	44	0.43	127	0.33	44	0.63	.004	.003

1: The p-values are obtained from the analyses of variance with treatment, site and treatment-by-site as effects.
The pooled analysis compares the pooled sertraline group to placebo.

Table 3.6.1b

PROTOCOL: 90CE21-0529
STUDY: DOUBLE-BLIND PARALLEL COMPARISON OF 3 DOSES OF SERTRALINE AND PLACEBO IN OUTPATIENTS WITH PANIC DISORDER

MEDIAN PERCENT TIME WORRYING AT EACH WEEK AND AT ENDPOINT

	SERTRALINE								PLACEBO	
	50 MG		100 MG		200 MG		POOLED			
	N	MED.(IQR)	N	MED.(IQR)	N	MED.(IQR)	N	MED.(IQR)	N	MED.(IQR)
Week 0	42	18.5(4.5- 28.2)	41	16.7(6.5- 30.9)	44	11.6(4.9-29.2)	127	14.3(4.8-30.9)	44	11.2(4.2-27.9)
Week 1	42	13.8(1.1- 32.6)	41	12.5(3.0- 25.0)	44	11.1(1.0-28.1)	127	12.5(1.4-28.0)	44	8.8(0.5-20.0)
Week 2	37	7.1(0.0- 15.0)	38	3.7(1.4- 18.6)	38	9.5(0.0-36.7)	113	7.1(0.7-21.7)	43	9.4(1.7-25.7)
Week 3	36	3.9(0.0- 17.0)	38	3.7(0.6- 15.0)	33	3.0(0.0-27.0)	107	3.6(0.0-20.0)	42	7.7(0.0-20.0)
Week 4	32	4.7(0.0- 24.5)	38	4.0(0.0- 13.4)	32	1.2(0.0-22.2)	102	4.0(0.0-20.0)	41	6.0(0.0-17.1)
Week 5	29	0.0(0.0- 10.0)	38	2.2(0.0- 10.7)	31	2.9(0.0-12.9)	98	2.0(0.0-10.7)	39	6.8(0.0-21.7)
Week 6	29	0.0(0.0- 12.1)	36	1.1(0.0- 9.3)	31	1.9(0.0-17.8)	96	1.3(0.0-12.5)	37	7.1(0.0-20.7)
Week 7	27	1.4(0.0- 10.0)	35	0.2(0.0- 8.6)	27	1.4(0.0-13.6)	89	1.1(0.0-10.0)	35	5.3(0.0-21.6)
Week 8	27	0.0(0.0- 9.3)	35	0.6(0.0- 3.6)	27	3.6(0.0-19.5)	89	0.6(0.0- 9.3)	34	6.9(0.0-19.0)
Week 9	26	0.4(0.0- 10.0)	34	0.0(0.0- 5.0)	26	0.5(0.0-12.8)	86	0.2(0.0-10.0)	32	2.0(0.0-14.0)
Week 10	26	0.9(0.0- 8.8)	34	0.0(0.0- 4.0)	26	0.5(0.0-10.0)	86	0.4(0.0- 7.7)	32	4.2(0.0-15.0)
Week 11	24	0.3(0.0- 5.7)	34	0.0(0.0- 4.6)	25	0.0(0.0-10.0)	83	0.0(0.0- 5.7)	31	3.7(0.0-25.7)
Week 12	24	1.4(0.0- 7.5)	34	0.3(0.0- 5.0)	25	0.0(0.0-10.0)	83	0.3(0.0- 6.6)	31	3.3(0.0-25.8)
Endpoint	42	2.8(0.0- 10.0)	41	0.6(0.0- 6.3)	44	4.3(0.0-15.2)	127	2.2(0.0-11.4)	44	6.7(0.3-25.3)

1: IQR is the interquartile range: (25th percentile - 75th percentile).

Table 3.6.2
Study: 0529
Mean Change from Baseline in Time Spent Worrying
Last Observation Carried Forward Analysis

	Treatment Groups								2-sided p-values for pairwise comparisons		
Week	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	42	21.71	42	23.94	44	18.89	44	19.45			
1	42	.68	41	-6.02	44	.28	44	-4.65	.289	.990	.342
2	42	-5.71	41	-10.11	44	.08	44	-3.51	.206	.026	.871
3	42	-6.10	41	-9.29	44	-2.71	44	-4.82	.237	.072	.376
4	42	-5.33	41	-9.63	44	-4.52	44	-7.35	.970	.188	.609
5	42	-9.39	41	-12.43	44	-6.52	44	-5.58	.059	.017	.386
6	42	-9.76	41	-11.77	44	-4.52	44	-5.90	.037	.010	.356
7	42	-10.84	41	-13.61	44	-6.80	44	-4.80	.052	.005	.450
8	42	-10.51	41	-14.04	44	-5.16	44	-4.93	.010	.001	.432
9	42	-11.12	41	-14.55	44	-6.40	44	-6.28	.059	.009	.573
10	42	-10.58	41	-14.86	44	-7.29	44	-5.96	.073	.003	.265
11	42	-11.47	41	-14.94	44	-7.30	44	-4.61	.020	.001	.181
12	42	-11.02	41	-15.06	44	-5.94	44	-4.36	.020	.001	.231

Table 3.6.3
Study: 0529
Mean Change from Baseline in Time Spent Worrying

Observed Cases Analysis											
	Treatment Groups								2-sided p-values for pairwise comparisons		
Week	Zoloft 50mg		Zoloft 100mg		Zoloft 200mg		Placebo				
	n	X	n	X	n	X	n	X	50 mg	100mg	200mg
BL Mean	42	21.71	42	23.94	44	18.89	44	19.45			
1	42	.68	41	-6.02	44	.28	44	-4.65	.289	.990	.342
2	37	-8.21	38	-10.63	38	.72	43	-3.54	.058	.037	.954
3	36	-8.19	38	-9.75	33	-4.96	42	-5.31	.077	.114	.294
4	32	-6.69	38	-10.11	32	-7.50	41	-8.05	.248	.411	.524
5	29	-12.63	38	-13.13	31	-8.80	39	-6.46	.003	.055	.237
6	29	-13.18	36	-11.97	31	-5.96	37	-6.66	.003	.042	.308
7	27	-14.36	35	-14.33	27	-10.44	35	-5.52	.012	.015	.210
8	27	-13.85	35	-14.83	27	-7.76	34	-4.84	.001	.002	.194
9	26	-12.28	34	-15.45	26	-9.82	32	-6.46	.050	.039	.392
10	26	-11.42	34	-15.83	26	-11.33	32	-6.02	.061	.015	.158
11	24	-12.98	34	-15.25	25	-11.72	31	-4.47	.036	.017	.107
12	24	-12.18	34	-15.40	25	-9.32	31	-4.12	.034	.012	.125

CHEMISTS REVIEW OF SUPPLEMENT

1. ORGANIZATION:	**HFD-120**
2. NDA NUMBER:	**19-839**
4. SUPPLEMENT NUMBERS/DATES:	**S-10**
LETTERDATE	19-SEP-95
STAMPDATE	19-SEP-95
5. AMENDMENTS/REPORTS/DATES:	
LETTERDATE	
STAMPDATE	
6. REC'D BY CHM:	21-SEP-95

7. APPLICANT NAME AND ADDRESS:

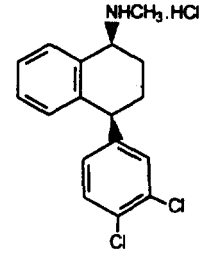
PFIZER
235 East 42nd Street
New York, N.Y. 10017-5755

OCT 12 1995

8. NAME OF DRUG: **ZOLOFT**

9. NONPROPRIETARY NAME: SERTRALINE HCl

10. CHEMICAL NAME/STRUCTURE: (1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine hydrochloride



11. DOSAGE FORM(S): Tablets

12. POTENCY(IES): 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg

13. PHARM. CATEGORY: Antidepressant

14. HOW DISPENSED: XXX (Rx) ___ (OTC)

15. RECORDS AND REPORTS CURRENT: XXX (YES) ___ (NO)

16. RELATED IND/NDA/DMF(S): IND

17. SUPPLEMENT PROVIDES FOR: Introduction of a new dosage form (25 mg Tablets) in addition to the 50, 100, 150, and 200 mg tablets in the approved NDA.

18. COMMENTS: The additional dosage form (25-mg tablets) is made from the and by the same process as the other four strengths in the approved NDA. The sponsor provides stability data for the additional dosage form and asks for a 24- month expiry date as in the NDA for the other strengths. The sponsor also provides a bioequivalence study comparing 4x25-mg tablets to a single 100-mg tablet. We sent a consult request to Biopharmaceuticals on September 26, 1995.

19. CONCLUSIONS AND RECOMMENDATIONS: Recommend APPROVAL of NDA 19-839/S-10 contingent upon concurrence of the Division of Biopharmaceuticals.

20. REVIEWER NAME	***SIGNATURE***	***DATE COMPLETED***
Mona Zarifa, Ph.D.	Mona Zarifa	10/6/95

Copies:
ORIG. NDA
HFD-120
HFD-120/PDavid
HFD-120/MZarifa/

Filename: **N019839.10**

INIT: SWB/ SWB 10/12/95

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

[ZOLOFT® TABLETS]
[Sertraline hydrochloride]

NDA 19-839/S011

(PANIC DISORDER)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-120

Finding of NO Significant Impact
NDA 19-839 / S-011
Zoloft
(Sertraline hydrochloride)
Tablets

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decision maker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their efficacy supplemental new drug application **S-011** for **Zoloft Tablets, Pfizer Inc.** has conducted a number of environmental studies and prepared environmental assessments (21 CFR 25.31a(a) which evaluate the potential environmental impacts of the manufacture, use and disposal of the drug product.

The new indication for Zoloft Tablets is for the treatment of Panic Disorder. The drug is intended for use as 50-mg, 100-mg, and 200-mg tablets to be taken orally and is currently approved for the treatment of Depression and Obsessive Compulsive Disorder (OCD).

The drug substance and the drug product are manufactured at the same sites as in the approved NDA. Updated permitting information has been provided. The maximum expected

environmental concentration (MEEC) has been revised based on the expected increase in use resulting from the new indication and it is provided in the April 18, 1996 amendment to this supplement. For details on the environmental effects of sertraline hydrochloride see the FONSI of the approved NDA and of the supplemental application S-002 (OCD).
The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. The increase in the MEEC of the substance due to increased usage is insignificant and is not expected to be toxic. Any residues of sertraline hydrochloride or its major metabolite entering the environment as a result of administering the drug to humans are expected to rapidly degrade.

6/28/96 Mona Zarifa

DATE PREPARED BY
Mona Zarifa, Ph.D.
Review Chemist
HFD-120

7/6/96 Stanley W. Blum

DATE DIVISION CONCURRENCE
Stanley W. Blum, Ph.D.
Supervisory Chemist
HFD-120

7/26/96 Nancy B Sager

DATE Approved
Nancy B. Sager
Environmental Scientist, CDER

Attachments: Environmental Assessment

CC: Original NDA 19-839/S-011/MMille copy to HFD-120
FONSI File NDA 19-839/S-011/HFD-357
Docket File NDA 19-839/S-011/HFD-357
FOI Copy/HFD-205

ENVIRONMENTAL ASSESSMENT

ZOLOFT™ TABLETS

Sertraline Hydrochloride for Use in Panic Disorder

Supplement to NDA #19-839

PFIZER INC

April 10, 1996

Non-Confidential Submission

ENVIRONMENTAL ASSESSMENT

21 CFR 25.31a(a), Format 1

ZOLOFT™ FOR PANIC DISORDER

(SERTRALINE HYDROCHLORIDE)

Reference: ZOLOFT™ Environmental Assessment [Freedom of Information Act (FOIA) version, submitted July 18, 1995; Finding of No Significant Impact dated August, 1995]

Changes/differences to the above-referenced FOIA Environmental Assessment (EA) -- and the lack of impact of these changes/differences on the environment -- are specifically provided below. For format items that do not differ substantively from the FOIA EA, reference to the FOIA EA is provided.

1. **DATE:** April 10, 1996.

2. **NAME OF APPLICANT/PETITIONER:** Refer to FOIA EA.

3. **ADDRESS:** Refer to FOIA EA.

4. **DESCRIPTION OF PROPOSED ACTION:**

   A. REQUESTED APPROVAL. The present request is for approval of a supplement to the original NDA for use of sertraline hydrochloride for the panic disorder indication. Mean dosage for this indication will be 100 mg (as sertraline) administered orally as tablets, once per day.

   B. NEED FOR THE ACTION. Clinical data indicate that sertraline hydrochloride is effective for the treatment of patients exhibiting symptoms of panic disorder. It is estimated that the total panic disorder patient population numbers about 1.5 million patients.

   C. PRODUCTION AND PROCESSING LOCATIONS AND ENVIRONMENTS. Sites identified in the FOIA EA will be used for the subject action.

   D. USE AND DISPOSAL LOCATIONS AND ENVIRONMENTS. Sites identified in the FOIA EA are applicable to the subject action. American REF-Fuel Company of Hempstead permits are now designated: Solid Waste Permit Number 1-2820-01727/00010-0, expiry 7/23/2000 and Air Pollution Control Permit Number 1-2820-01727/00001-0, expiry 8/96.

5. **IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION:**

   A. DRUG SUBSTANCE -- Refer to FOIA EA.

   B. DRUG PRODUCT -- Refer to FOIA EA. The recommended mean dosage for the panic disorder indication is 100 mg/day (as sertraline).

6. **INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:**

   A. MANUFACTURE -- Refer to FOIA EA. Applicable exposure and emissions requirements for the occupational, atmospheric, aquatic and terrestrial environments

and applicable permit/licence numbers, issuing authorities and expirations dates have been upgraded as presented in Appendix 5 (Revised).

B. USE. -- Refer to FOIA EA. The projected quantities of sertraline hydrochloride to be used in a mature U.S. market for the previously-approved and the subject-approval indications -- and the bases for these projections -- are provided in Confidential Appendix 5 (Revised). The incremental addition from the subject approval to the baseline usage of sertraline hydrochloride associated with the previously-approved indications is judged insignificant.

2. Usage Emissions -- Quantities and Concentrations. These have been revised to reflect the changes outlined in Confidential Appendix 5 (Revised). See (Confidential Appendix 8).

C. DISPOSAL. See FOIA EA.

7. FATE IN ENVIRONMENT VIA USE OF DRUG PRODUCT: Refer to FOIA EA.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES: The incremental addition from the subject approval to the baseline release of sertraline hydrochloride into the environment from use for the previously-approved indications is judged insignificant with regard to potential effects on environmental organisms, with margins of safety to test organisms remaining essentially unchanged.

9. USE OF RESOURCES AND ENERGY: Refer to FOIA EA.

10. MITIGATION MEASURES: Refer to FOIA EA.

11. ALTERNATIVES TO THE PROPOSED ACTION: Refer to FOIA EA.

12. PREPARERS: Refer to FOIA EA.

13. CERTIFICATION:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of Pfizer's knowledge.

Name: Irving M. Goldman, Ph.D

Title: Director
Environmental Sciences
Department
Developmental Research
Pfizer Central Research

Irving M. Goldman
Signature

April 10, 1996
Date

14. REFERENCES: Refer to FOIA EA.

15. APPENDICES: Refer to FOIA EA. A revised Appendix is attached:

Appendix 5 (Revised). Applicable Exposure and Emissions Requirements for the Occupational, Atmospheric, Aquatic and Terrestrial Environments. Applicable Permit/License Numbers, Issuing Authorities and Expiration Dates.

15A. CONFIDENTIAL APPENDICES: Refer to FOIA EA. Two Confidential Appendices to the subject EA are provided in a separate jacket. These are:

Confidential Appendix 5 (Revised). Projected Usage of Sertraline Hydrochloride in a Mature Market.

Confidential Appendix 8 (Revised). Usage Emissions -- Quantities and Concentrations

Appendix 5 (Revised)

Applicable Exposure and Emissions Requirements for the Occupational, Atmospheric, Aquatic and Terrestrial Environments

1. Occupational.- Workplace exposure will be in compliance with the following requirements:

   i. Groton, Barceloneta and Brooklyn facilities:
   - Permissible Exposure Limits according to 29 CFR 1910.100

   ii. Ringaskiddy facility:
   - Permissible Exposure Limits as defined by the Republic of Ireland National Health and Safety Authority

2. Atmospheric.- Emissions will be in compliance with the following requirements:

   i. Groton facility:
   - Federal Clean Air Act and Regulations
   - Connecticut General Statutes Title 22a, Chapter 446c, Air Pollution Control Laws
   - CT DEP Air Pollution Control Regulations, Title 22a, Chapter 174
   - Connecticut State Implementation Plan
   - Resource Conservation and Recovery Act
   - RCRA Regulations 40 CFR Parts 260-268
   - Connecticut General Statutes Title 22a, Chapter 446d (Connecticut Solid Waste Management Acts), and Title 22a, Chapter 445 (Connecticut Hazardous Waste Law)
   - Connecticut Hazardous Waste Management Regulations, Title 22a, Chapter 449

   ii. Barceloneta facility:
   - Federal Clean Air Act and Regulations
   - Puerto Rico State Implementation Plan
   - Resource Conservation and Recovery Act
   - RCRA Regulations 40 CFR Parts 260-268
   - Puerto Rico Public Law No. 9, Regulation for the Control of Hazardous and Non-Hazardous Waste, Part III, Section 302, and Part IV, Sections 402, 404 and 405

   iii. Brooklyn facility:
   - Federal Clean Air Act and Regulations
   - New York State Air Pollution Regulations, Title 6, Chapter III, Subchapter A, Parts 201 through 212 and Part 233

   iv. Ringaskiddy facility:
   - Requirements for Integrated Pollution Control License, EPA

3. Aqueous.- Emissions will be in compliance with the following requirements:

   i. Groton facility:
   - Federal Clean Water Act
   - 40 CFR Parts 124 and 125 (Federal Clean Water Regulations)
   - Connecticut General Statutes Title 22a, Chapter 446k, Water Pollution Control
   - Connecticut DEP Discharge Permit Regulations, Title 22a, Chapter 430

ii. Barceloneta facility:
- Federal Clean Water Act
- Federal Clean Water Regulations, 40 CFR Parts 124 and125
- Puerto Rico Water Pollution Control Law, Laws of Puerto Rico Annot., Title 24, Chapter 35
- Puerto Rico Water Quality Standards, Environmental Quality Board, Article 1-10

iii. Brooklyn facility:
- Federal Clean Water Act
- Federal Clean Water Regulations, 40 CFR Parts 124 and125
- New York City Charter, Section 1105, Administrative Code of New York City, Section 1403, Section 683e, Sections 687 and 689, New York City Bureau of Water Pollution Control
- New York City DEP Commissioner's Order and Directive for Effluent Pre-treatment, dated September 12, 1990

iv. Ringaskiddy facility:
- Requirements for Integrated Pollution Control License, EPA

4. Terrestrial.- Non-hazardous and hazardous waste emissions will be in compliance with the following requirements:

I. Groton facility:
- Resource Conservation and Recovery Act
- RCRA Regulations 40 CFR Parts 260-268
- Connecticut General Statutes Title 22a, Chapter 446d (Connecticut Solid Waste Management Acts), and Title 22a, Chapter 445 (Connecticut Hazardous Waste Law)
- Connecticut Solid Waste Management Regulations, Title 22a, Chapter 209
- Connecticut Hazardous Waste Management Regulations,Title 22a, Chapter 449

ii. Barceloneta facility:
- Resource Conservation and Recovery Act
- RCRA Regulations 40 CFR Parts 260-268
- Puerto Rico Public Law No. 9, Regulation for the Control of Hazardous and Non-Hazardous Waste, Part III, Section 302, and Part IV, Sections 402, 404 and 405

iii. Brooklyn facility:
- Resource Conservation and Recovery Act
- RCRA Regulations 40 CFR Parts 260-268
- New York Solid and Hazardous Waste Management Laws, New York Consolidated Laws Service; Environmental Conservation Law, Article 27
- New York Hazardous Waste Regulations, New York Compilation of Rules and Regulations, Title 6, Chapter 370, 371 and 372

iv. Ringaskiddy facility:
- Requirements for Integrated Pollution Control License, EPA

Appendix 5 (Revised) cont'd

Applicable Permit/License Numbers, Issuing Authorities and Expiration Dates

	Permit Designation	Issuing Authority	Expiration Date
Barceloneta, Puerto Rico.-			
Water	Facility Agreement	(1) PRASA (Puerto Rico Aqueduct and Sewer Authority) (2) AFICA (Puerto Rico Industrial, Medical, and Environmental Pollution Control Facilities and Financing Authority	Bonds mature August 1, 1998, but Entitlements do not expire.
Water	Pretreatment Permit GDA-92-202-038	PRASA	May 23, 1998
Air	Air Permit PFE 09-1393-0282-I-II-III-0	EQB	Effective July 7, 1993. (Continues in effect until issuance of Title V permit.)
Waste	RCRA Permit PRD 0903446909	US EPA	May, 1995 -- Renewal pending. Continues in effect until new permit issues.
Brooklyn, New York.-			
Water	Commissioner's Order/ Directive	NYC DEP	May 4, 2000
Air	PA530-93J	NYC DEP	Approval pending
	PA533-73Y	NYC DEP	May 11, 1997
	PA537-73N	NYC DEP	May 19, 1997
	PA237-92L	NYC DEP	May 12, 1996
	PA233-95H	NYC DEP	March 21, 1996. Continues in effect until new permit issues.
Groton, CT.-			
Water	NPDES Permit # CT0000957	CT DEP	July 30, 1996
Air	Permit to Operate #0081	CT DEP	Issued Dec. 14, 1995. No designated expiration date.
Air	RACT Order 8021	CT DEP	Issued Aug. 15, 1995. No designated expiration date.
Ringaskiddy, Ireland.-			
Air,Water, Waste	Integrated Pollution Control License #13	EPA	Issued May 18, 1995. No designated expiration date.