NDA 19-839/S-002

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

OCT 25 1996

Dear Dr. Longshore:

Please refer to your May 14, 1992, 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.

This supplemental application provides for the use of Zoloft to treat obsessive compulsive disorder (OCD).

We also refer to an Agency Approvable letter dated August 1, 1995, and we also acknowledge receipt of your additional communications dated August 11, 1995, October 4, 1995, December 7, 1995, February 23, 1996 and March 19, 1996, May 8, 1996, May 14, 1996, May 28, 1996, September 13, 1996, and September 27, 1996.

We have completed our review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that Zoloft is safe and effective for use as recommended in the version of labeling attached to this action letter. Accordingly, this supplemental application for Zoloft's use in OCD is approved effective on the date of this letter.

This letter 1) explicates the basis for our decision to approve your supplemental application for Zoloft's use in the treatment of OCD under the conditions of use described in the version of product labeling attached to this letter and 2) explains the reasoning underlying a number of other changes that we have made to Zoloft's product labeling that pertain to its use for all its approved indications.

Final Product Labeling

The product labeling attached to this approval letter provides 1) a new indication for Zoloft's use in the treatment of OCD, 2) new safety information pertinent to that indication, and 3) instructions for the dosing regimen recommended for this new use. In addition, so that Zoloft labeling will conform to current regulatory requirements, we have made a number of other changes, the more important of which include a Clinical Trials subsection describing the controlled clinical trials that are the source of the substantial evidence supporting Zoloft's use in both depression and OCD, a revised pregnancy category, and a description of the evidence that supports the conclusion that sertraline has little capacity to interfere with the clearance of drugs metabolized by CYP3A4.

We are mindful, given the extensive negotiations among our respective staffs, that the text of the labeling under which we have concluded that Zoloft may be marketed for use in OCD is not identical in every

respect to the draft version of labeling that you proposed. After reviewing the issues in dispute, which, incidentally, we believe are relatively minor ones, we concluded that further negotiation would be unlikely to resolves these differences, in large part because we concluded that the statements you sought either to include or exclude could be viewed as rendering the labeling false and misleading in some particular. Accordingly, as current agency policy allows, your supplemental application is approved for use under a version of labeling that we have concluded accurately and fairly summarizes the uses, risks of use and directions of use for Zoloft. In the sections that follow we explain how we arrived at our judgments on these points of disagreement.

Issue 1: Details of the Description of Clinical Trials supporting the efficacy of Zoloft (Clinical Trials Subsection of the Clinical Pharmacology section)

The labeling of Zoloft that is being approved to allow its use in OCD includes a Clinical Trials subsection that differs in limited ways from the version you sought. The differences involved the interpretation of the fixed dose studies and whether or not to provide information about the doses used in the flexible dose studies.

Interpretation of the fixed dose studies

Information about optimal dosing is best derived from adequate and well controlled fixed dose studies. Unfortunately, neither of the fixed dose studies you conducted, i.e., 1 for depression and 1 for OCD, provided useful information on the relationship between dose and response. In the depression trial, patients assigned to the highest dose group experienced a much higher rate of premature discontinuations than those assigned to lower doses of sertraline. As a consequence, the study could not fairly evaluate the effectiveness of the highest dose. In the OCD trial, response could not be regressed upon dose and accordingly, the trial must be viewed as a failed experiment, at least from the standpoint of it serving as a source of valid dose response information. In sum, neither study can be defended as a source of useful information about the presence and/or the lack of a dose response. We trust that this explains why we prefer the language adopted in the version of labeling under which you may market Zoloft for OCD.

Information about dose in the flexible titration studies

Prescribers do need to be informed, however, about the evidential basis for dosing recommendations provided for a drug. Given the failings of the fixed dose studies, we concluded that we are obliged to describe the doses of sertraline used in all clinical studies (both the fixed and flexible dose) that were able to distinguish sertraline from placebo.

We are mindful of your concern that mention of the mean doses in the flexible titration studies might be misconstrued as a recommendation to employ them. We believe this risk is remote because the Dosage and Administration section, ordinarily relied on by clinicians as a source of advice about dosing, recommends 50 mg as the starting dose for both indications, with further titration within a dose range of 50-200 mg/day being left up to the judgement of clinicians.

Incidentally, these points aside, it is common practice in recently approved psychotropic drug products to provide the mean dose information in describing flexible dose trials in the Clinical Trials subsection.

Issue 2: Dosage and Administration Section

You have made clear a preference for including, in this section, mention of the fact that a proportion (perhaps as many as 118 of the 325 randomized) of patients completing the double-blind placebo controlled OCD trials (trials 371/372) continued in treatment with apparent good results. Although we are aware that a greater proportion of sertraline than placebo randomized patients entered this extension, we have no basis to conclude that the status of the patients during the extension was in any way affected by the administration of sertraline. Accordingly, it would be misleading to provide information about this experience because it would allow prescribers to infer, falsely, that the drug had an effect which it had not been shown to have.

For the reasons enumerated, we have not adopted the labeling text that you requested.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING FOR APPROVED SUPPLEMENTAL NDA 19-839/S-002". Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated December 7, 1995. These commitments, and their associated schedules for completion, are listed below.

1.

2.

Protocols, data, and final reports should be submitted to IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, submit protocols, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly labeled "Phase 4 Commitments." In addition, we request that each annual report to this NDA include a section that summarizes the status of each Phase 4 commitment, identifying each submission and its related commitment. If you feel the situation has changed and the data a Phase 4 study was designed to provide

are no longer necessary, fully explain why you believe you should be released from the commitment. All annual reports to this NDA should include an update on Phase 4 studies until you are notified that we consider all commitments to be satisfactorily fulfilled or canceled.

As requested in our approvable letter dated August 1, 1995, please submit three copies of the 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

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,

10/25/96

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

ATTACHMENT

Memorandum

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

DATE: October 25, 1996

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

SUBJECT: Zoloft™ [sertraline hydrochloride] for OCD
NDA 19-839/S-002 Approval Action Memorandum

TO: File NDA 19-839

This memorandum documents for the administrative file the basis for my decision to approve NDA 19-839/ S-002 for Zoloft's use in OCD. The basis for my affirmative conclusions about sertraline's safety for use and effectiveness in use as a treatment for OCD are explicated in my 8/1/95 approvable action memorandum.

Post-approvable Action Issues and their Resolution:

The approvable action letter (issued 8/1/95) informed Pfizer Pharmaceuticals that final approval of the Zoloft OCD effectiveness supplement was conditioned upon the acceptability of their response to a number of requests enumerated in our letter.

In his comprehensive supervisory memorandum (9/30/96) recommending approval of the Zoloft OCD effectiveness supplement, Dr. Laughren reviews the regulatory issues pending at the time the approvable action was taken in regard to whether or not they have been satisfactorily resolved from the agency's perspective.

There are 3 issues concerning product labeling about which the sponsor and the Division review team have, despite extensive negotiations, failed to agree. In his memorandum, Dr. Laughren explicates the basis for these disagreements, and explains why he believes the Division Review Team's position on them should prevail.

I have discussed each of these issues in detail with Dr. Laughren, and I am persuaded that the Review Team's proposals for labeling are preferable (more accurate, less misleading, and/or better substantiated by the evidence) to the firm's.

For the record, I should also note that I am in full agreement with the manner in which the Review team and Pfizer have resolved all other issues[1] affecting the final approval of the supplement.

I note, in particular, that the evidence relied upon to support the text and placement of the sections of Zoloft product labeling about sertraline's lack of effect on the clearance of two drug products metabolized by CYP450 3A4 derives from reports made in other supplements and/or submissions[2] to the NDA.

I take note also of the fact that the firm has agreed, as requested, to make commitments to

Finally, I note that the set of reports ordinarily made by a sponsor following the receipt of an approvable action (i.e., Safety Update, archival literature review and summary of adverse foreign regulatory actions) have, upon review, been found to provide no new evidence that would cause the Division to revise and/or substantively modify its conclusion that Zoloft will be safe for use and effective in use as a treatment for OCD

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[1] A minor concern that I had about the possible misinterpretation of a comparison of suicide rates in adults and children offered in the medical officer's review has been satisfactorily clarified by Dr. Laughren in his memorandum to the file of October 25, 1996.

[2] The matter of 3A4 enzyme inhibition was not immediately critical to the OCD approvable action decision. For technical regulatory reasons, however, it had to be considered in the approvable action letter because a "changes being effected" labeling supplement bearing on this PK/safety issue was pending at the time that action was taken.

provided that Zoloft is marketed under the conditions of use described in the version of labeling developed by the Division. Mention of this linkage is made in the approval action letter which advises the sponsor that marketing of Zoloft under labeling other than that incorporated in the approval action letter would make the product misbranded and subject it to a new drug charge.

Approval in the face of unresolved disputes concerning drug product labeling:

Although the labeling under which a new drug is marketed is viewed as "belonging to" the drug's sponsor, the content of that labeling is ordinarily developed jointly by the agency's review team and the sponsor's representatives. Joint labeling development is the rule rather than the exception, not because FDA regulation requires it, but because experience has shown that joint development speeds the process of negotiation through which accurate and informative product labeling is ordinarily developed at the end of a review cycle.

There are occasions, however, when, despite extended negotiations, agreement on the precise wording of one or more sections of labeling cannot be reached. In such circumstances, the agency has two choices: 1) to disapprove the application on the grounds that product labeling is false or misleading, or 2) to approve the application, but under a version of labeling that the agency determines will allow the product to be marketed under conditions that satisfy the requirements of law. The latter choice, in my view, is invariably superior to the former.

I make note of this because the Division's Review Team and Pfizer's representatives, despite extensive efforts to resolve their differences, have failed to reach agreement on what I believe to be three relatively minor labeling issues. Two concern details about the text[3] best used to describe the clinical trials from which substantial evidence of sertraline's effectiveness have been adduced. The third concerns whether or not the firm, in the absence of evidence from valid clinical trials, may

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[3] presented in the Clinical Trials subsection of the Clinical Pharmacology Section

assert that sertraline, in extended use, has a sustained effect on OCD phenomena.

In my judgment, the Division Review Teams's proposed labeling is unquestionably more accurate and less subject to misleading interpretation than the firm's. Moreover, I find nothing in the labeling text advanced by the Division Review Team that promotes anything that is at odds with the facts or undermining of the product.

Accordingly, I have concluded that Pfizer's OCD supplement should be approved, but under the labeling that has been developed by the Division. If Pfizer finds this version of labeling unacceptable, they are not compelled to market Zoloft for OCD.

It is my understanding, in approving the supplement under these conditions, that the marketing of Zoloft under any labeling other than that attached to the approval action letter (with the obvious exception of currently approved product labeling) would be in violation of the requirements of the FD&C Act and would, therefore, be a basis for adverse regulatory action.

Conclusion and Action:

For the reasons explicated, I have determined that NDA 19-839/S002 may be approved under the conditions of use recommended in the version of labeling attached to the approval action letter that is issuing under my signature.

Paul Leber, M.D.
October 25, 1996

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: September 30, 1996

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

SUBJECT: Recommendation for Approval Action for Zoloft (sertraline) for Obsessive Compulsive Disorder (OCD)

TO: File NDA 19-839/S-002
[**Note**: This overview should be filed with the 12-7-95 response to the approvable letter.]

1.0 BACKGROUND

An approvable letter for this supplement was issued 8-1-95, and a response was submitted 12-7-95. Subsequent submissions critical to this approval recommendation were study reports for in vivo interaction studies of sertraline with carbamazepine (3-22-96) and terfenadine (8-13-96). All of the issues in our approvable letter have now been addressed, including our concern about the potential for sertraline to interact with certain substrates of the P450 enzyme 3A4 (see Biopharmaceutics below).

Through an exchange of faxes, we achieved agreement on most remaining labeling issues, however, we were unable to reach agreement on several clinical issues that are discussed later in more detail under 6.0 Labeling. Faxes from the Agency to Pfizer were sent 9-6-96 and 9-20-96, and faxes from Pfizer to the Agency were sent 9-13-96 and 9-27-96. The labeling attached to the approval letter represents labeling agreements achieved at a Team Leader level, along with proposed language in those clinical sections where agreement could not be reached.

2.0 CHEMISTRY

The environmental assessment issue raised in our 8-1-96 approvable letter has now been satisfactorily resolved.

3.0 PHARMACOLOGY

The sponsor has accepted our recommendation for a pregnancy category C.

4.0 BIOPHARMACEUTICS

The data supporting the "changes being effected" submitted in SLR-003 have been reviewed by the Division of Biopharmaceutics and this supplement was approved in an agency letter dated 9-14-95.

In vivo interaction studies of sertraline with carbamazepine and terfenadine, both 3A substrates, have demonstrated no effect of sertraline on the pharmacokinetics of these substances. In fact, the data were suggestive of slight induction by sertraline, resulting in a slight increase in the clearance of these substrates. Consequently, I don't see any need to ask for additional in vitro assays for other potentially important 3A substrates, e.g., astemizole, cisapride, etc. I believe the labeling proposed by Pfizer to address this issue in the 8-13-96 submission is adequate, and I have incorporated this language into the Precautions section of the final labeling proposal.

5.0 CLINICAL DATA

5.1 Efficacy Update

5.1 1 Age and Gender Analyses

In their 12-7-95 response to our approvable letter, the sponsor provided the results of age and gender analyses. These included individual analyses of studies 248, 272, and 546, as well as analyses of a pool of all three studies. Overall, the pattern of results was not suggestive of age or gender effects, and a statement to this effect will be included in labeling.

5.1.2

5.1.3 Pediatric OCD Studies

5.2 Safety Update

The sponsor's obsessive compulsive disorder final safety update (OCD-FSU) had a cutoff date of 6-30-95 and included as a subset all the data from the original OCD-NDA, for which the cutoff date was 4-17-91. For the FSU, the integrated database included only patients from completed studies, however, the serious adverse events (SAE) events listing included any SAEs from ongoing studies as well (same 6-30-95 cutoff date). A summary enumeration of the adult sertraline exposed OCD patients in the OCD development program follows:

	OCD-FSU	OCD-NDA
Completed Studies	627	290[1]
Ongoing Studies[2]	954	
Total	1581	

1 The 290 patients are included in the FSU total of 627
2 This is an estimate, since many patients are still unblinded

In addition to the adult patients, the FSU included pediatric OCD patients exposed to sertraline. A summary enumeration of the pediatric sertraline exposed OCD patients in the OCD development program follows:

	Ped-OCD
Completed Studies	153
Ongoing Studies[1]	67
Total	220

1 This is an estimate, since many patients are still unblinded

The sponsor's strategy in conducting the safety update was to compare the findings from the OCD-FSU total adult database with the original OCD-NDA database, and also to compare the OCD-FSU adult database with the pediatric OCD database.

For the adult databases, the sertraline exposure and demographics were comparable, as were the overall rates of discontinuation for adverse events. Overall, there were 57 patients with serious adverse events among the adult patients in the OCD-FSU, including 30 for sertraline, 11 for placebo, 8 for active control, and 8 unblinded. There were no deaths among these patients, several suicide attempts, and 1 seizure. The overall adverse event profiles for the FSU and NDA databases were the same, and were similar to the recognized profile for sertraline in depression. There were no obvious age or gender differences in adverse events. There were also no patterns of laboratory, VS, or ECG findings suggestive of any clinically important sertraline related effects.

For the pediatric patients, the average maximum sertraline dose was somewhat higher than in the adult FSU population (185 vs 148 mg/day). Sixteen of the pediatric patients experienced serious adverse events, all among sertraline patients. The adverse event profile in the pediatric OCD patients was similar to that seen in adults. The one difference worth noting was the finding of 3 seizures among the pediatric patients (3/220; 1.4%). That seizure rate compares with an estimated rate of 0.06% (1/1581) in the adult OCD population. However, the 3 pediatric patients with seizures were aged 14, 15, and 15, i.e., they might reasonably be grouped with the adults, yielding a seizure risk of 4/1800 (0.2%). It is also important to note that 2 of the three children with seizures likely had coexisting seizures disorders, and the third had a strong family history of seizure disorder. Nevertheless, this finding needs to be noted in labeling.

The safety update also included an update on spontaneous reports. There were 114 such reports in patients identified as being treated with sertraline for OCD. Of these, 11 were considered serious. These serious reports included a suicide, a seizure, and a patient having a hypomanic episode. Overall, there was no pattern of findings among these reports suggestive of a different profile of adverse events for sertraline in OCD patients compared to other patients treated with this drug.

Dr. James Knudsen concluded in his 3-28-96 review of this safety update that there were no findings that would preclude the approval of this supplement, and I agree.

6.0 LABELING

I examined the foreign labeling provided with the 12-7-95 response to our approvable letter, and my impression was that our labeling is generally more complete and stronger than foreign labeling.

As noted above, through an exchange of faxes, we were able to reach agreement on most remaining labeling concerns, but we were unable to reach agreement on the precise wording in two sections of the labeling:

Clinical Trials Subsection of Clinical Pharmacology

Inclusion of Information about Mean Dose Achieved in Flexible Dose Trials

Pfizer objected to the inclusion of data regarding the mean dose utilized in the flexible dosing design depression and OCD trials. They argued that patients in these trials may have been titrated more rapidly than necessary, thereby achieving higher doses than was necessary or would likely be utilized in usual clinical practice. They expressed concern that the inclusion of such information may mislead clinicians into believing that these doses are the optimally effective doses.

Ordinarily, information about optimal dosing would be expected to come from adequate and well controlled fixed dose studies. Unfortunately, neither of the fixed dose studies conducted, i.e., 1 for depression and 1 for OCD, is readily interpretable. Consequently, there is no information directly pertinent to the issue of optimal dose, for either indication. Nevertheless, truth in labeling requires that the studies supporting a claim be accurately described. There is no suggestion in our proposed descriptions that the mean doses were the optimal doses. Rather, the proposed trial summaries simply state the facts, both regarding mean dose in the flexible dose trials and the fact that the fixed dose studies did not provide clear advice about optimal dose. Moreover, the Dosage and Administration section, ordinarily relied on by clinicians as a source of advice about dosing, recommends 50 mg as the starting dose for both indications, with further titration within a dose range of 50-200 mg/day being left up to the judgement of clinicians.

On the basis of the above arguments, I have not deleted information about mean doses for the flexible dose depression and OCD trials.

Lack of Interpretability of Fixed Dose Depression Study

Pfizer objected to our proposed statement regarding the fixed dose depression study as not being readily interpretability due to high dropouts at the higher doses. They argued that this statement does not provide clear guidance to clinicians and is "potentially confusing, inaccurate, and misleading." Alternatively, they proposed a statement suggesting that "there was no clear indication of a dose response relationship for effectiveness." I disagree, again from the standpoints of truth in labeling and what useful information can be gleaned from a clinical trial. To state that there was no indication of a dose response relationship suggests that the data from the fixed dose study were interpretable, when they were not. Alternatively, I have proposed a revised statement to simply indicate that the study was not readily interpretable regarding dose response for efficacy, rather than getting into speculation about the reasons.

Dosage and Administration Section

Pfizer indicated that they feel it is important for them to be able to refer to the results of continuation trials for OCD suggesting no loss of benefit in responding patients for periods of up to 1 year. They argued that this is important information to provide to clinicians. I disagree with including these data, since, as noted previously, it is my view that studies of this design are basically flawed, i.e., the randomization is violated, since only responding patients are continued in the extension phase. Consequently, these studies cannot provide definitive data pertinent to the question of long-term efficacy, and to include these data undermines our current approach to labeling on this matter. While it is true that examples can be found for previously approved labeling where this principle is violated, labeling policy is constantly evolving, and our current approach is to not include such data. In any case, the labeling acknowledges the usual practice of continuing responding patients, so that including this information does not strengthen labeling in any way from the clinician's standpoint.

On the basis of the above arguments, I have not further modfied this section as proposed in Pfizer's September 27, 1996 fax.

7.0 WORLD LITERATURE

In their 12-7-95 response to our approvable letter, the sponsor provided details of their world wide literature update, including copies of all pertinent papers, and they warranted that no findings adversely affected their conclusions about the safety of sertraline in the treatment of OCD. Dr. Knudsen reviewed this material as well and he did not discover any previously unrecognized important safety concerns for this drug.

8.0 FOREIGN REGULATORY ACTIONS

According the the 12-7-95 response to our approvable letter, Zoloft has been approved for the treatment of OCD in 12 countries and applications are under review in 34 additional countries. The response included a listing of what other regulatory agencies considered interim deficiencies, none of which we were not also aware of.

9.0 APPROVAL LETTER

The approval letter acknowledges the areas of disagreement in the clinical sections of labeling and provides discussion of why we have not agreed to Pfizer's proposed changes in those sections.

10.0 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 OCD. I recommend that we issue the attached approval letter with our proposal for final labeling.

cc:
Orig NDA 19-839/S-002
HFD-120/Div File
HFD-120/TLaughren/PLeber/AMoshclder/HLee/JKnudsen/PDavid

DOC: MEMZLOCD.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: October 25, 1996

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

SUBJECT: Comment on data in the OCD database pertinent to the emergence of suicidal ideation, gestures, and attempts in association with sertraline use

TO: File NDA 19-839/S-002
[**Note:** This overview should be filed with the 12-7-95 response to the approvable letter.]

A concern about the possibility of a signal of emergent suicidality (suicide attempts, gestures, or ideation) associated with sertraline use in pediatric patients was raised in the 3-28-96 review by Dr. James Knudsen. In his review, Dr. Knudsen reported a crude incidence of suicidality for adults taking sertraline of 9/1581 (0.6%) compared to 1/426 (0.2%) for placebo patients. The comparable crude incidence data for pediatric patients were 6/220 (3.0%) for sertraline and 0/95 for placebo. There were no suicides, and only 2 attempts among adults and 1 among pediatric patients. Dr. Knudsen provided person-time data only for the sertraline exposed patients, yielding adjusted estimates of 0.035/PEY for adults and 0.25/PEY for pediatric patients. He commented on the 7-fold greater incidence of suicidality in children taking sertraline compared to adults taking sertraline, but concluded that this finding may have been a result of a higher incidence of comorbid depression in the pediatric patients.

I agree that the adult and pediatric populations may have differed regarding comorbid depression, and that is one reason why the comparison of incidence data for sertraline exposed patients in these 2 databases may not have been appropriate. Four pediatric studies contributed patients to the pediatric database, two of which permitted the entry of patients with either OCD or major depression. In fact, 4 of the 6 pediatric subjects having suicidality had diagnoses of major depression. OCD was required

for all the adult studies, and my impression is that there was minimal comorbid major depression. Thus, it is not reasonable, in my view, to compare adults to children on the incidence of suicidality in sertraline exposed patients. It would have been more informative to compare the risk ratios, i.e., drug to placebo, after adjusting for persone-time, within each of the adult and pediatric strata. Unfortunately, person-time data were provided only for sertraline exposed subjects, and not placebo. In fact, 3 of the 4 pediatric studies were open label, and 2 of these were long-term, thus drug exposed patients had a much greater opportunity for having events than placebo exposed patients.

In summary, I don't consider these data to represent a signal of risk for suicidality for either adults or children. Supplements are planned for both depression and OCD in pediatric patients, and when we have more complete data, including HAMD data, we can look more critically at this issue, using the now standard approach of comparing the proportions of drug and placebo exposed patients who show worsening on Item 3 (suicidality item) of the HAMD during treatment. At the present time, current labeling simply notes that Zoloft has not been adequately evaluated for safety and effectiveness in pediatric patients.

cc:
Orig NDA 19-839/S-00[illegible]
HFD-120/Div File
HFD-120/TLaughren/PLeber/AMosholder/PDavid

DOC: MEMZLOCD.AP2

NDA 19-839/S-002

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

AUG 1 - 1995

Dear Dr. Longshore:

Please refer to your supplemental New Drug Application dated May 14, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act providing for the use of Zoloft® (sertraline Hydrochloride) 50 and 100 mg tablets in obsessive compulsive disorder (OCD).

We acknowledge receipt of your amendments dated:

May 14, 1992	September 3, 1992	December 21, 1993
January 13, 1994	March 10, 1994	April 13, 1994
June 29, 1994	July 15, 1994	July 26, 1994
August 17, 1994	September 21, 1994	September 28, 1994
October 27, 1994	November 23, 1994	February 14, 1995
April 3, 1995	May 10, 1995	

We have completed the review of this supplemental application 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 issues:

CLINICAL

1. Labeling

Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Zoloft®. Our proposal is based on your labeling proposal submitted in a February 14, 1995 amendment.

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.

Please note that SLR-003, submitted under "Changes Being Effected", may not be acted upon at this time since the Division of Biopharmaceutics has not completed its review of the hepatic impairment study nor the drug interaction studies conducted by Pfizer. We have not highlighted, in the attached labeling, revisions proposed in pending labeling supplement S-003 nor requests which the Division has made in previous

correspondences. It is our intention that all of these pending revisions can be resolved as part of a final action on this supplement.

2. Safety Update

Our review of the safety of sertraline in the treatment of OCD was based on data accumulated through 6-30-94 for the US integrated database. You will need to submit a final safety update including safety data accumulated since this cutoff date. It is our understanding that the number of patients exposed to sertraline in your OCD development program at present may be approximately three-fold that in the original integrated database. Thus, the final safety update will need to duplicate your original integrated safety summary, for the greatly expanded database.

This expanded integrated safety summary should also update on spontaneous reports for Zoloft worldwide. We note that in your earlier safety submission, you did not segregrate and report separately on reports in patients being treated for OCD. We ask that, as part of this safety update, you provide such a report, for the entire postmarketing experience for Zoloft thus far.

In addition, we ask that you conduct analyses to explore for age and gender effects on adverse event incidence.

3. World Literature Update

Prior to the approval of sertraline for OCD we require an updated report on the world's archival literature pertaining to the safety of sertraline in this population. 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 conclusions about the safety of sertraline 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 sertraline in the treatment of OCD, 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 sertraline is approved for use in OCD in any countries, we ask that you provide us current labeling for sertraline in those countries, along with English translations when needed.

5. Efficacy Data

Age and Gender Analyses

We ask that you perform and provide to us the results of exploratory analyses of the efficacy data for interactions on the basis of age and gender.

Absence of Relapse Prevention Data

One of the weaknesses of your development program for the OCD indication was the absence of adequate relapse prevention data. Such data are needed to assist clinicians in managing chronic conditions such as OCD. In the absence of adequate data bearing on this question, we have taken the same approach for labeling that we have with the other drugs approved for this indication, i.e., acknowledgement of the absence of data, along with a suggestion that it would not be unreasonable to continue responding patients beyond the acute treatment phase.
application, we ask that you commit

6. Pediatric OCD Studies

Another weakness in your development program for this indication was the absence of safety and efficacy data for children and adolescents. This is regrettable because of the very early age of onset for this disorder (peak age of onset is 9 for males and 12 for females). In fact, it is likely that many children and adolescents are already being treated with sertraline for OCD, and it would be expected that such treatment would increase with the approval of this new indication. Although there is no reason to anticipate that age will affect the efficacy and safety of Zoloft®, empirical confirmation of this is desirable.

PHARMACOLOGY

As with other serotonin reuptake inhibitors, we find it necessary to change the pregnancy category of Zoloft® from B to C. Because of the findings of decreased fertility, decreased pup birth weights, increased numbers of stillbirths and increased pup deaths in rats, Zoloft® must be labeled pregnancy category C. Please refer to 21 CFR 201.57(f)(6)(i)(b) wherein it states that pregnancy category B is for drugs in which "reproduction studies ... have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug)".

ENVIRONMENTAL ASSESSMENT

We note that your response dated May 10, 1995, to an Agency facsimile transmission dated February 13, 1995, providing for the Environmental Assessment deficiencies was not complete. Reference is also made to additional EA deficiencies that were

communicated to Dr. Margaret Blumfield of your office by Mr. Paul David of this Agency on June 8, 1995. Please note that a satisfactory environmental assessment, along with an FOI-releasable summary, will be required prior to approving this application.

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-240, 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 on your part, the FDA may proceed to withdraw the application.

In accordance with the policy described in 21 CFR 314.102(d) and in the Center for Drug Evaluation and Research Staff Manual Guide CDB 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, or should any questions arise concerning this NDA, please contact Mr. Paul David, Regulatory Management Officer, at (301) 594-2777.

This drug may not be legally marketed for the indication provided by this application until you have been notified in writing that the application is approved.

Sincerely yours,

8/1/95

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

ATTACHMENT

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

DATE: August 1, 1995

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

SUBJECT: Zoloft™ [sertraline hydrochloride] for OCD
NDA 19-839/S-002 Approvable Action Memorandum

TO: File NDA 19-839

This memorandum documents for the administrative file the basis for my decision, as Division Director, to issue an approvable action letter on NDA 19-839/ S-002 for Zoloft's use in OCD.

The action is taken both upon the recommendation of the agency review team, headed by Dr. Laughren (see his memorandum of 6/19/95), and my own assessment of the individual review documents and draft labeling presented in the approvable action package.

The later materials, in my judgment, reasonably support the conclusion that Zoloft, initially approved for domestic marketing in December of 1991 as an antidepressant, will be both safe for use and effective in use for the management of OCD under the conditions of use recommended in the draft labeling prepared by the Division.

Effectiveness:

The supplement contains results of 4 adequate and well controlled clinical investigations. Two of the studies, 371/372 and 546 were found upon review (statistical and clinical) to provide substantial evidence of sertraline's effectiveness as a treatment for OCD. A third study, 237/248, although providing results directionally favorable to sertraline, can only be deemed supportive of the latter's effectiveness. The 4th study, 495, however, failed to detect a beneficial effect of sertreline; importantly, the lack of response cannot be attributable to the sample of OCD patients studied because the study did detect statistically significant favorable response among patients assigned to clomipramine as compared to those assigned to

placebo[1].

Only one study, 371/372 was by virtue of its fixed graded dose design capable of determining whether or not a relationship exists between sertraline dose and sertraline response. Although, overall, 371/372, documents that sertraline is superior to placebo, it provides no evidence of a monotonic relationship between assigned dose and response.

As noted by Dr. Laughren, the clinical development program for the study of Zoloft in OCD is not as extensive nor robust (duration of trials, evaluation in children) as one might desire. These limitations, however, are not an adequate regulatory basis upon which to refuse to approve the supplement.

Safety

Zoloft has been marketed for about 3.5 years at doses identical to those that will be recommended when it is approved for use in OCD. Nothing that has been reported from post-marketing surveillance during this interval raises, in my judgment at least, a substantive concern about the product's safety for use. Findings among OCD patients exposed to sertraline in the course of the conduct of OCD effectiveness trials are basically identical to those reported during depression studies and, therefore, the current experience in OCD provides no findings of concern[2].

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[1] In other words, although the study had assay sensitivity, it failed to detect a beneficial effect of sertraline. This finding, incidentally, is consistent with an impression among clinicians expert in the management of OCD that drugs that selectively inhibit serotonin re-uptake [SSRI's], although effective in OCD , are not as potent as clomipramine, the drug product first approved domestically as a specific treatment for OCD. This clinical impression is supported by a recently published meta-analysis of realized effect sizes of several OCD treatments that have been published in the archival literature. (Stein et al. International Clin. Psychopharm 10:11-18 (1995)

[2] Dr. Laughren does take note that a crude risk of 0.3% of seizure was detected among OCD users and that this incidence differs from the zero incidence observed among 2700 patients in the depression data base. In my view, the incidence reported is within the range seen with SSRI's in other application databases. Moreover, a rate of 0.3% may well fall within the historical spontaneous incidence range. Accordingly, I do not find the issue of seizure a matter of concern.

Labeling

The labeling proposed by Dr. Laughren's group is acceptable.

Conclusion:

Based on the information provided in the review package, the application is approvable. I have directed that some minor changes be made in the wording of the approvable action letter, but, save these changes, the letter will be issued basically as drafted.

Paul Leber, M.D.
August 1, 1995

David

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: June 19, 1995

TPL

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

SUBJECT: Recommendation for Approvable Action for Zoloft (sertraline) for Obsessive Compulsive Disorder (OCD)

TO: File NDA 19-839/S-002
[Note: This overview should be filed with the 5-14-92 original submission.]

1.0 BACKGROUND

Zoloft (sertraline) is a selective serotonin reuptake inhibitor that was approved for the treatment of depression in December, 1991 (NDA 19-839). Supplement S-002 includes data from clinical trials supporting the use of sertraline in the treatment of obsessive compulsive disorder (OCD).

Since the proposal is to use the currently marketed sertraline formulations for this new indication, there was no need for substantial chemistry, pharmacology, or biopharmaceutics reviews of this supplement. Consequently, the focus was on clinical data. The primary review of the efficacy data was done by Robert Hamer, Ph.D., a statistician who is a consultant to the Division of Biometrics. I served as clinical contact for Dr. Hamer during the process of his review, and my views on the efficacy data are contained in this memo. The safety data for this NDA were reviewed by James Knudsen, M.D.

The original supplement for OCD was submitted 5-14-92. Major amendments containing full study reports for Studies 546 and 495 were submitted 1-13-94 and 7-26-94, respectively.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

There is one chemistry issue requiring resolution:

Environmental Assessment: An environmenatal assessment package and review were needed, since the original NDA for Zoloft was approved before this requirement was introduced. The deficiencies were originally conveyed in mid Feb, 95, and the company has partially responded. They are aware of any remaining deficiencies, and we will note this in our approvable letter.

3.0 PHARMACOLOGY

The only pharmacological/toxicology issue requiring resolution was the pregnancy category. Current labeling provides for category B. However, in keeping with current Division policy regarding recently approved antidepressants, we have changed the category to C. We have explained this change in the approvable letter and advised the sponsor regarding what would be needed to achieve a category B status again.

4.0 BIOPHARMACEUTICS

Several labeling changes needing biopharmaceutics review were made under "changes being effected." We still need to obtain Division of Biopharmaceutics comments on these changes before final approval, and we will note this in the approvable letter.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Studies Pertinent to Efficacy

Our review of the effectiveness of Zoloft in the treatment of OCD focused on 4 placebo-controlled studies for which we had full study reports (i.e., 237/238, 371/372, 546, and 495). Study 495 comparing sertraline, clomipramine, and placebo was considered a failed study by the biometrics reviewer, and consequently, he did not review it. However, upon further examination, I considered this study to be positive for clomipramine, and I have included data and comments for this study.

5.1.1.1 Study 237/248

This was a randomized, 6-center, double-blind, parallel group, 8-week, dose-titration study comparing sertraline (up to 200 mg/day during the first 2 weeks, qd schedule) and placebo for the treatment of OCD in adult outpatients meeting DSMIII criteria for

OCD. Patients were required to have a HAMD-24 total score less than 15 and a score of less than 2 on the depression item.

Patients were rated at baseline and the ends of weeks 1, 2, 4, 6, and 8 on the following: YBOCS (range: 0-40), NIMH-OC (range: 1-15), CGI [range: 1-7, for both improvement (I) and severity (S) scales], Maudsley Obsessive Compulsive Inventory (MOC) [range: 0-30], and the HAMD-24 (range: 0-73). The YBOCS total score was identified as the primary outcome variable. I focused on change from baseline for the following 3 variables: YBOCS total score; NIMH-OC; CGI-S. [It should be noted that data were collected through week 10, however, patients were supposed to be tapered to 0 dose between weeks 8 and 10, so I didn't include data beyond week 8.]

Patients were predominantly male (approximately 85%), virtually all Caucasian, and the mean age was mid-30s. The treatment groups were comparable at baseline on the demographic and the key efficacy variables. The mean sertraline dose for completers to week 8 was 186 mg/day.

Study Results

The intent-to-treat dataset was as follows: Sertraline (43), Placebo (44).

Completion rates to 8 weeks were as follows:

Sertraline	40/43 (93%)
Placebo	36/44 (82%)

The following results focus on change from baseline as the dependent variable. ANOVA was utilized, with the independent variables being fixed effects for site, treatment, and site-by-treatment interaction. Baseline was used as a covariate only for CGI-S.

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Sertraline vs Placebo) in Study 237/248					
Key Outcome Variables	Week[2] 1	2	4	6	8
YBOCS Total Score					
LOCF	-	-	*	t	*
OC	-	-	*	t	t
NIMH OC Score					
LOCF	-	-	t	*	*
OC	-	-	t	*	t
CGI Severity					
LOCF	-	-	*	t	*
OC	-	-	*	-	-

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$
2 End of weeks 1, 2, 4, 6, and 8

Size of Treatment Effect in Study 237/248			
YBOCS Total Score			
Group	Baseline[1]	BL - Wk 8[2]	Difference[3]
Placebo	22.6	- 1.5	
Sertraline	23.4	- 3.8	2.3
NIMH-OC Total Score			
Group	Baseline[1]	BL - Wk 8[2]	Difference[3]
Placebo	9.3	- 0.6	
Sertraline	9.8	- 1.5	0.9
CGI Severity Score			
Group	Baseline[1]	BL - Wk 8[2]	Difference[3]
Placebo	4.7	- 0.2	
Sertraline	4.9	- 0.6	0.4

1 Mean score at baseline
2 Change from baseline to week 8 (LOCF)
3 Difference in change from baseline to week 8 endpoint (LOCF) between sertraline and placebo

Impression: Although these results are suggestive of a positive effect, they are not consistently positive and I agree with Dr. Hamer that this study can be considered at most supportive. The effect sizes were similar to those observed in the later (positive studies), and this marginal outcome may be the result of inadequate power. It should be noted that Dr. Hamer performed a post hoc power analysis which estimated a power of less than 50% to detect the observed differences.

5.1.1.2 Study 371/372

This was a randomized, 11-center, double-blind, parallel group, 12-week, fixed-dose study comparing sertraline at 3 fixed doses (50 mg, 100 mg, and 200 mg/day; titration up to fixed dose over 2 weeks; qd schedule) and placebo for the treatment of OCD in adult outpatients meeting DSMIIIR criteria for OCD. Patients were required to have a HAMD-24 total score less than 17.

Patients were rated at baseline and the ends of weeks 1, 2, 4, 6, 8, 10, and 12 on the following: YBOCS, NIMH-OC, CGI, MOC, and the HAMD-24. The YBOCS total score was identified as the primary outcome variable. I focused on change from baseline for the following 3 variables: YBOCS total score; NIMH-OC; CGI-S.

Patients were slightly greater male (approximately 60%), approximately 98% Caucasian, and the mean age was about 40. The treatment groups were comparable at baseline on the demographic and the key efficacy variables.

Study Results

The intent-to-treat dataset was as follows:

Sertraline 50 mg/day	(79)
Sertraline 100 mg/day	(81)
Sertraline 200 mg/day	(80)
Placebo	(84)

Completion rates to 12 weeks were as follows:

Sertraline 50 mg/day	(85%)
Sertraline 100 mg/day	(74%)
Sertraline 200 mg/day	(79%)
Placebo	(73%)

The following results focus on change from baseline as the dependent variable. ANCOVA was utilized, with the independent variables being fixed effects for site and treatment. They tested for site-by-treatment interaction, and finding no effect, excluded this term from the model. Baseline was used as a covariate for all 3 key outcome variables.

Summary of Significance Levels[1] for Pairwise Comparisons (Sertraline vs Placebo) in Study 371/372																			
Key Outcome Variables	Sertraline Dose Groups																		
	50 mg							100 mg							200 mg				
	Week[2]							Week							Week				
	1	2	4	6	8	10	12	1	2	4	6	8	10	12	1	2	4	6	8	10	12
YBOCS Total																					
LOCF	-	*	*	*	*	*	*	-	-	t	*	-	-	-	-	-	*	*	*	*	*
OC	-	*	*	*	t	*	-	-	-	-	*	-	-	-	-	-	*	*	*	*	*
NIMH-OC Total																					
LOCF	-	-	*	*	*	*	*	-	-	*	*	t	*	*	-	-	*	*	*	*	*
OC	-	-	*	*	*	t	-	-	-	*	*	-	-	t	-	-	t	*	*	*	*
CGI Severity																					
LOCF	-	-	*	*	*	*	*	-	-	*	*	-	-	-	-	-	-	*	*	*	*
OC	-	-	*	*	*	*	t	-	-	-	*	t	t	-	-	-	-	*	t	t	-

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 1, 2, 4, 6, 8, 10, and 12

Size of Treatment Effect in Study 371/372			
YBOCS Total Score			
Group	Baseline[1]	BL - Wk 12[2]	Difference[3]
Placebo	23.4	- 3.4	
Sert. 50 mg	23.2	- 6.0	2.6
Sert. 100 mg	24.6	- 4.5	1.1
Sert. 200 mg	23.5	- 6.2	2.8
NIMH-OC Total Score			
Group	Baseline[1]	BL - Wk 12[2]	Difference[3]
Placebo	9.2	- 1.0	
Sert. 50 mg	9.2	- 1.8	0.8
Sert. 100 mg	9.7	- 1.7	0.7
Sert. 200 mg	9.0	- 1.9	0.9
CGI Severity Score			
Group	Baseline[1]	BL - Wk 12[2]	Difference[3]
Placebo	4.7	- 0.5	
Sert. 50 mg	4.7	- 0.9	0.4
Sert. 100 mg	4.9	- 0.6	0.1
Sert. 200 mg	4.6	- 0.8	0.3

1 Mean score at baseline
2 Change from baseline to week 12 (LOCF)
3 Difference in change from baseline to week 12 endpoint (LOCF) between sertraline and placebo

Impression: This study is solidly positive for both the 50 and 200 mg/day doses, but curiously negative for the 100 mg/day group, at least on two key variables (YBOCS and CGI Severity). This study was positive on the NIMH-OC score in the LOCF analysis, but not in the OC analysis, perhaps due to the somewhat higher dropout rate in this group. Dr. Hamer found this lack of dose response troubling, but nevertheless considered this a positive study overall. Given the overall consistency of the results over time and type of analysis for the 50 and 200 mg/day groups, I agree that this should be considered a positive study. However, it is difficult to recommend dosing on the basis of this study.

5.1.1.3 Study 546

This was a randomized, 10-center, double-blind, parallel group, 12-week, dose-titration study comparing sertraline (up to 200 mg/day, qd schedule) and placebo for the treatment of OCD in adult outpatients meeting DSMIIIR criteria for OCD. Patients were required to have a HAMD-24 total score less than 15 and a score of less than 2 on the depression item. Dose titration was very gradual, with the initial dose of 50 mg/day being maintained for 3 weeks. Titration above 50 mg was in 50 mg/day increments at intervals of at least 1 week.

Patients were rated at baseline and the ends of weeks 1, 2, 3, 4, 6, 8, 10, and 12 on the following: YBOCS, NIMH-OC, CGI, and the HAMD-24. The YBOCS total score was identified as the primary outcome variable. I focused on change from baseline for the following 3 variables: YBOCS total score; NIMH-OC; CGI-S.

Patients were slightly great male (approximately 57%), approximately 96% Caucasian, and the mean age was mid-30s. The treatment groups were comparable at baseline on the demographic and the key efficacy variables. The mean sertraline dose for completers at week 12 was 185 mg/day.

Study Results

The intent-to-treat dataset was as follows: Sertraline (85), Placebo (79).

Completion rates to 8 weeks were as follows:

Sertraline	61/85 (72%)
Placebo	56/79 (70%)

The following results focus on change from baseline as the dependent variable. ANCOVA was utilized, with the independent variables being fixed effects for site, treatment, and site-by-treatment interaction. Baseline was used as a covariate for all 3 key outcome variables.

Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons (Sertraline vs Placebo) in Study 546								
Key Outcome Variables	Week[2] 1	2	3	4	6	8	10	12
YBOCS Total Score								
LOCF	-	-	*	-	t	*	*	*
OC	-	-	*	-	*	*	*	*
NIMH OC Score								
LOCF	-	-	-	-	-	*	*	t
OC	-	-	-	-	*	*	*	*
CGI Severity								
LOCF	-	-	-	-	-	t	t	-
OC	-	-	-	-	-	*	*	*

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$
2 End of weeks 1, 2, 3, 4, 6, 8, 10 and 12

Size of Treatment Effect in Study 546			
YBOCS Total Score			
Group	Baseline[1]	BL - Wk 12[2]	Difference[3]
Placebo	25.0	- 3.6	
Sertraline	25.2	- 6.5	2.9
NIMH-OC Total Score			
Group	Baseline[1]	BL - Wk 12[2]	Difference[3]
Placebo	9.1	- 1.2	
Sertraline	9.0	- 1.8	0.6
CGI Severity Score			
Group	Baseline[1]	BL - Wk 12[2]	Difference[3]
Placebo	4.7	- 0.5	
Sertraline	4.6	- 0.8	0.3

1 Mean score at baseline
2 Change from baseline to week 12 (LOCF)
3 Difference in change from baseline to week 12 endpoint (LOCF) between sertraline and placebo

Impression: Although it took a longer time to see an effect, likely due to the fairly slow titration, the results for this study were quite consistently positive for both the YBOCS and NIMH-OC scales, and less so for the CGI Severity scale. Overall, I agree with Dr. Hamer that this can be considered a positive study.

5.1.1.4 Study 495

This was a randomized, 17-center, double-blind, parallel group, 16-week, dose-titration study comparing sertraline (up to 200 mg/day, qd schedule)clomipramine (up to 250 mg/day, bid schedule), and placebo for the treatment of OCD in adult outpatients meeting DSMIIIR criteria for OCD. Patients were required to have a HAMD-24 total score less than 17 and a score of less than 2 on the depression item. Dose titration for sertraline involved an initial 50 mg dose, an increase to 100 mg after 3 days, and then increased of 50 mg/week, up to a 200 mg/day maximum, depending on response and tolerance. Dose titration for clomipramine involved an initial 25 mg, with increases of 25 mg/day every 3-4 days, up to maximum of 250 mg/day, depending on response and tolerance.

Patients were rated at baseline and the ends of weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16 on the following: YBOCS, NIMH-OC, and CGI. The YBOCS total score was identified as the primary outcome variable. I focused on change from baseline for the following 3 variables: YBOCS total score; NIMH-OC; CGI-S.

Patients were approximately half male (42-53%), approximately 89% Caucasian, and the mean age was mid-30s. The treatment groups were comparable at baseline on the demographic and the key efficacy variables. The mean sertraline dose for completers at week 16 was 151 mg/day, and the mean clomipramine dose for completers at week 16 was 201 mg/day.

Study Results

The intent-to-treat dataset was as follows:

Sertraline	(83)
Clomipramine	(83)
Placebo	(87)

Completion rates to 16 weeks were as follows:

Sertraline	48/83 (58%)
Clomipramine	40/83 (48%)
Placebo	58/87 (67%)

The following results focus on change from baseline as the dependent variable. ANCOVA was utilized, with the independent variables being fixed effects for site, treatment, and site-by-treatment interaction. Baseline was used as a covariate for all 3 key outcome variables.

Summary of Significance Levels[1] for Pairwise Comparisons (Sertraline and Clomipramine vs Placebo) in Study 495																	
Key Outcome Variables	Sertraline vs Pbo									Clomipramine vs Pbo							
	Week[2]									Week							
	1	2	4	6	8	10	12	14	16	1	2	4	6	8	10	12	14	16
YBOCS Total																		
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	*	*	*	*	*
OC	-	-	-	-	-	-	-	-	-	-	-	-	*	*	*	*	*	*
NIMH-OC Total																		
LOCF	-	-	-	-	-	-	-	-	-	-	-	t	*	t	*	*	*	*
OC	-	-	-	-	-	-	-	-	-	-	*	*	*	*	*	*	*	*
CGI Severity																		
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	t	-	*	*	t	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	*	t	*	*	t	t

1 * = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16

Size of Treatment Effect in Study 495			
YBOCS Total Score			
Group	Baseline[1]	BL - Wk 16[2]	Difference[3]
Placebo	25.7	- 5.0	
Sertraline	25.6	- 5.4	0.4
Clomipramine	25.4	- 7.3	2.3
NIMH-OC Total Score			
Group	Baseline[1]	BL - Wk 10[2]	Difference[3]
Placebo	9.1	- 1.4	
Sertraline	9.3	- 1.6	0.2
Clomipramine	9.2	- 2.2	0.8
CGI Severity Score			
Group	Baseline[1]	BL - Wk 10[2]	Difference[3]
Placebo	4.7	- 0.7	
Sertraline	4.6	- 0.6	+ 0.1
Clomipramine	4.8	- 0.9	0.2

1 Mean score at baseline
2 Change from baseline to week 16 (LOCF)
3 Difference in change from baseline to week 16 endpoint (LOCF) between sertraline and placebo

Impression: I consider this to be a consistently positive study for clomipramine, for both LOCF and OC analyses, despite substantial attrition by 16 weeks, but a uniformly negative study for sertraline.

5.1.2 Additional Comments on Efficacy Data

Evidence Bearing on the Question of Dose/Response for Efficacy

Only one of the four placebo-controlled trials in the OCD development program involved comparisons of different fixed doses of sertraline, i.e., 371/372. As noted, this study was positive for both the 50 and 200 mg/day dose groups, but negative for the 100 mg/day group, at least for the YBOCS and CGI Severity. The other positive study, i.e., 546, involved the titration of patients in a dose range of 50-200 mg/day. Thus, the most that it is reasonable to recommend on the basis of these studies is to initiate treatment at 50 mg/day, and advance doses for

nonresponding patients up to a maximum dose of 200 mg/day, as is recommended for sertraline in the treatment of depression. We will ask the sponsor to commit to a more adequate evaluation of dose response in phase 4.

Clinical Predictors of Response

I am not aware of the sponsor having done any exploratory analyses of the effectiveness data to search for predictors of response, in particular on the basis of gender or age. We will ask for such analyses in the approvable letter.

Size of Treatment Effect

An approach to estimating treatment effect size is to examine the differences between sertraline and placebo on mean change from baseline for the key effectiveness measures in the 4 studies in this development program, as follows:

Size of Treatment Effect in Four OCD Studies (Mean Change from Baseline for Sertraline and Placebo, and Difference between Sertraline and Placebo, for Key Efficacy Variables (LOCF at Endpoint[1])			
Study 237/248			
Variables	Sertraline	Placebo	Difference
YBOCS	- 3.8	- 1.5	- 2.3
NIMH-OC	- 1.5	- 0.6	- 0.9
CGI Severity	- 0.6	- 0.2	- 0.4
Study 371/372			
Variables	Sertraline[2]	Placebo	Difference
YBOCS	- 6.2	- 3.4	- 2.8
NIMH-OC	- 1.9	- 1.0	- 0.9
CGI Severity	- 0.8	- 0.5	- 0.3
Study 546			
Variables	Sertraline	Placebo	Difference
YBOCS	- 6.5	- 3.6	- 2.9
NIMH-OC	- 1.8	- 1.2	- 0.6
CGI Severity	- 0.8	- 0.5	- 0.3
Study 495			
Variables	Sertraline	Placebo	Difference
YBOCS	- 5.4	- 5.0	- 0.4
NIMH-OC	- 1.6	- 1.4	- 0.2
CGI Severity	- 0.6	- 0.7	+ 0.1

1 Endpoint in weeks is 8 for 237/248, 12 for 371/372 and 546, and 16 for 495

2 Sertraline 200 mg/day

Treatment effect size as measured by difference between sertraline and placebo in change from baseline in YBOCS total score ranged from 2-3 units for 3 of the 4 sertraline studies, a finding almost identical to that seen for fluvoxamine, the most recently approved drug for OCD. For the fourth study, 495, the placebo effect was so large that the sertraline effect (-5.4) was not sufficient to be statistically significantly different from placebo, although

clomipramine in that same study had a sufficiently large effect to beat placebo. The sertraline effect seen in this program was also reasonably consistent with that seen for fluoxetine, the other SSRI approved for OCD. As noted in a recent meta-analysis of SSRI and clomipramine studies in OCD, the SSRI effect does not appear to be as robust as that seen with clomipramine (Greist, et al, Arch Gen Psychiatry, vol 52(1), pp. 53-60, 1995). Nevertheless, this effect for sertraline is sufficient in my view to justify the approval of this product for the treatment of OCD.

Duration of Treatment

The only data in the development program pertinent to long-term effectiveness came from study 371/372, which provided for a 40-week double-blind extension for responders on sertraline or placebo in the short-term phase. 118 patients (out of the originally randomized intent-to-treat sample of 325 patients) entered into this extender phase, including 40% of sertraline patients and 22% of placebo patients. We have not considered such extensions adequate substitutes for well-designed relapse prevention trials, and consequently, we did not review the data from this phase of 371/372. We have deleted the sponsor's proposed labeling statements suggesting long-term benefits with sertraline for OCD, and we have noted the need for adequate long-term data in the approvable letter. Nevertheless, in the absence of adequate relapse prevention data, I have recommended that we take the same approach in labeling for this indication that we have for other drugs indicated for OCD. i.e., acknowledge the absence of data, yet suggest that it would not be unreasonable to continue responding patients beyond the acute treatment phase.

5.1.3 Overall Conclusions Regarding Efficacy Data

Although, as noted above, it is troubling that the 100 mg/day dose group in study 371/372 was not distinguishable from placebo on several key measures, the other two dose groups in that study were positive, and overall, I consider this study positive. Study 546 was also positive. While study 237/248 did not beat placebo with sufficient consistency to be considered positive, the effect sizes in that study were comparable to those seen in the two positive studies, and I am inclined to accept the argument that it was not sufficiently powered to show a difference from placebo. The placebo effect in the fourth study, 495, was likely too large to enable sertraline to be distinguished from placebo, even though clomipramine was distinguishable from placebo in that study. Overall, I believe that Pfizer has shown that sertraline has an effect in OCD comparable to that seen with other SSRIs, but not with clomipramine.

5.2 Safety Data

The safety data for Zoloft/OCD were reviewed by James knudsen, M.D. (review completed and signed 3-6-95. Since Zoloft has been widely available in the US and elsewhere for approximately 3 years for the treatment of depression, a major part of our approach to the safety data was to compare the findings from the relatively small OCD database with the database for depression. Dr. Knudsen concluded that Zoloft is acceptably safe for use in the treatment of OCD, and I agree with that conclusion.

The three studies for which data were available for the integrated database (371/372/494, 237/248, and 546) were briefly described under 5.1 (efficacy). These were 8 or 12 week, placebo-controlled trials. The cutoff date for the integrated database for these three studies was 6-30-94, and this database included approximately 376 patients exposed to sertraline. A number of additional studies were ongoing and not yet reported at the time of the submission of this supplement, and these studies included an additional approximately 900 patients exposed to sertraline. These studies were screened for serious events, with a cutoff date of 10-7-94. The supplement also included an update on spontaneous reports for Zoloft worldwide. It was noted that there have been 5158 spontaneous reports to Pfizer, including 1099 serious reports, of which 145 were reports of deaths. A line listing of these 145 cases was provided. Unfortunately, specific information was not provided on spontaneous reports for patients identified as receiving Zoloft for the treatment of OCD, and we will ask for this breakdown in the approvable letter.

For the integrated OCD database, sertraline-exposed patients ranged in age from 18-77 (mean=37), were 61% male, and were 98% caucasian. The exposure tended to be short-term, however, about 25% were exposed for greater than 6 months. About 75% of patients received mean doses in a range of 50-200 mg/day.

There were no deaths among the sertraline-exposed patients in the integrated database or among those patients in the ongoing studies.

A search of the integrated database and the ongoing trials database for serious events yielded a total of 36 among sertraline-exposed patients. Four of these events were seizure, yielding an estimated seizure incidence of 4/1295=0.3%. This finding is of some concern, since seizure was not observed among the approximately 2700 depressed patients exposed to sertraline in the original NDA database. Otherwise, neither the numbers nor types of events were unexpected for this population. A search for suicidality also did not reveal any indication of a sertraline-associated risk for suicidal behavior.

The common and drug-related adverse events leading to dropout (incidence $\geq$ 1% and at least twice the placebo rate) included:

somnolence, anxiety, insomnia, libido decreased, nervousness, nausea, headache, fatigue, and pain). This list was similar to the adverse events associated with dropout in the depression database.

The common and drug-related adverse events overall (from the integrated database; incidence ≥ 5% and at least twice the placebo rate) included: sweating increased, nausea, diarrhea/loose stools, dyspepsia, anorexia, weight increase, tremor, paresthisia, sexual dysfunction, and insomnia. This list was similar to the adverse events associated with sertraline in the depression database.

Explorations of the integrated database for laboratory and vital signs variables, including analyses of change from baseline, analyses of proportions of patients meeting criteria for potentially clinically significant change on these variables, and dropouts for changes in any of these variables didn't reveal any new or clinically important findings.

In conclusion, the safety experience for sertraline in patients with OCD did not reveal any adverse findings that are unique for this population, except for seizures, and none that would preclude its use in this population. We have added a revised precautions statement about seizure to the labeling. We have requested a safety update in the approvable letter.

5.3 Clinical Sections of Labeling

We have made a number of changes (mostly clinical) in the draft labeling for Zoloft that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Knudsen reviewed the published literature for sertraline and OCD included in the NDA and did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

Zoloft is marketed in a number of countries around the world for the treatment of depression. To my knowledge, it is not yet marketed anywhere for the treatment of OCD. We will ask for an update on the regulatory status of Zoloft for OCD in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this supplement to the PDAC.

9.0 DSI INSPECTIONS

Routine inspections are no longer done for supplements. However, we have been assured that only one of the investigators (Jenike) for the critical studies for this supplement has in the past received a rating of VAI-3, and none worse ratings. In the case of the earlier Jenike study, apparently, DSI was satisfied with his response to the action letter, and no further action was considered necessary.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes (mostly clinical) to the sponsor's draft dated 2-14-95. Other sections have also been substantially modified.

10.2 Foreign Labeling

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

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, a regulatory status update, a request for a gender analysis of the effectiveness data, a commitment to conduct a

a final response to EA deficiencies, and an explanation for our change from pregnancy category B to C.

11.0 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 OCD. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

LBLING CONT.

ATTACHMENT

FINAL LABELING

Note: This final labeling is based on your 12-7-95 draft labeling proposal, and additional exchanges with Agency staff during September, 1996 (see letter). For some sections, few changes were made, while others required more extensive modification. Please note that we have now included the changes made under S-013 and also the recently submitted S-014/S-015, regarding 3A4 inhibition. For ease in supervisory review of the labeling modifications, we have shaded ('redline font') all the changes to the currently approved labeling.

ZOLOFT®
(sertraline hydrochloride)
Tablets

DESCRIPTION

ZOLOFT (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI), for oral administration. It is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NCl_2.HCl$ is represented by the following structural formula:

[Insert structural formula here]

Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

ZOLOFT is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, FD & C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (alpha 1, alpha 2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to downregulate brain norepinephrine receptors, as has been observed with other clinically effective antidepressants. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability

In man, following oral once daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours postdosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the Cmax and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range. The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

The effects of food on the bioavailability of sertraline were studied in subjects administered a single dose with and without food. AUC was slightly increased when drug was administered with food but the Cmax was 25% greater, while the time to reach peak plasma concentration decreased from 8 hours post dosing to 5.5 hours.

Metabolism

Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. N-desmethylsertraline has a plasma terminal

elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40-45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline..

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0-24 hour), Cmax and Cmin, with about a 5-9 fold increase in these pharmacokinetic parameters between day 1 and day 14.

Protein Binding

In vitro protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/ml. However, at up to 300 and 200 ng/ml concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin and propranolol (see Precautions).

Age

Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.

Liver Disease

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. The elimination half-life of sertraline was prolonged in a single dose study of patients with mild, stable cirrhosis, with a mean of 52 hours compared to 22 hours seen in subjects without liver disease. In hepatically impaired patients, it was observed that the Cmax and AUC were increased by 1.7 and 4.4 fold, respectively, compared to healthy subjects. This suggests that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver disease, a lower or less frequent dose should be used (see Precautions and Dosage and Administration).

Renal Disease

The pharmacokinetics of sertraline in patients with significant renal dysfunction have not been determined.

Clinical Trials

Depression

The efficacy of Zoloft was established in two placebo-controlled trials in adult outpatients meeting DSM-III criteria for depression. Study 1 was a 6-week study with flexible dosing of Zoloft in the range of 50 to 200 mg/day; the mean dose for completers was 154 mg/day. Study 2 was a 6-week fixed-dose study, including Zoloft dosages of 50, 100, and 200 mg/day. Overall, these studies demonstrated Zoloft to be superior to placebo on the Hamilton Depression Rating Scale and the Clinical Global Impression Severity and Improvement scales. Study 2 was not readily interpretable regarding a dose response relationship for effectiveness.

Obsessive Compulsive Disorder (OCD)

The effectiveness of Zoloft in the treatment of OCD was demonstrated in three multicenter placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had moderate to severe OCD (DSM-III-R or DSM-III) with mean baseline ratings on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) total score ranging from 23 to 25.

Study 1 was an 8-week study with flexible dosing of Zoloft in a range of 50 to 200 mg/day; the mean dose for completers was 181 mg/day. Patients receiving Zoloft experienced a mean reduction of approximately 4 points on the YBOCS total score, which was significantly greater than the mean reduction of 2 points in placebo-treated patients.

Study 2 was a [redacted] fixed-dose study, including Zoloft doses of 50, 100, and [redacted] and 200 mg/day [redacted] points on [redacted] which [redacted] greater than the [redacted] reduction in placebo-treated patients.

Study 3 was [redacted] study with flexible dosing of Zoloft in a range of [redacted] mean dose for completers was 185 mg/day. Patients receiving Zoloft experienced a mean reduction of approximately [redacted] points on the YBOCS total score, which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

INDICATIONS AND USAGE

Depression

ZOLOFT (sertraline hydrochloride) is indicated for the treatment of depression.

The efficacy of ZOLOFT in the treatment of a major depressive episode was established in six to eight week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see Clinical Trials under Clinical Pharmacology).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The antidepressant action of ZOLOFT in hospitalized depressed patients has not been adequately studied.

A study of depressed outpatients who had responded to ZOLOFT during an initial eight week open treatment phase and were then randomized to continuation on ZOLOFT or placebo demonstrated a significantly lower relapse rate over the next eight weeks for patients taking ZOLOFT compared to those on placebo. However, the effectiveness of ZOLOFT in long-term use, that is, for more than 16 weeks, has not been systematically evaluated in controlled trials of depressed patients. Therefore, the physician who elects to use ZOLOFT for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Obsessive [redacted]

ZOLOFT is [redacted] treatment of obsessions and compulsions in patients with [redacted] compulsive disorder (OCD), as defined in the DSM-III-R, [redacted] obsessions or compulsions cause marked distress, are time consuming, or significantly interfere with social or occupational functioning.

The efficacy of ZOLOFT [redacted] in 12-week trials with obsessive compulsive outpatients having diagnoses of obsessive

compulsive disorder as defined according to DSM-III or DSM-III-R criteria (see Clinical Trials under Clinical Pharmacology).

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are experienced as time consuming or excessive or unreasonable.

The effectiveness of Zoloft [redacted] more than [redacted] placebo-controlled trials [redacted] use Zoloft for extended periods [redacted] evaluate the long-term usefulness of the drug for [redacted] individual patient (see Dosage and Administration).

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).

WARNINGS

Cases of serious, sometimes fatal, reactions have been reported in patients receiving ZOLOFT (sertraline hydrochloride), a selective serotonin reuptake inhibitor (SSRI), in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.

PRECAUTIONS

General

Activation of Mania/Hypomania - During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT

(sertraline hydrochloride) treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressant and antiobsessional drugs.

Weight Loss - Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.

Seizure - ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with Zoloft in the development program for depression. However, 4 patients out of approximately 1800 exposed during the development program for obssessive compulsive disorder experienced seizures, representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, like other antidepressant and antiobsessional drugs, ZOLOFT should be introduced with care in patients with a seizure disorder.

Suicide - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Weak Uricosuric Effect - ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown and there have been no reports of acute renal failure with ZOLOFT.

Use in Patients with Concomitant Illness - Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities.

ZOLOFT is extensively metabolized by the liver. In subjects with mild, stable cirrhosis of the liver, the clearance of sertraline was decreased, thus increasing the elimination half-life. A lower or less frequent dose should be used in patients with cirrhosis.

Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until the pharmacokinetics of ZOLOFT have been studied in patients with renal impairment and until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with ZOLOFT, it should be used with caution in such patients.

Interference with Cognitive and Motor Performance - In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance.

Hyponatremia - Several cases of hyponatremia have been reported and appeared to be reversible when ZOLOFT was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Platelet Function - There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking ZOLOFT. While there have been reports of abnormal bleeding or purpura in several patients taking ZOLOFT, it is unclear whether ZOLOFT had a causative role.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT:

> Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely.
>
> Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol in depressed patients or OCD [redacted] is not advised.
>
> Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests

None.

Drug Interactions

Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins - Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein, (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound ZOLOFT by other tightly bound drugs.

In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped.

Cimetidine - In a study assessing disposition of ZOLOFT (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in ZOLOFT mean AUC (50%), Cmax (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

CNS Active Drugs - In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in Tmax for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium.

Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose.

The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required.

There is limited controlled experience regarding the optimal timing of switching from other antidepressants to ZOLOFT. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established.

Monoamine Oxidase Inhibitors - See **CONTRAINDICATIONS** and **WARNINGS**.

Drugs Metabolized by P450 3A4 - In two separate in vivo interaction studies, sertraline was coadministered with the cytochrome P4503A4 substrates, terfenadine or carbamazepine, under steady state conditions. The results of these studies demonstrated that sertraline coadministration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P4503A4 activity is not likely to be of clinical significance.

Drugs Metabolized by P450 2D6 - Many antidepressants, e.g, the SSRIs, including sertraline, and most tricyclic antidepressants inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressants and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the antidepressants in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with ZOLOFT® may require lower doses than usually prescribed for the other drug. Furthermore, whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the co-administered drug may be required (see Tricyclic Antidepressants under **PREAUTIONS**).

Tricyclic Antidepressants (TCAs) - The extent to which SSRI - TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with Zoloft, because sertraline may inhibit TCA metabolism. Plasma TCA concentrations [redacted] may need to be [redacted] (see Drug Metabolism [redacted]).

Hypoglycemic Drugs - In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.

Atenolol - ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.

Digoxin - In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance.

Microsomal Enzyme Induction - Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism.

Electroconvulsive Therapy - There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT.

Alcohol - Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol in depressed patients or OCD patients is not recommended.

Carcinogenesis

Lifetime carcinogenicity studies were carried out in [redacted] mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses

correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25 - 1.0 times the MRHD on a mg/m^2 basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and their clinical significance is unknown. There was an increase in uterine adenomas of the uterus in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m^2 basis) which was accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10 mg/kg (0.5 - 2.0 times the MRHD on a mg/m^2 basis) compared to placebo controls, this effect was not clearly drug related.

Mutagenesis

Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.

Impairment of Fertility

A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).

PREGNANCY - PREGNANCY CATEGORY C:

Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. There was no evidence of teratogenicity at any dose in pregnant rats and rabbits were given sertraline during the period of organogenesis. Delayed ossification was observed at 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis) and above in rats that received sertraline throughout lactation. There was an increase in the number of stillborn pups and in the number of pups who died during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 2 mg/kg (1 times the MRHD on a mg/m^2 basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m^2 basis). The decrease in pup survival was shown to be dependent on exposure to sertraline. The clinical significance of these effects is

unknown. There are no adequate and well-controlled studies in pregnant women. Zoloft should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of ZOLOFT on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients.

ADVERSE REACTIONS

Commonly Observed

Among patients treated with Zoloft in placebo controlled premarketing studies, the most commonly observed adverse events associated with the use of ZOLOFT (sertraline hydrochloride) and not seen at an equivalent incidence among placebo treated patients were: gastrointestinal complaints, including nausea, diarrhea/loose stools and dyspepsia; tremor; dizziness; insomnia; somnolence; increased sweating; dry mouth; and male sexual dysfunction (primarily ejaculatory delay).

In placebo-controlled clinical trials for OCD, adverse events observed at [redacted] sertraline-treated patients and at an incidence [redacted] more than incidence among placebo-treated patients were: nausea, insomnia, diarrhea, decreased libido, [redacted] dyspepsia, ejaculation failure (primarily ejaculatory delay), tremor, and increased sweating.

Associated with Discontinuation of Treatment

Fifteen percent of 2710 patients who received ZOLOFT in premarketing multiple dose clinical trials discontinued treatment due to an adverse event. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea, and fatigue.

In placebo-controlled clinical trials for OCD [illegible] patients treated with ZOLOFT discontinued treatment due to adverse events. The more common events were nausea [illegible] and diarrhea

Incidence in Controlled Clinical Trials

Depression - Table 1 enumerates adverse events that occurred at a frequency of 1% or more among ZOLOFT patients who participated in controlled trials comparing titrated ZOLOFT with placebo. Most patients received doses of 50 to 200 mg per day. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Table 1

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Depression

	(Percent of Patients Reporting)	
Adverse Experience	**Zoloft (N=861)**	**Placebo (N=853)**
Autonomic Nervous System Disorders		
Mouth dryness	16%	9%
Sweating increased	8%	3%
Cardiovascular		
Palpitations	<1%	2%
Centr. & Periph. Nervous System Disorders		
Headache	20%	19%

Dizziness	12%	7%
Tremor	11%	3%
Hypoesthesia	2%	1%
Twitching	1%	0%
Hypertonia	1%	0%
Gastrointestinal Disorders		
Nausea	26%	12%
Diarrhea/Loose Stools	18%	9%
Constipation	[illegible]	6%
Dyspepsia	[illegible]	3%
Vomiting	[illegible]	2%
Anorexia	3%	2%
General		
Fatigue	11%	8%
Hot Flushes	2%	1%
Fever	2%	1%
Back Pain	2%	1%
Psychiatric Disorders		
Insomnia	16%	9%
Sexual Dysfunction-Male (1)	16%	2%
Somnolence	13%	6%
Agitation	6%	4%
Nervousness	3%	2%
Anxiety	3%	1%
Yawning	2%	0%
Sexual Dysfunction-Female (2)	2%	0%
Special Senses		
Vision Abnormal	4%	2%
Urinary System Disorders		
Micturition Frequency	2%	1%

*Events reported by at least [illegible] patients treated with Zoloft are included, except for the following events which had [illegible] placebo greater than or equal to Zoloft: flatulence, abdominal pain, rash, [illegible], tinnitus, micturition disorder, appetite increased, concentration impaired, pharyngitis, taste perversion, menstrual disorder (2), and chest pain.

(1) - Primarily ejaculatory delay; % based on male patients only: 271 Zoloft and 271 placebo patients.
(2) - % based on female patients only: 590 Zoloft and 582 placebo patients.

Obsessive Compulsive Disorder - Table 2 enumerates adverse events that occurred at a frequency of 2% or more among patients on Zoloft who participated in controlled trials comparing Zoloft with placebo in the treatment of OCD.

Table 2
Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder

	(Percent of Patients Reporting)	
Adverse Experience	**Zoloft (N=533)**	**Placebo (N=373)**
Autonomic Nervous System Disorders		
Mouth Dry	14%	9%
Sweating Increased	6%	1%
Cardiovascular		
Palpitations	3%	2%
Chest Pain	3%	2%
Centr. & Periph. Nerv. System Disorders		
Headache	30%	24%
Dizziness	17%	9%
Tremor	8%	1%
Paresthesia	3%	1%
Hypertonia	2%	1%
Disorders of Skin and Appendages		
Rash	2%	1%
Gastrointestinal Disorders		
Nausea	30%	11%
Diarrhea	24%	10%
Anorexia	11%	2%
Dyspepsia	10%	4%
Constipation	6%	4%
Flatulence	4%	1%
Vomiting	3%	1%
Appetite Increased	3%	1%
General		
Fatigue	14%	10%
Pain	3%	1%
Hot Flushes	2%	1%
Back Pain	2%	1%

Metabolic and Nutritional Disorders		
Weight Increase	3%	0%
Psychiatric Disorders		
Insomnia	28%	12%
Somnolence	15%	8%
Libido Decreased	11%	2%
Anxiety	8%	6%
Nervousness	7%	6%
Agitation	6%	3%
Depersonalization	3%	1%
Paroniria	2%	1%
Respiratory System Disorders		
Pharyngitis	4%	2%
Special Senses		
Vision Abnormal	4%	2%
Taste Perversion	3%	1%
Urogenital		
Ejaculation Failure (1)	17%	2%
Impotence (2)	5%	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: abdominal pain, respiratory disorder, depression, and amnesia.
(1) - Primarily ejaculatory delay; % based on male patients only: 296 Zoloft and 219 placebo patients.
(2) - % based on male patients only: 296 Zoloft and 219 placebo patients.

Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline Hydrochloride)

During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 2700 subjects. The conditions and duration of exposure to ZOLOFT varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for indications other than depression. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the approximately 2700 individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous table and those reported in terms so general as to be uninformative. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

Autonomic Nervous System Disorders - *Infrequent*: flushing, mydriasis, increased saliva, cold clammy skin; *Rare*: pallor.

Cardiovascular - *Infrequent*: postural dizziness, hypertension, hypotension, postural hypotension, edema, dependent edema, periorbital edema, peripheral edema, peripheral ischemia, syncope, tachycardia; *Rare*: precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins.

Central and Peripheral Nervous System Disorders - *Frequent*: confusion; *Infrequent*: ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo; *Rare*: local anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis.

Disorders of Skin and Appendages - *Infrequent*: acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin; *Rare*: bullous eruption, dermatitis, erythema multiforme, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discoloration, abnormal skin odor, urticaria.

Endocrine Disorders - Rare: exophthalmos, gynecomastia.

Gastrointestinal Disorders - *Infrequent*: dysphagia, eructation; *Rare*: diverticulitis, fecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, hemorrhoids, hiccup, melena, hemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative

stomatitis, tenesmus, tongue edema, tongue ulceration.

General - *Frequent*: asthenia; *Infrequent*: malaise, generalized edema, rigors, weight decrease, weight increase; *Rare*: enlarged abdomen, halitosis, otitis media, aphthous stomatitis.

Hematopoietic and Lymphatic - *Infrequent*: lymphadenopathy, purpura; *Rare*: anemia, anterior chamber eye hemorrhage.

Metabolic and Nutritional Disorders - *Rare*: dehydration, hypercholesterolemia, hypoglycemia.

Musculoskeletal System Disorders - *Infrequent*: arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness; *Rare*: hernia.

Psychiatric Disorders - *Infrequent*: abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide ideation and attempt, teeth-grinding, abnormal thinking; *Rare*: hysteria, somnambulism, withdrawal syndrome.

Reproductive - *Infrequent*: dysmenorrhea (2), intermenstrual bleeding (2); *Rare*: amenorrhea (2), balanoposthitis (1), breast enlargement (2), female breast pain (2), leukorrhea (2), menorrhagia (2), atrophic vaginitis (2).

(1) - % based on male subjects only: 1005
(2) - % based on female subjects only: 1705

Respiratory System Disorders - *Infrequent*: bronchospasm, coughing, dyspnea, epistaxis; *Rare*: bradypnea, hyperventilation, sinusitis, stridor.

Special Senses - *Infrequent*: abnormal accommodation, conjunctivitis, diplopia, earache, eye pain, xerophthalmia; *Rare*: abnormal lacrimation, photophobia, visual field defect.

Urinary System Disorders - *Infrequent*: dysuria, face edema, nocturia, polyuria, urinary incontinence; *Rare*: oliguria, renal pain, urinary retention.

Laboratory Tests - In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

The safety profile observed in OCD patients treated with Zoloft is similar to the safety profile in depressed patients.

Other Events Observed During the Postmarketing Evaluation of Zoloft - Reports of adverse events temporally associated with ZOLOFT that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug include the following: galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, psychosis, rare reports of pancreatitis, and liver events-clinical features (which in the majority of cases appeared to be reversible with discontinuation of Zoloft) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class - ZOLOFT (sertraline hydrochloride) is not a controlled substance.

Physical and Psychological Dependence - ZOLOFT has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. However, the premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior. As with any new CNS active drug, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g. development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience - As of November, 1992, there were 79 reports of non-fatal acute overdoses involving ZOLOFT, of which 28 were overdoses of ZOLOFT alone and the remainder involved a combination of other drugs and/or alcohol in addition to ZOLOFT. In those cases of overdose involving only ZOLOFT, the reported doses ranged from 500 mg to 6000 mg. In a subset of 18 of these patients in whom ZOLOFT blood levels were determined, plasma concentrations ranged from <5 ng/ml to 554 ng/ml. Symptoms of overdose with ZOLOFT alone included somnolence, nausea, vomiting, tachycardia, ECG changes, anxiety and dilated pupils. Treatment was primarily

supportive and included monitoring and use of activated charcoal, gastric lavage or cathartics and hydration. Although there were no reports of death when ZOLOFT was taken alone, there were 4 deaths involving overdoses of ZOLOFT in combination with other drugs and/or alcohol. Therefore, any overdosage should be treated aggressively.

Management of Overdoses - Establish and maintain an airway, ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose.

Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

There are no specific antidotes for ZOLOFT.

Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

DOSE AND ADMINISTRATION

Initial Treatment

ZOLOFT (sertraline hydrochloride) should be administered at a dose of 50 mg once daily. A relationship between dose and either antidepressant or antiobsessive effect has not been established. Patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the antidepressant and antiobsessive effectiveness of ZOLOFT. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

ZOLOFT should be administered once daily, either in the morning or evening.

As indicated under Precautions, a lower or less frequent dosage should be used in patients with hepatic impairment. In addition, particular care should be used in patients with hepatic or renal impairment.

Maintenance/Continuation/Extended Treatment

There is evidence to suggest that depressed patients responding during an initial 8 week treatment phase will continue to benefit during an additional 8 weeks of treatment. While there are insufficient data regarding any benefits from treatment beyond 16 weeks, it is generally agreed among expert psychopharmacologists that acute episodes of depression require several months or longer of sustained pharmacological therapy. Whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Although the efficacy of ZOLOFT beyond 12 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments may be needed to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with ZOLOFT. In addition, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI (see "**CONTRAINDICATIONS**" and "**WARNINGS**").

HOW SUPPLIED

ZOLOFT capsular-shaped scored tablets, containing sertraline hydrochloride equivalent to 50 and 100 mg of sertraline, are packaged in bottles.

ZOLOFT 50 mg Tablets: light blue film coated tablets engraved on the front with ZOLOFT and on the back scored and engraved with 50 mg.

NDC 0049-4900-50 Bottles of 50
NDC 0049-4900-66 Bottles of 100
NDC 0049-4900-73 Bottles of 500
NDC 0049-4900-41 Unit Dose Packages of 100

ZOLOFT 100 mg Tablets: light yellow film coated tablets engraved on the front with ZOLOFT and on the back scored and engraved with 100 mg.

NDC 0049-4910-50 Bottles of 50
NDC 0049-4910-66 Bottles of 100
NDC 0049-4910-73 Bottles of 500
NDC 0049-4910-41 Unit Dose Packages of 100

Store at controlled room temperature, 59°F to 86°F (15° to 30°C).

Doc LABZFOCD.AP3

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ZOLOFT™

(sertraline hydrochloride)

TABLETS

NDA 19-839/S-002

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL
DRUG PRODUCTS
(HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 19-839/S-002

Zoloft

(sertraline hydrochloride)

Tablets

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

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 supplemental new drug application for **Zoloft Tablets**, **Pfizer Inc.** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Sertraline hydrochloride is a synthetic drug which is administered as an oral tablet and is currently approved for use in the treatment of depression. The supplemental application is for approval to indicate the use of the drug in the treatment of obsessive compulsive disorder. The drug substance will be manufactured by Pfizer at facilities in Groton, CT, Puerto Rico and/or Ringaskiddy, Ireland. The drug product will be manufactured by Pfizer at facilities in Brooklyn, NY and/or Barceloneta, Puerto Rico. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Sertraline hydrochloride may enter the environment from excretion by patients or from emissions from manufacturing sites. Chemical and physical test results indicate that the drug will exist predominantly in the aquatic environment. Data indicates that the substance is susceptible to aerobic aquatic biodegradation and photolysis.

As sertraline is expected to persist in the aquatic environment for some time, the toxicity of the material to organisms was characterized. Acute static toxicity studies in water fleas (*Daphnia magna*) and microbial inhibition studies indicate that the substance is not expected to affect the environment at the expected environmental concentrations.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Off-specification drug substance will be disposed of at a licensed landfill or incineration facility and unused or rejected drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of 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. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

8/7/95 Nancy B Sager
DATE PREPARED BY
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

8/10/95 Robert A. Jerussi
DATE CONCURRED
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

SENSITIVE

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NA 19-839/S-002

ZOLOFT TABLETS

(Sertraline Hydrochloride)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CENTER FOR DRUG EVALUATION AND RESEARCH

HFD-120

DATE COMPLETED: August 7, 1995

ENVIRONMENTAL ASSESSMENT

1. Date:

Supp. submitted:	05/14/1992
Amendment:	04/13/1994
EAR review #1:	06/27/1994
Amendment:	09/21/1994
EAR review #2:	01/27/1995
Amendment:	05/10/1995*
T-con:	06/06/1995
Amendment:	07/18/1995*

*Reviewed

CSO: Paul David 4-5530

2. Name of applicant/petitioner:

Pfizer Inc.

3. Address:

U.S. Pharmaceuticals Group
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5755

RESPONSE TO DEFICIENCY LETTER (MEMO DATED JANUARY 27, 1995):

1. Regarding Item 4:

   A- Please revise this section to include the full address of each manufacturing facility.

   RESPONSE: The addresses have been provided. **ADEQUATE**

B. Please submit evidence of contractual agreements with your contract disposal firms. A formal letter from each firm indicating knowledge of the type of waste and a brief description of the disposal methods to demonstrate the adequacy of the methods should be sufficient. Note that since the potential for incineration of PVC/PVDC material from the packaging is possible, the documents should clearly demonstrate the adequacy of the incineration processes for this type of waste.

RESPONSE: The current facilities are identified and the contractual information provided. The incineration facilities include adequate controls for the incineration of PVC/PVDC materials. **ADEQUATE**

2. Item 5: Please indicate which of the structures of Related Compounds submitted in Confidential Appendix 1 are to be considered impurities in the drug substance and submit the applicable limits for each impurity.

RESPONSE: The information is provided. The impurities are maintained at low levels. **ADEQUATE**

3. Regarding Item 6:

A. Please revise your list of potential emissions for each manufacturing site to include the expected concentrations of drug substance in the wastestreams.

RESPONSE: The information is provided. For the various facilities 0.381 ppm is the maximum concentration at a WWTP while 0.024 ppm is the maximum entering the aqueous compartment. The calculations appear to be appropriate. There is an adequate "safety factor" between the EEC and the toxic/inhibitory concentration. **ADEQUATE**

B. Please submit certification of compliance with applicable environmental regulations from the appropriate authorities for your facility in Ireland. Alternately, please submit sufficient wastestream analysis to demonstrate conformance to applicable license/permit limits.

RESPONSE: The company has provided the monitoring data for January, 1995 which demonstrates compliance with requirements. **ADEQUATE**

C. Please submit a table of all applicable permit/license numbers, issuing authorities, and expiration dates for each manufacturing facility.

RESPONSE: The information has been provided. There are several permits at the Brooklyn, NY facility that have expired. It should be indicated whether these have been renewed or if the request for renewal has been submitted and is pending. **DEFICIENT**

D. Please transfer the MSDS for the drug substance from the Confidential Appendices to the EAR.

RESPONSE: The MSDS has been moved. **ADEQUATE**

4. Regarding Item 7: The studies for aerobic biodegradation in water appear to address biodegradation in sludge more than in the aqueous compartment, while the discussion of the results for indirect aqueous photodegradation fail to address how the results relate to actual environmental conditions (e.g. cloud cover, latitude, seasonal variations in solar flux). Therefore, while the studies submitted suggest that the drug substance should not persist in the environment, it is not possible to estimate the removal rate. Please revise this section to include either test results demonstrating aerobic biodegradation in the aqueous phase, a more complete discussion to support indirect aqueous photodegradation as a viable removal mechanism or both.

RESPONSE: The section has been revised to indicate that although testing according to standard methods indicates that Sertraline Hydrochloride is inherently biodegradable, the rate is too slow t serve as a relevant environmental depletion mechanism. The photolysis discussion has been revised to indicate the variability due to environmental conditions and the estimated half-life has been revised to 2-18 days. The company has adequately demonstrated an environmental depletion mechanism. **ADEQUATE**

5. Regarding Item 8: Please revise this item to address the impact of the point source of manufacturing emissions for the drug substance requested in Item 6. The discussion should include a comparison of emission concentrations to MIC and LD_{50}/NOEL levels established by testing.

RESPONSE: The data indicates that there is an adequate "safety factors" between the expected environmental concentration and the toxicity levels:

No inhibition/toxicity to activated sludge at 450x the expected concentration at the Barceloneta WWTP. Note this study, which was primarily done to assess the impact of conventional and priority pollutants from production on the WWTP, was conducted at a concentration lower than what is expected at the Groton facility. The microbial inhibition study conducted (see below) adequately demonstrates that there should be no disruption of waste water treatment due to production.

3-6 orders of magnitude between the EEC from use and MIC for the microorganism screen (at least 1 order of magnitude greater than the worst case concentration at the WWTP).

2-3 orders of magnitude between the EEC and the EC_{50} and the NOEC in *Daphnia magna*.

ADEQUATE

6. Regarding Item 14: Please revise this item to include all references used in the preparation of the EAR, to include all literature article and testing methods (e.g. TAD and OECD protocols).

RESPONSE: Response was not submitted. **DEFICIENT**

7. Regarding Item 15: Please revise your summary of Physico-Chemical Data to include the environmental effects testing results submitted in support of Item 8.

RESPONSE: The summary has been revised. **ADEQUATE**

8. Regarding Aquatic Aerobic Biodegradation:

   A. The report is inadequate in that it failed to include all reporting requirements (e.g. testing protocols) as defined in the Environmental Assessment Technical Handbook/Technical Assistance Documents for all tests performed. Please revise the report to meet all reporting requirements.

   RESPONSE: A revised report has been submitted. There are some deviations from the EATAD, but the study design is scientifically sound. The conclusions are supported by the data. **ADEQUATE**

   B. The testing results as reported appear to support aerobic biodegradation in a static sludge environment, but do not address aerobic biodegradation in an aqueous or dynamic environment. Please comment.

RESPONSE: The test information is not directed toward aerobic biodegradation in an aqueous or dynamic environment. As photolysis was identified as a removal mechanism and preliminary biodegradation studies did not indicate that this would be a likely removal mechanism, a definitive biodegradation study was not performed. **ADEQUATE**

9. You have indicated that Item 7 and 8 testing was conducted in accordance with an agreement with the Agency resulting from a meeting held with the Agency on February 6, 1992. Reference to the meeting, and inclusion of the meeting minutes in a confidential appendix is appropriate. However, any suggested testing scenarios resulting from the meeting should be considered recommendations or suggestions and should not be construed as a formal agreement with the Agency or the Agency's Environmental Assessment Officer. We respectfully request that any reference to an agreement with the Agency or the Agency's Environmental Assessment Officer be removed from the EAR and the appendices.

RESPONSE: Reference to the meeting has been removed from items 7 and 8 but retained in the confidential section.

Additional Change: The projected usage has been increased, but the maximum EEC is from production. The conclusions regarding effects remain the same. **ADEQUATE**

THE FOLLOWING COMMENTS WERE COMMUNICATED TO THE FIRM ON JUNE 6, 1995:

1. We are awaiting response to deficiency #6 (February 13, 1995 facsimile).

RESPONSE: The references (section 14) have been updated. **ADEQUATE**

2. There are several permits listed for the Brooklyn, NY facility which have expired (Response Appendix 6). It should be indicated whether these have been renewed and the new expiration date or if the request for renewal has been submitted and is pending. Please revise the list of permits accordingly.

RESPONSE: The list has been updated. **ADEQUATE**

3. A revised non-confidential EAR incorporating the changes submitted on May 10, 1995 should be submitted. Please include the list of permits (Response Appendix 6) as a non-confidential appendix.

RESPONSE: The revised EA has been submitted and is acceptable.
ADEQUATE

SUMMARY:

A FONSI is recommended. The material will exist predominantly in the aquatic environment. The MEEC's have been predicted as 381 ppb (at Groton facility WWTP, 12 ppb to aqueous environment) 24 ppb (max. to aquatic from manufacturing), 1.46 ppb (use) and 0.19 ppb (use considering metabolism). The microbial study indicated MIC's of 4 to >1000 ppm with the Nostoc being the lower end. The blue-green algae would not be of concern at the WWTP and there is significant "safety margin" for this species in the aquatic environment. The EC_{50} for *Daphnia magna* is 0.56 ppm (560 ppb) and the NOEC is 0.28 ppm (280 ppb). There are greater than 2 orders of magnitude between these toxicity values and the MEEC use. There is greater than 1 order of magnitude between these toxicity values and the production concentrations. These maximum expected concentrations do not include any dilution which will occur rather rapidly in the environment and further reduce the exposure concentrations.

ENVIRONMENTAL ASSESSMENT

ZOLOFT™ TABLETS

Sertraline Hydrochloride for Use in Obsessive Compulsive Disorder

Supplement to NDA #19-839

PFIZER INC

June 15, 1995

Non-Confidential Submission

TABLE OF CONTENTS

ENVIRONMENTAL ASSESSMENT

ZOLOFT™

SERTRALINE HYDROCHLORIDE

NDA #19-839

1. **DATE:** June 15, 1995

2. **NAME OF APPLICANT/PETITIONER:** Pfizer Inc

3. **ADDRESS:** 235 East 42nd Street, New York, NY 10017

4. **DESCRIPTION OF THE PROPOSED ACTION:**

A. REQUESTED APPROVAL

Sertraline hydrochloride is currently approved for use in the treatment of depression (NDA #19-839, approved December 30, 1991). The present request is for approval of a supplement to the original NDA for use of sertraline hydrochloride for another indication, the treatment of obsessive compulsive disorder (OCD). Mean dosage for this indication will be 175 mg (as sertraline) administered orally as tablets, once per day.

B. NEED FOR THE ACTION

OCD is a disorder believed to be associated with dysregulation of central serotonergic function. Sertraline, a selective inhibitor of serotonin uptake into presynaptic neurons, has been shown to ameliorate the symptoms of OCD. In accord with its selective biochemical activity, sertraline does not cause certain adverse effects associated with other antidepressant/antiobsessive drugs. Approval of the present NDA will permit usage of sertraline in patients having OCD. It is estimated that the total treated OCD patient population comprises about 0.55 million patients, as compared to a depression patient population of about 20 million treated patients.

C. PRODUCTION AND PROCESSING LOCATIONS AND ENVIRONMENTS

Manufacture of bulk drug substance for U.S. use is currently being carried out at the Pfizer Groton, CT and Barceloneta, Puerto Rico production facilities in support of the depression indication; manufacture will also be carried out at these sites in support of the OCD indication. Manufacture of bulk drug substance for U.S. use may also be carried out at the Pfizer Ringaskiddy, Ireland production facility. Manufacture of drug product is being carried out at the Pfizer Brooklyn, NY, and Barceloneta, Puerto Rico production facilities in support of the depression indication; manufacture will also be carried out at these sites in support of the OCD indication.

The Groton facility [Pfizer Pharmaceuticals, Eastern Point Road, Groton, CT 06340] is located in an urban residential/industrial environment bounded on the north by the oil distribution facilities of Hess, Inc., on the east and south by single-family residential houses, and on the west by the Thames River. The Brooklyn facility [Pfizer Inc, Brooklyn Plant & Laboratories, 630 Flushing Ave., Brooklyn, NY 11206-5092] is located in an urban environment in New York City in an area zoned

for commercial use. South of the plant is a parking lot, to the east are multi-story tenements, to the west is a high-rise housing project, and to the north are vacant urban properties and industrial buildings. The Barceloneta facility [Pfizer Pharmaceuticals Inc., KM 58.2 Road #2, Barceloneta, Puerto Rico 00617-0628] is located in a mixed agricultural/industrial environment adjacent to other pharmaceutical manufacturing facilities and a food-processing plant. The Ringskiddy facility [Pfizer Pharmaceuticals Production Corporation, Ringaskiddy, Co. Cork, Ireland] is located in a semi-rural environment bounded on the north and east by Cork Harbor. All locations are in temperate climates except for Barceloneta which is tropical.

D. USE AND DISPOSAL LOCATIONS AND ENVIRONMENTS

Sertraline hydrochloride is being used as a prescription agent in both hospital and home-use environments throughout the US. The usage pattern will be unchanged with approval of the subject supplement.

Outdated or returned drug product (exclusive of returned samples) is consolidated at the Pfizer Memphis Logistics Center, 1855 Shelby Oaks Drive North, Memphis, TN 38134, and shipped under manifest to either of two disposal facilities:

(a) WMI Medical Services of Ohio, Inc., 4343 Infirmary Road, Dayton, OH 45449, under a purchase order agreement, dated 4/3/95 for destruction via incineration under Ohio EPA Application Number 0857751858 N002, expiry 10/3/97. The agreement defines the types of pharmaceutical wastes, and the incineration method is adequate for disposal of PVC/PVDC-containing wastes. The WMI Medical Services facility is located outside of Dayton, OH, in a rural/industrial area.

(b) Environmental Healthcare, Incorporated, P.O. Box 2286 Delray Beach, FL 33447, under a contract agreement dated 3/17/95. Environmental Healthcare subcontracts the disposal to Ogden Martin Systems of Lake, Inc., which operates an incineration facility under Florida Department of Environmental Regulation, Permit A035-193817, expiry 10/25/96, at 3830 Rogers Industrial Park Road, Okahumpka, Lake County, FL 34762. The agreements define the types of pharmaceutical wastes, and the incineration method is adequate for disposal of PVC/PVDC-containing wastes. The Ogden Martin Systems facility is located in an isolated environment without neighboring residences or industrial facilities.

Returned samples of drug product are consolidated at the Pfizer Brooklyn facility [Pfizer Pharmaceuticals Inc., 630 Flushing Ave., Brooklyn, NY 11206-5092] and shipped under manifest to BFI Pharmaceutical Services, 812 Corporate Way, Valley Cottage, NY 10989 under a purchase order agreement dated 2/3/95. BFI subcontracts the disposal to American REF-FUEL Company of Hempstead, 600 Avenue C at Stewart Avenue, Westbury, NY 11590, for destruction via incineration under NY State Department of Environmental Conservation, Permits Number 10-86-0345, expiry 5/14/95, under renewal review. The agreements define the types of pharmaceutical wastes, and the incineration method is adequate for disposal of PVC/PVDC-containing wastes. There are several residences near the American REF-FUEL facility and the topography is flat.

Rejected drug substance/drug product from the production facilities is disposed as follows:

Groton.- Disposal is carried out under contract with Rollins Environmental Services, Inc., Rte. 322 and Interstate 295, Bridgeport, NJ 08014 for incineration under EPA permit ID # NJD053288239. The facility is located on a 50 acre active site in a rural area; the topography is flat with wetlands.

Brooklyn.- Disposal is carried out as described above for disposal of returned samples of drug product.

Barceloneta.- Rejected drug product is disposed of at Ogden Martin Systems of Lake, Inc., as described above for disposal of outdated or returned drug product. Disposal of rejected drug substance is carried out at any of the following locations:

(a) Rollins Environmental Services (LA), Inc. (RESLA), 13351 Scenic Highway (U.S. 61), Baton Rouge, LA 70807-4137. Rollins carries out the disposal via rotary kiln incineration under RCRA Part B Permit # LAD 010395127-P. The Rollins facility is located on 400 acres of land in a rural/ industrial area seven miles north of Baton Rouge. The topography is flat.
(b) Advanced Environmental Technology Corporation (AETC), Eden Lane, Flanders, NJ 07836. AETC in Flanders operates under a TSDF facility permit NJD980536593 which defines permit limits and acts a broker in the transportation of wastes to one of three disposal sites:
(1) Giant Resource Recovery, Inc., Highway 453 North at Interstate 26, Harleyville, SC 29448. Giant Resource Recovery operates under Interim Status, Part A RCRA Permit Number SCD003351699. Giant Resource Recovery operates a cement kiln incinerator and is located in a rural area; topography is flat.
(2) Thermalkem, Inc., Rockhill, SC 29731. Thermalkem operates under permit number SCD044442333. Thermalkem carries out disposal via multiple fixed hearth incineration. The Thermalkem facility is located on 42 acres of land in a rural area; topography is flat.
(3) Marisol, Inc., 125 Factory Lane, Middlesex, NJ 08846. The Marisol facility operates under permit number NJD002454544. The Marisol facility carries out cement kiln incineration. The Marisol facility is located on a 4-acre industrial site; topography is flat.
(c) Safety Kleen Envirosystems of Puerto Rico, Highway 2, KM. 51.0, Manati, Puerto Rico 00701. Safety Kleen operates under permit number PRD090399718. Safety Kleen carries out cement kiln incineration. The Safety Kleen facility is located in a rural area and the topography is flat.

Ringaskiddy.- Disposal of rejected drug substance from the Ringaskiddy facility may be at any of four locations, all of which have a temperate climate:

(a) Rechem International Ltd., Pontypool, Wales, UK. Licensing authority: Torfaen Borough Council. License number: 1. The facility is in a rural environment on the outskirts of a city and in a valley.
(b) Rechem International Ltd. in Southampton, England. Licensing authority: Hampshire County Council. License number: 7/82A. The facility is in an industrial park approximately 13 miles outside the city in a flat area less than a mile from the sea.
(c) Cleanway Ltd. in Ellesmere Port, England. License number: 60877.The facility is in a heavily industrialized area, on the outskirts of a city, and surrounded by an oil refinery. The topography is flat and the nearest housing is more than one mile away.
(d) Ekokem OY, in Riihimaki, Finland. License numbers: 281/A231 and 230/A231. The facility is in a rural, hilly area with only 2 to 3 residences within 500 meters.

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

A. DRUG SUBSTANCE

USAN: sertraline hydrochloride

Chemical Name: (1S-cis)-4-(3,4-dichlorophenyl)-1, 2, 3, 4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride

Code: CP-51,974-01

Molecular Formula: $C_{17}H_{17}NCl_2 \cdot HCl$

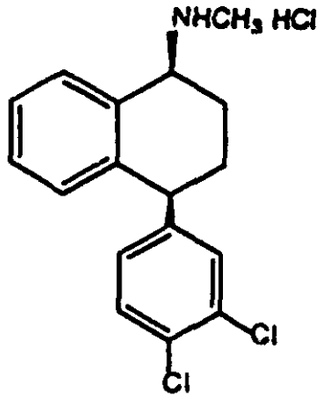
Molecular Weight: 342.7

Chemical Abstracts Service Registry Number: 79559-97-0

Physical Description: White powder

Impurities: Pharmaceutical Grade, purity not less than 97%. The structures of Related Compounds submitted in Confidential Appendix 1 that are impurities in drug substance are identified along with applicable limits in Confidential Appendix 25.

Structural Formula:



B. Drug Product

The drug product is an aqueous-film-coated tablet comprised of drug substance formulated with pharmaceutically-acceptable excipients (Confidential Appendix 1), available in 50 and 100 mg strengths (as sertraline). Packaging will be in HDPE bottles, with suitable closures (metal and/or plastic), and in blister packaging [Al foil and 3-component film (PVC/PE/PVDC)]; additional paper, paper board and corrugated packaging will be employed. The approved dosage formulations will be used for the OCD indication. The recommended dosage for the OCD indication is 50 to 200 mg per day.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT:

Summary.- The manufacture of sertraline hydrochloride drug product and drug substance needed for the subject action will not have a significant impact on manufacturing emissions or controls at any of the above-cited manufacturing sites.

The applicant certifies that applicable national, state and local environmental and occupational emissions standards and requirements will be met.

Introduction of sertraline into the environment through use for both the subject action and the previously-approved indication is projected to result in a maximum expected environmental concentration (MEEC) in the wastewater treatment plant (WWTP) and ensuing aquatic release environments of less than 2 parts per billion (ppb) of total excretion products comprising less than 0.2 ppb of sertraline.

A. MANUFACTURE

Summary.- A supplement to the NDA, which included changes in the Process Monograph Description (PMD), was submitted to FDA on 2/19/91. In this supplement the original PMD (#03388, dated 2/2/88) was replaced with a modified PMD (# 35190, dated 12/17/90). A supplemental application providing for the manufacture of drug substance at the Barceloneta, PR facility was submitted 1/24/92 and approved 6/2/92.

Manufacture of sertraline hydrochloride for use in the U.S. is currently being carried out at the Pfizer plants in Groton, CT and Barceloneta, PR. Manufacture of sertraline hydrochloride drug product is currently being carried out in the Pfizer Brooklyn, NY, and Barceloneta, PR facilities. Manufacture of sertraline hydrochloride drug substance and drug product for the subject action will be carried out at the same sites. In addition, the Pfizer plant in Ringaskiddy, Ireland, which now produces sertraline hydrochloride for non-U.S. use, may also produce sertraline hydrochloride drug substance for use in the U.S. These plants are modern, multipurpose facilities designed for the efficient production of pharmaceuticals and chemicals, management of process wastes, and minimization of occupational and environmental releases.

Emissions from manufacture of sertraline hydrochloride drug substance and drug product are delineated below, along with a listing of controls exercised, a citation of applicable site-related emissions regulations and requirements, a statement of compliance with applicable emissions requirements, and a discussion of the effect of approval on current applicable emissions requirements. In summary, the expected increase upon current production loading from approval of the proposed action will not have significant impact on the controls, emissions or compliance at these facilities.

1. Emissions

Emissions from manufacture of sertraline hydrochloride drug substance and drug product into the occupational, atmospheric, aquatic and terrestrial environments are delineated in the Confidential Appendix 1. Environmentally-insignificant amounts of drug substance, drug product, and manufacturing process components and intermediates will be emitted into these environments, based on the controls applied. Total emissions of these materials will conform to applicable emissions requirements and permits identified in Item 6.A.2 below. Concentrations/quantities of drug substance expected to be emitted in wastestreams are outlined in Confidential Appendix 24.

a. Occupational.- Based on equipment design and materials handling procedures and volatility, substances which could be emitted into the workplace environment at or below permissible levels are listed in the Confidential Appendix 1 "Oc" column.

b. Atmospheric.- Based on criteria of volatility, equipment design and volume of use, substances which could be emitted into the atmospheric compartment at or below permitted or regulated levels are listed in the Confidential Appendix 1 "At" column. Insignificant amounts of drug substance will be release to the atmospheric compartment as outlined in Confidential Appendix 24.

c. Aquatic.- Liquid discharges from the manufacturing facility, comprising aqueous process streams and wash waters and equipment and facilites washings are estimated to contain substances at or below permitted, regulated or contracted levels as listed in the Confidential Appendix 1 "Aq" column. Concentrations of drug substance expected to be released into the aquatic compartment at the several manufacturing sites are outlined in Confidential Appendix 24.

d. Terrestrial.- Solid wastes comprising filter cakes containing insignificant amounts of adsorbed process constituents, non-dischargeable liquid wastes containing process by-products such as still-bottoms, and routine solid wastes, packaging materials and components, and certain work-in-process streams, are estimated to contain substances at or below permitted, regulated or contracted levels as listed in the Confidential Appendix 1 "Te" column. Quantities of drug substance expected to be released as solid waste at the several manufacturing sites are outlined in Confidential Appendix 24.

2. Controls, Exposure/Emissions Requirements

Emissions controls are used in the manufacturing process to ensure compliance with occupational exposure limits and with general emissions requirements, specific standards (including priority pollutants and ozone depleting chemicals), permit limits, and contract requirements for the atmospheric, aquatic and terrestrial release environments.

a. Occupational.- Workplace exposures are controlled via appropriate equipment design, material and product transfer procedures and protective equipment. Properly designed equipment and facilities, administrative controls and personal protective equipment are used to minimize worker exposure in the handling of solids and liquids. Examples include use of closed reaction systems, pipe-line additions and transfers, local ventilation and dust collection. Gas transfers will of necessity be carried out via close-piping systems. The use of masks, self-contained breathing apparatus, protective clothing, etc, will be prescribed as necessary when engineering and administrative controls are insufficient to ensure worker protection.

Monitoring of work areas is carried out periodically to assure compliance with all required occupational exposure limits (eg, PEL's/STEL's). In U.S. facilities employees are informed of potential workplace hazards via a routine training program in compliance with the OSHA Hazard Communication Rule, 29 CFR 1910.1200. Material Safety Data Sheets (MSDS's) for materials used in the manufacture of drug substance and drug product are provided to workers, as required. Pertinent MSDS's are provided in Confidential Appendix 2. The MSDS for sertraline hydrochloride is provided in Appendix 3.

Workplace exposure will be in compliance with the emissions requirements listed in Appendix 5.

b. Atmospheric.- Air emissions from the manufacturing process will be controlled through the use of filters (HEPA and the like) and scrubbers on powder systems; emissions from liquid and gaseous handling systems will be controlled via use of proper operational procedures (eg back-venting during solvent transfer) and properly designed condensing and scrubbing systems (eg vent condensers and substance-specific scrubbers). Solvent streams will be recovered/ recycled as much as is practicable; disposal of unusable solvent streams will be via pyrolysis/ incineration. Some liquid and solid waste streams are to be pyrolysed/ incinerated. Off-site incineration will be conducted at fully-licensed contract facilities.

   Atmospheric emissions will be in compliance with the requirements listed in Appendix 5; applicable permit/license numbers, issuing authorities and expiration dates are listed in Appendix 5.

c. Aqueous.- Liquid discharges from the manufacturing process, comprising primarily aqueous process streams and wash waters and equipment/facilities washings, will be treated and disposed of using on-site or publicly-owned/operated WWTP's.

   Aqueous emissions will be in compliance with the requirements listed in Appendix 5; applicable permit/license numbers, issuing authorities and expiration dates are listed in Appendix 5.

d. Terrestrial.- Non-hazardous and hazardous wastes will be managed as follows:

   On-site incineration/pyrolysis.- Regulations pertaining to operation of the on-site incineration/pyrolysis facilities are outlined under "(b) Atmospheric" and "(c) Aqueous" above. Off-site incineration will be conducted at fully-licensed contract facilities.

   Solids and liquids that are not incinerated/pyrolysed and residues emanating from incineration/ pyrolysis facilities will be disposed of by licensed contractors or at approved landfill sites in accordance with the requirements listed in Appendix 5; applicable permit/license numbers, issuing authorities and expiration dates are listed in Appendix 5.

3. Citation of Compliance With Applicable Emissions Requirements

   The applicant certifies that emissions, discharges and wastes from production of sertraline hydrochloride drug substance and drug product for the previously-approved and the subject OCD indications will be in compliance with applicable occupational health and safety standards and federal, state and local emissions regulations and permits, or with applicable consent orders and administrative orders and directives for the following facilities: Groton, CT; Barceloneta, PR; Brooklyn, NY; and Ringaskiddy, Ireland. Official responses from Pfizer Pharmaceutical Production Corporation to the Environmental Protection Agency (Ireland) with respect to environmental monitoring data for the month of February, 1995, documenting full compliance with applicable license requirements at the Ringaskiddy plant, are enclosed as Confidential Appendix 26.

4. Effect of Approval of the Action on Compliance With Current Emissions Requirements

Approval of the proposed action will have a minimal effect upon compliance with existing emissions requirements at the applicable manufacturing sites.

B. USE

Sertraline hydrochloride is to be used both in hospitals and in home-use environments. The projected quantities of sertraline hydrochloride to be used in a mature U.S. market for the earlier-approved (depression) and subject-approval (OCD) indications -- and the basis for this projection -- are provided in Confidential Appendix 5. Assessment of potential environmental effects from sertraline hydrochloride use (item 8, below) will be based on projected combined emissions from both indications.

1. Metabolism/Excretion Summary

Sertraline undergoes extensive first-pass metabolism in man. The results of excretion studies with orally-administered labeled sertraline are summarized in Confidential Appendices 6 and 7.

2. Usage Emissions -- Quantities and Concentrations

The maximum expected environmental concentration (MEEC) in the WWTP hydraulic of the sum total of excretion products from sertraline hydrochloride usage for both indications in a mature market is projected to be less than 2 part per billion (ppb), calculated as follows (Reference 1):

MEEC (ppm in environment) = (lb/yr production) x 8.9 E^{-9} = (confidential) x 8.9 E^{-9} = less than about 2 ppb

In a similar fashion the maximum expected environmental concentration (MEEC) in the WWTP hydraulic of excreted sertraline from sertraline hydrochloride usage for both indications in a mature market is projected to be less than 0.2 parts per billion (ppb).

The basis for these calculations is presented in Confidential Appendix 8.

C. DISPOSAL

Disposal of outdated/returned product, samples and rejected/off-specification drug substance and drug product are carried out as described under Item 4.D above. The permitted incineration procedures employed at the disposal facilities, as outlined above, preclude emissions of drug substance or other toxic substances into the environment.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Summary.- Physico-chemical fate data were obtained on sertraline hydrochloride as representative of drug-related substances emitted to the environment through use. Sertraline hydrochloride is a cationic substance over the range of environmental pH's and has moderate-to-low water solubility as a function of pH. Sertraline hydrochloride exhibits a pH-related octanol:water partition coefficient, with a log P of 2.9 at pH 7. Its potential to sorb to sewage sludge has been determined with the conclusion that sertraline will be retained to the extent of about 20% on sludge within WWTPs and be released to the extent of about 80% in the aqueous effluent under typical wastewater treatment plant operating conditions.

An exploratory batch activated sludge biodegradation test was carried out indicating that sertraline hydrochloride is inherently biodegradable.

A photolysis study was carried out in the presence of synthetic humic substances; a corrected photolytic half-life of 4.6 days was determined, indicating the sertraline would not be expected to persist in the external aquatic environment.

- Sertraline would not be expected to bioconcentrate based on its overall physico-chemical/fate profile.

A. PHYSICO-CHEMICAL/FATE DATA SUMMARY AND CALCULATIONS

See Appendix 1 for a detailed summary of physico-chemical/fate data. An abbreviated summary of key data is presented in the Table below. See Confidential Appendices for physico-chemical/fate study reports.

Table

Sertraline Hydrochloride
Physico-Chemical/Fate Data Summary

1. Melting Temperature: Melting points of 224.8 ±1.6 ^{0}C and 253.4 ±1.3 ^{0}C were observed for non-resolidified and resolidified samples, respectively.

2. Ultraviolet Absorption Spectrum: Absorption was observed for wavelengths at approximately 205, 266, 273 and 281 nm, with mean molar extinction coefficients of approximately 5×10^4, 0.9×10^3, 1×10^3, and 0.6×10^3 L./mol-cm, respectively.

3. Ionic Form: cation; pKa = 9.48-9.58

		pH 5	pH 7	pH 9
4.	Solubility (mg/L):	3690	588	8.46
5.	Log Kow:	2.0-2.1	2.9	4.4-4.8

6. Sludge Sorption: Kd =1,580, corresponding to retention of about 20% on sludge and 80% in the aqueous effluent under typical WWTP conditions.

7. Aerobic Aquatic Biodegradation: An exploratory batch activated sludge study indicated that sertraline hydrochloride was biotransformed to a mixture of more-polar and less-polar degradants, with approximately 9% and 32% of the original sertraline remaining in the 1 ppm and 20 ppm test levels, respectively, at day 45 of the study.

8. Indirect Photolysis: Sertraline was observed to undergo indirect aqueous photolysis in the presence of synthetic humic substance, with a corrected environmental half-life of 4.6 days.

B. TREATMENT PROCESSES

Emissions of sertraline and metabolites from drug usage will primarily be into municipal WWTPs.

1. Excretion/Sewer Line Residency Sertraline excreted into sewage systems will experience a mean 24-hour sewer line residency prior to WWTP entry. This environment is anaerobic.

2. WWTP Residency The majority of sewage in WWTP's is treated via the aerobic activated sludge process, with a mean hydraulic detention time of 8 hr and a mean sludge detention time of 1-8 days. The majority of sludge in WWTP's is then subjected to anaerobic sludge digestion (mean detention time of 30-60 days) or to incineration.

C. RELEASE COMPARTMENTS AND INITIAL RELEASE CONCENTRATIONS Sertraline hydrochloride is not expected to be substantially biotransformed during WWTP residency. The release environment for sertraline hydrochloride following WWTP residency will be primarily the external aquatic environment based on sludge sorption data.

The initial release concentration of sertraline hydrochloride into the external aquatic environment, assuming no change during WWTP residency and no sorption to sludge, is projected to be less than 0.1 ppb (see calculation, Item 6.B.2 above). Based on sludge sorption data (Kd = 1,580) the per cent retained on sludge within the WWTP environment will be about 20% (see Appendices 1 and 2):

Calculation of % removal onto sludge, assuming Kd = 1,580, 0.182 g/L primary and secondary sludge solids (dry weight, based on plant flow) and an aqueous effluent of 1000 g:

(amount of sludge) (Kd) / [(amount of sludge) (Kd) + (amount of water)] = fraction removed

(0.182 gms) (1580) / [(0.182 gms) (1580) + 1000 gms] = fraction removed onto sludge solids = 0.223

Correction for carry-over of sludge solids into the hydraulic:

(amount sludge carried over)/(total amount of sludge) = fraction of sludge carried over with the hydraulic = (0.015)/(0.182) = 0.082

fraction of fraction removed onto sludge solids that is carried over with the hydraulic = (0.082)(0.223) = 0.018

(0.223) - (0.018) = fraction retained on WWTP sludge solids = 0.205

D. FATE OF EMITTED SUBSTANCES

SUMMARY.- Based on the physico-chemical/fate data summarized above, sertraline would be expected to be released primarily into the external aquatic environment following WWTP residency and then to be degraded photolytically and/or microbiologically by environmental organisms. Sertraline would not be expected to persist, nor would it be expected to bioconcentrate based on its overall physico-chemical/fate profile.

1. Air. As a non-volatile, water-soluble, high-molecular-weight amine salt with a pKa above 9, sertraline will not enter the atmospheric environment from WWTP's or from effluents from WWTP's.

2. Soil Ecosystem. The potential for sertraline hydrochloride to be released to the soil environment following WWTP residency via retention on sludge and sludge amendment to soil is judged minimal based on current patterns of WWTP sludge utilization.

3. Aquatic Ecosystem. Sertraline is expected to enter -- and remain in -- the external aquatic environment following WWTP residency and then to be degraded via indirect photolysis and/or to be biodegraded by aerobic aquatic microorganisms.

A series of biodegradation screening tests was carried out to assess the potential for sertraline hydrochloride to biodegrade in the presence of high levels of microbial inocula from diverse environmental compartments. The results of these studies suggested that sertraline hydrochloride would not likely biodegrade under stringent test conditions (eg, such as those in the FDA Technical Assistance Document 3.11, Aquatic Aerobic Biodegradation). An exploratory batch activated sludge biodegradation test was then carried out in which typical levels of WWTP sludge organisms were exposed to sertraline hydrochloride while being maintained on a synthetic sewage feed. The results of this study showed that WWTP organisms have the capability to biotransform sertraline to a mixture of more-polar and less-polar substances, albeit at a rate that is too slow to serve as a relevant environmental depletion mechanism. Based on this data sertraline hydrochloride is judged inherently biodegradable, however, and would not be expected to persist in the aquatic environment.

The subject indirect photolysis study indicated that the half-life under the explicit test conditions employed was 4.6 days. The study was conducted in Wareham, MA (42^0 N latitude) using natural sunlight during September 1992. During the study, cloud cover ranged from thick, heavy clouds with rain, to sunny days with no clouds.

Unlike the situation with direct photolysis, there are no equations relating environmental half-life to season or latitude for indirect photolysis. The output of a direct photolysis study is a quantum yield determination which can be used to calculate half-life at any latitude and season. Nonetheless, there are literature studies comparing the effect of season, cloud cover, and humic source. On the basis of these studies, as detailed in Appendix 4, half-lives for sertraline might be expected to range from approximately 18 days during northern winters to 2 days during southern summers. Based on these considerations, sertraline would not be expected to persist in the external aquatic environment based on its photo-lability in the presence of humic substances.

The potential for sertraline to bioconcentrate is considered low based on its physico-chemical properties, its photolytic lability and its potential to biodegrade.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES :

SUMMARY.- Effects data were obtained on sertraline hydrochloride as representative of drug-related substances emitted to the environment through use.

No adverse effects are projected to humans, animals, plants or environmental organisms from usage of sertraline hydrochloride for the depression and OCD indications following excretion of unchanged drug into the WWTP and ensuing aquatic release environments. Sertraline hydrochloride at the projected MEEC of less than 0.2 ppb in WWTP's would not be expected to be toxic nor inhibitory to sewage treatment organisms. Sertraline hydrochloride would not be expected to be toxic to aquatic organisms. These conclusions are based on data on representative mammalian and environmental organisms showing: (a) a low level of toxicity to mammals, (b) absence of adverse effects in a WWTP treatability study, (c) toxicity to microbial species at concentrations orders of magnitude above the MEEC; and

(d) toxicity to daphnids, which are useful indicators of environmental toxicity, at concentrations orders of magnitude above the MEEC. The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin, a mechanism which is not likely to have a counterpart effect in non-mammalian organisms.

In addition, no adverse effects are projected from the point-source entry of sertraline hydrochloride into the WWTP and ensuing release environments from the drug substance and drug product manufacturing processes.

A. HEALTH EFFECTS (SAFETY TO ANIMALS AND HUMANS) Sertraline hydrochloride is a substance with a low order of mammalian toxicity consonant with its anticipated therapeutic use in man at 50 - 200 mg per day (as sertraline) for the OCD indication . Animal health effects data on sertraline hydrochloride are documented in the Confidential Appendix 20.

B. ENVIRONMENTAL EFFECTS – USE The potential environmental effects of emitted substances from sertraline hydrochloride use can be considered from the perspective of the two major release compartments: (1) WWTP's and (2) aquatic ecosystem, as outlined in item 7 above.

1. WWTP's Simulated waste streams from the projected manufacture of sertraline hydrochloride were shown to be neither toxic nor inhibitory to a model activated sludge sewage treatment process simulating the operation of the Barceloneta, PR, Regional Treatment Plant at a sertraline hydrochloride concentration of 0.09 ppm (Confidential Appendix 21).

MEEC levels of < 0.2 ppb sertraline hydrochloride within WWTP's are, therefore, judged inconsequential to the assorted autotrophic aerobes and other microorganisms necessary for effective activated sludge sewage treatment. See also test data from the Microbial Growth Inhibition test, Item 8.B.2 below, for further evidence of safety to representative environmental organisms.

2. External Aquatic Environment Levels of sertraline hydrochloride of the order of < 0.2 ppb are projected to be present in the immediate vicinity of the WWTP effluent release environment – assuming no biodegradation and no dilution (worst case scenario). This MEEC level of sertraline hydrochloride is judged inconsequential to aquatic organisms based on results of Microbial Growth Inhibition and Daphnia magna static acute toxicity test data:

Microbial Growth Inhibition.- The following test data from the Microbial Growth Inhibition test (FDA 4.02; see Confidential Appendix 22) are cited:

Species	Sertraline MIC* (ppm)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	40.0
Bacillus subtilis	10.0
Nostoc	4.0

* lowest concentration that inhibited growth, as ppm sertraline free base

- Implications: Sertraline hydrochloride shows a safety margin to the major classes of environmental microbial organisms of 4 to 7 orders of magnitude at its projected MEEC in the aquatic release environment.

Acute Toxicity to Daphnids.- The following test data from the Acute Toxicity to Daphnids (*Daphnia magna*) Under Static Conditions (FDA 4.02; see Confidential Appendix 23) are cited:

48-hour EC (effective concentration)$_{50}$ = 0.56 ppm

NOEC (no observed effect concentration) = 0.28 ppm

- Implications: Sertraline hydrochloride shows a safety margin of >3 orders of magnitude to daphnids, which are useful indicators of environmental toxicity, at its projected MEEC in the aquatic release environment.

C. ENVIRONMENTAL EFFECTS – MANUFACTURE The potential environmental impact of point-source entry of sertraline hydrochloride manufacturing emissions can be considered from the perspective of the two major release compartments: (1) WWTP's and (2) aquatic ecosystem. As noted in theTable, Confidential Appendix 27, the MEEC/MIC (Microbial Growth Inhibition, taken as an index of safety to WWTPs) and the MEEC/daphnia NOEC (taken as an index of safety to external aquatic organisms) ratios for each of the manufacturing sites portend substantial safety factors to both WWTP and external aquatic organisms, based on the maximum projected release concentrations documented in Confidential Appendix 24.

9. USE OF RESOURCES AND ENERGY:

As noted in manufacturing item 6, a major portion of raw materials used in the manufacture of sertraline hydrochloride is recovered including recoverable and recyleable solvents. About 1.3 x 10^5 BTU's of steam and 1.7 x 10^9 BTU's of electricity are estimated to be required to produce1000 kilograms of sertraline hydrochloride and the resultant drug product. Insignificant amount of minerals will be used in the production process. No effects of manufacture are expected upon endangered or threatened species or upon property listed in or eligible for listing in the Federal Register of Historic Places.

10. MITIGATION MEASURES:

In addition to the stringent controls exercised to ensure workplace and environmental compliance, the manufacture of sertraline hydrochloride will be carried out under the supervision of pharmaceutical professionals and will entail an active equipment maintenance program. Procedures are in place providing for containment of spills or leaks and maintaining personnel training for emergency action in the event of an unusual situation which might result in an emission or occupational exposure. Employees are provided necessary personal protective equipment, and MSDS's are available, as required, for all employees who work in the manufacturing areas.

11. ALTERNATIVES TO THE PROPOSED ACTION:

No significant potential adverse environmental impacts are envisioned for the usage or manufacture of sertraline for the existing depression and proposed OCD indications, based on available data and projected fate and effects scenarios. Therefore, no alternatives to the proposed action are needed. An alternative to the proposed action is, however, no action. In this case the therapeutic benefits of sertraline -- namely, that it does not cause certain adverse effects associated with other antidepressant/ antiobsessive drugs -- would not be available to the OCD patient population.

12. PREPARERS:

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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, Developmental Research

Irving M. Goldman — June 15, 1995

Signature Date

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15. APPENDICES

1. Physico-Chemical/Fate/Effects Data Summary
2. Methodology for Use of Sludge Kd Values
3. MSDS for Sertraline Hydrochloride
4. Discussion in Support of Indirect Aqueous Photodegradation as a Viable Removal Mechanism
5. Applicable Exposure and Emissions Requirements for the Occupational, Atmospheric, Aquatic and Terrestrial Environments. Applicable Permit/License Numbers, Issuing Authorities and Expiration Dates

1. Physico-Chemical/Fate/Effects Data Summary

Appendix 1

Physico-Chemical/Fate and Effects Data Summary

This Appendix provides physico-chemical/fate and effects data summaries.

1. Hydrolytic Stability:

   Examination of sertraline under a variety of severe challenge conditions of pH and temperature provided evidence that sertraline is hydrolytically stable under conditions of environmental exposure and fate/effects testing.

   Reference: Confidential Appendix 10, NDA # 19-839, p. 3 013

2. Melting Point (FDA 3.06):

   Melting points of 224.8 ±1.6 ^{0}C and 253.4 ±1.3 ^{0}C were observed for non-resolidified and resolidified samples, respectively.

   Reference: Confidential Appendix 11 (Study #2438-0991-6167-805)

3. Ultraviolet-Visible Absorption Spectrum (FDA 3.05):

   Absorbance was observed for wavelengths at approximately 205, 266, 273 and 281 nm, with mean molar extinction coefficients of approximately 5 x 10^4, 0.3 x 10^3, 1 x 10^3, and 0.6 x 10^3 L/mol-cm, respectively.

   • Implications: Lack of substantive absorption above 290 nm precludes facile direct photolysis; see results of indirect photolysis, item 9 below.

   Reference: Confidential Appendix 12 (Study #2438-0991-6170-850).

4. Water Solubility (FDA 3.01)

   The following mean solubility values were observed:

pH	5	7	9
mg/L	3690	558	8.46
SD	263	16	0.46

   • Implications: The lower solubility at pH 9 is at the extreme of environmental pH. High water solubilities are associated with retention in aquatic environments and low tendancy to bioconcentrate.

   Reference: Confidential Appendix 13 (Study #2438-6164-0991-700).

5. Dissociation Constant (pKa) (Pfizer Laboratory Methods and FDA 3.04):

A. Pfizer Laboratory Methods: pKa Values of

9.48 ± 0.04 and 9.58 ± 0.05

were obtained using a potentiometric method with calculations by the method of Clarke and Cahoon and by the method of curve subtraction, respectively. This pKa range is consistent with values for analogous tetraryl amines.

Reference: Confidential Appendix 14 (Pfizer Laboratory Study)

B. FDA 3.04: Following the procedure of FDA Technical Assistance Document 3.04, a cosolvent (50% methanol) was employed owing to the limited aqueous solubility of sertraline at alkaline end of the titration curve. An apparent pKa of:

8.60 ±001

was obtained in this study.

Reference: Confidential Appendix 15 Study #2438-0991-6166-855)

- Implications: Sertraline will exist primarily as the cationic species over the range of environmental pH's, diminishing its tendency to bioconcentrate.

6. n-Octanol/Water Partition Coefficient (Kow) (FDA 3.02):

The following log mean Kow values were obtained:

pH		7	9
Log(Mean Kow)	2.0-2.1	2.9	4.4-4.8

- Implications: As noted in Technical Assistance Document 3.02, Log Kow values greater than 2 - 3 portend possible bioconcentration in lipoidal tissues, based on Kow/BCF (bioconcentration factor) correlations developed using a variety of neutral substances (mostly pesticides). The relevance of this correlation to the present situation, in which sertaline exists primarily as the salt form at environmental pH's and is not persistent in the environment (see results of biodegradation and indirect photolysis studies, below) is not established. There are also correlations of Kow with Koc (soil/sediment organic carbon partition coefficient), but the relevance of these correlations to cationic substances and to sorption to sludge is not established. Results of a sludge sorption study are reported below.

Reference: Confidential Appendix 16 Study #2438-0991-6165-705)

7. Sludge Sorption (Kd) (Generally Following FDA 3.08):

Mean sludge Kd values of 2440 (S.D. 271) and 814 (S.D. 210) were obtained in the preliminary test using liquid scintillation counting of the sorbed and unsorbed phases for non-hardened synthetic sewage and hardened synthetic sewage, respectively, indicating that sertraline may be sorbing by a cation exchange mechanism. The following mean sludge Kd value was obtained using three sludge sources in the presence of hardened synthetic sewage in the definitive test:

1,580 (S.D. 403)

- Implications: This Kd translates to a retention of about 20% of sertraline onto sludge and the release of about 80% in the aqueous effluent under typical wastewater

treatment plant conditions (see Appendix 2 for methodology for use of sludge Kd values). Furthermore, the preliminary test data suggest that greater than 20% of sertraline may be removed from the hydraulic in wastewater treatment facilities in soft water regions.

Reference: Confidential Appendix 17 (Study # 2438-0892-6184-710)

8. Aquatic Aerobic Biodegradation (Batch Activated Sludge Exploratory Test):

An exploratory matrix study using a variety of environmenal inocula under diverse acclimation conditions was carried out to assess the inherent biodegradability of sertraline hydrochloride. Included in these studies were WWTP and soil matrices as well as a modified SCAS test (OECD Test Guideline 302A). A batch activated sludge (BAS) screening study was then carried out and shown to provide conditions under which sertraline was biotransformed to a mixture of more-polar and more-nonpolar degradants. At test termination (day 45), approximately 9% and 32% of the original sertraline remained in the 1 ppm and 20 ppm test concentration levels, respectively.

[During the course of this exploratory probe a definitive photolysis study was carried out with positive results as described in item 9, below.]

- Implications: This data -- along with the results of the indirect photolysis study below -- suggest that sertraline would not persist in the external aquatic environment.

Reference: Confidential Appendix 18 Study # 2438-0991-6171)

9. Determination of Indirect Photolysis (EPA-TSCA 40 CFR 795.70).-

A photolytic depletion mechanism was observed when sertraline was subjected to indirect aqueous photolysis in the presence of synthetic humic substance according to the above-identified test guideline. A corrected photolytic half-life of:

4.6 days

was determined in this study.

- Implications: Sertraline would not be expected to persist in the external aquatic environment owing to its lability under indirect photolysis conditions.

Reference: Confidential Appendix 19 Study #2438-0892-6189-720)

10. Microbial Growth Inhibition (FDA 4.02):

Species	Sertraline MIC* (ppm)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	40.0
Bacillus subtilis	10.0
Nostoc	4.0

* lowest concentration that inhibited growth, as ppm sertraline free base

- Implications: Sertraline hydrochloride shows a safety margin to the major classes of environmental microbial organisms of 4 to 7 orders of magnitude at its projected MEEC in the aquatic release environment.

Reference: Confidential Appendix 22 Study #2438-0991-6168-770)

11. Acute Toxicity to Daphnids (FDA 4.08):

48-hour EC (effective concentration)$_{50}$ = 0.56 ppm

NOEC (no observed effect concentration) = 0.28 ppm

- Implications: Sertraline hydrochloride shows a safety margin of >3 orders of magnitude to daphnids, which are useful indicators of environmental toxicity, at its projected MEEC in the aquatic release environment.

Reference: Confidential Appendix 23 Study #2438-0991-6169-110)

2. Methodology for Use of Sludge Kd Values

APPENDIX 2

METHODOLOGY FOR USE OF

SLUDGE Kd VALUES

REMOVAL OF SUBSTANCES WITH WASTEWATER TREATMENT PLANTS.-

Assuming the simplest case in which volatilization, biodegradation and hydrolysis are negligible, the removal of substances from wastewater onto and/or into the non-aqueous components within WWTPs (eg., grit, sludges, oils and greases) will depend on their partition coefficients, K_d. K_d may be defined as follows:

$$K_d = C_S/C_L$$

where C_S is the concentration of material sorbed to and/or partitioned in the solid phase (g/g), and C_L is the concentration of material in wastewater (g/g). In this way the partition coefficient, K_d, is unitless.

For a given discharge, the fraction of a substance removed from the aqueous phase onto a non-aqueous phase (eg., sludge) is given by the following relationship.

$$\text{Fraction on solid} = \frac{(\text{amount of solid})(K_d)}{[(\text{amount of solid})(K_d) + (\text{amount of water})]}$$

Case 1.- For the simplest case, in which sorption to sludge in the secondary aeration chamber is the only removal mechanism (ie., sorption to and/or partitioning into coarse screenings, grit, primary sludge and surface skimmings are neglected, and no biological breakdown or volatilization occur), the distribution of a drug substance between the secondary sludge and the aqueous effluent leaving the secondary clarifier would be determined as illustrated below.

- Note that although the concentration of sludge in the secondary aeration chamber is approximately 2500 ppm, in the sludge return line is approximately 10,000 ppm, and in secondary sludge is approximately 6,000 - 10,000 ppm, it is the amount of sludge that is wasted per unit of aqueous effluent leaving the WWTP that determines the relationship between measured K_p and the fraction removed on sludge. The amount of secondary sludge wasted is 135 mg/L, based on plant flow, and is comprised of 120 mg/L secondary sludge solids and 15 mg/L suspended solids carried over into the liquid effluent.

Computation:

- Assume K_p = 1000, based on determination using secondary sludge solids, one liter of wastewater, and sludge solids having the same density as the wastewater
- Assume amount of sludge = 120 mg/L; concentration of suspended solids in the treated effluent = 15 mg/L
- Amount of sludge in one liter = (0.120 g/L + 0.015 g/L) x 1 L = 0.135 g
- Amount of liquid in one liter = (1,000 g/L - 0.135 g/L) x 1 L = 999.865 g
- Thus, the fraction on the solids is:

$$\text{Fraction on solid} = \frac{(\text{amount of solid})(K_p)}{[(\text{amount of solid})(K_d) + (\text{amount of water})]}$$

$$= \frac{(0.135\ g)(1000)}{[0.135\ g)(1000) + (999.865 g)]} = 0.12$$

The percentage distribution between the three components considered in this example would be as follows:

- Percentage in treated effluent = 88.1
- Percentage in the suspended solids in treated effluent = 1.3
- Percentage in dewatered sludge = 10.6

Case 2.- For the case in which sorption to primary sludge solids and to sludge in the secondary aeration chamber are the only removal mechanism (ie., sorption to and/or partitioning into coarse screenings, grit and surface skimmings are neglected, and no biological breakdown or volatilization occur), the distribution of a drug substance between the sludges and the aqueous effluent leaving the secondary clarifier would be determined as illustrated below.

In addition to the comments under Case 1 above, note that the suspended solids from the primary clarifier comprising 150 mg/L based on plant flow consist of 25% microbial biomass; this contrasts with the composition of suspended solids and secondary sludge from the secondary clarifier which is 80% organic. It is possible, therefore, to derive a distribution into the relevant release compartments using K_p as measured using secondary sludge solids.

Computation:

- Assume K_d = 1000, based on determination using secondary sludge solids, one liter of wastewater, and sludge solids having the same density as the wastewater

- Assume amount of secondary sludge = 120 mg/L; amount of primary sludge = [(150 mg/L)(0.25)]/(0.80) = 47 mg/L, corrected on a secondary sludge basis; concentration of suspended solids in the treated effluent = 15 mg/L

- Amount of sludge in one liter = (0.120 g/L + 0.047 g/L + 0.015 g/L) x 1 L = 0.182 g

- Amount of liquid in one liter = (1,000 g/L - 0.182 g/L) x 1 L = 999.818 g

- Thus, the fraction on the solids is:

$$\text{Fraction on solid} = \frac{(\text{amount of solid})(K_d)}{[(\text{amount of solid})(K_d) + (\text{amount of water})]}$$

$$= \frac{(0.182\ g)(1000)}{[0.182\ g)(1000) + (999.818g)]} = 0.154$$

The percentage distribution between the three components considered in this example would be as follows:

- Percentage in treated effluent = 84.6
- Percentage in the suspended solids in treated effluent = 1.27
- Percentage in dewatered sludge (origin: secondary solids) = 10.15
- Percentage in dewatered sludge (origin: primary solids) = 3.98

The corresponding distribution for other K_d values is given in the following table, based on Case 2 assumptions.

K_d value	Percentage distribution in		
	Wastewater	Suspended solids	Dewatered sludge
610	90	0.82	9.18
1830	75	2.05	22.95
5495	50	4.1	45.9
16480	25	6.15	68.85
49450	10	7.38	82.62

3. MSDS for Sertraline Hydrochloride

CENTRAL RESEARCH
EXPERIMENTAL SUBSTANCE
MATERIAL SAFETY DATA SHEET

Pfizer, Inc.
Central Research Division
Eastern Point Road
Groton, Connecticut 06340
Emergency Telephone: (203)441-410

August, 1990
[supersedes July 1987]

MSDS # 0104

Sertraline Hydrochloride Salt

[CP-51,974; d-cis-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-napthalenamine-hydrochloride]

SECTION I: *PHYSICAL DATA*

Melting Point:	251°C
Appearance:	White to off-white crystalline powder
Solubility:	Sparingly in water
Description:	Sertraline hydrochloride is a white crystalline solid which is intended for use in the treatment of depression. Sertraline is orally active and, thus, ingestion or inhalation must be avoided.
Molecular Formula:	$C_{17}H_{17}NCl_2HCL$ (MW = 342.7)

SECTION II: *FIRE AND EXPLOSION HAZARD*

Sertraline hydrochloride is weakly flammable when exposed to an open flame. This material is a stable organic material, however, normal precautions must be taken to control the creation of dusts, particularly in milling and grinding operations. Sertraline has been noted as a moderate explosion hazard with a severity rating of 0.93 relative to pittsburg coal dust. Sertraline does not present a fire hazard. Fires involving Sertraline hydrochloride may be extinguished with any appropriate medium, including water.

SECTION III: *HEALTH HAZARD INFORMATION*

Sertraline has relatively low toxicity. The potential hazards of Sertraline hydrochloride are associated with its therapeutic activity and pharmaceutical action. Sertraline is not a class B poison by DOT protocols. Normal handling precautions are adequate to control exposure to Sertraline. Overexposure to Sertraline is most likely through ingestion or inhalation of the material. One time ingestion of up to 2 gm of Sertraline has resulted in no adverse effect.

SECTION IV: *FIRST AID INFORMATION*

Ingestion: In the event of ingestion of Sertraline (solid or liquid solutions), medical attention should be summoned immediately.

Inhalation: Personnel who have inhaled Sertraline should be removed to fresh air and observed by medical personnel.

Skin Contact: Skin contact with solids or solutions of Sertraline should be washed thoroughly with water. Sertraline hydrochloride is not corrosive by DOT protocols. Contaminated clothing should be removed. If any effects are observed, medical attention should be sought. Sertraline may be slightly irritating to skin or eyes.

SECTION V: *REACTIVITY DATA*

Sertraline should be stored in closed containers away from heat and contact with oxidizers.

SECTION VI: *SPILL OR LEAK PROCEDURE*

Spills of Sertraline should be collected (scooped or swept) into appropriate recovery containers. Personnel involved in clean-up of spills, particularly solids, must wear respiratory protection; gloves and eye protection.

The area may be washed with water (weak alkaline solution to increase solubility).

SECTION VII: *PRECAUTION INFORMATION*

When handling Sertraline, normal protective measures that minimize the creation of dusts and personnel exposure must be employed. Gloves, respiratory protection, eye protection, and appropriate clothing should be worn when handling Sertraline solids.

issued by: D. P. Brannegan

4. Discussion in Support of Indirect Aqueous Photodegradation as a Viable Removal Mechanism

Appendix 4

Discussion in Support of Indirect Aqueous Photodegradation as a Viable Removal Mechanism

The indirect photolysis study conducted with sertraline hydrochloride indicated that the half-life under the explicit test conditions employed was 4.6 days. The study was conducted in Wareham, MA (42 degrees N latitude) using natural sunlight during September 1992, as documented in Confidential Appendix 19, following EPA-TSCA guideline 40 CFR 795.70. During the study cloud cover ranged from thick, heavy clouds with rain to sunny days with no clouds. The following discussion is provided to address the relevance of the experimental results to projected rate of depletion in the aquatic environment, taking into consideration cloud cover, latitude, and seasonal variations in solar flux.

A search of the literaturedid not provide equations for calculating environmental half-life as a function of season and latitude for indirect photolysis as exist for direct photolysis. The output of a direct photolysis study is the quantum yield determination which can b e used to calculate half-life at any latitude and season. Nonetheless, several studies have been conducted comparing the effect of season, cloud cover, and humic acid source on photolysis rate. Zepp, et al, (Zepp, R.G., Baughman, G.L., Schlotzhauer, P.F., *Chemosphere*, 1981, 10, 109 and 119; Zepp et al, *Envir. Sci. and Techn.*, 1985, 19, 74; and Zepp et al. *Nature*, 1977, 278, 421) determined that the indirect photolysis of 2,5-dimethyulfuran was first order in the presence of humic acid. Over the period of a year, under a variety of meteorological conditions at Athens, GA, 2,5-dimethylfuran and disulfoton were exposed to sunlight in solutions containing humic acid. Calculated rate constants were found to be directly proportional to the light intensity. In distilled water, no degradation was observed, confirming that the degradation for these compounds was entirely due to indirect photolysis. During the same set of studies, a comparison of humic acid sources was made, with the result being that the origin of humic acid has only a slight effect on photolysis half-life. A comparison of 9 different humic acids gave relative half-lives within a factor of 2. The half-life of 2,5-dimethylfuran at solar noon ranged from 5 to 10 minutes in the summer to approximately 20 minutes in winter. For disulfoton, the half-lives ranged from 5 hours in the summer to 12 hours in the winter. Rate constants determined for 2,5-dimethylfuran and disulfoton were directly proportional to light intensity.

This literature information can be applied to the relevance of the experimental half-life data obtained for the indirect photolysis of sertraline hydrochloride, for which the rate of indirect photolysis was 19-times faster than direct photolysis. Light intensity has been shown to be a function of both season and latitude. On a shorter scale, light intensity is a function of cloud cover, but data for the United States has been compiled showing latitudinal averages for light intensity as a function of season (Liefer, A., The Kinetics of Environmental Aquatic Photochemistry, ACS, (1988), p. 256). Tables of day-averaged specific light absorption rate constants for sunlight absorption by p-nitroanisole (PNA) and p-nitroacetophenone (PNAP) as a function of season and decadic latitude are presented. These tables give relative rate information for the degradation of these two compounds. The highest rate constants occur at 30 degrees N latitude during the summer when the sun is directly overhead (the earth is tilted 23 degrees toward the sun during summer in the northern hemishpere). These summer, 30 degrees N rate constants are 51.40 day^{-1} for PNA and 551 day^{-1} for PNAP. Next to 0 day^{-1} for 70 degrees N latitude in the winter, the lowest rate constants for the continental U.S. (30 to 50 degrees N) are 668 day^{-1} for PNA and 63.7 day^{-1} for PNAP. These rate constants are less than a factor of ten less than the largest, and indicate that sunlight intensity varies by less than an order of magnitude over the U.S. considering all seasons and latitudes. The values for 40 degrees N and fall season

(when the sertraline hydrochloride indirect photolysis study was carried out) are 2390 day^{-1} for PNA and 245 day^{-1} for PNAP. These are approximately one-half of the largest values and four times the lowest.

Based on the above considerations, half-lives for sertraline in the external aquatic environment, therefore, might be expected to range from approximately 18 days during northern winters to 2 days during southern summers, with the former value being suggested for calculational purposes to be on the conservative side. These projected environmental half-lives do not take into account variations in solar penetration into the water column and are, therefore, best-case indirect photolysis depletion rates.

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

Appendix 5

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:
- License No. AP 32/92, dated 8/14/92. License issued under Section 30 Air Pollution Act, 1987, by Cork County Council
- Licenses to Rechem International Ltd., Cleanaway Ltd., and Ekokem, Finland

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)
- NPDES permit CT 00000957
- 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 and 125
- Puerto Rico Sewer and Aquaduct Authority Facility Agreement, dated May 31, 1978 and amended August 23, 1978
- 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 and 125
- 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:
- License No. 49192 dated Novermber 25, 1992 granted by Cork County Council in accordance with the Local Government (Water Pollution) Acts, 1977 and 1990

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
- Resource Conservation and Recovery Act, permit PRD090346909 dated March 30, 1990, valid for 5 years
- 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:
- Landfill sites approved by Cork County Council
- Rechem International Ltd., Pontypool, Wales, UK. Licensing authority: Torfaen Borough Council. License number: 1
- Rechem International Ltd., Southampton, England. Licensing authority: Hampshire County Council. License number: 7/82A
- Cleanaway Ltd., Ellesmere Port, England. License number: 60877
- Ekokem, Finland. License numbers: 281/A231 and 230/A231

Appendix 5 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	PRASA	May 23, 1998
Water	PR0021237 (Expired June 1, 1993) NPDES permit for POTW	EPA	Expired June 1, 1993, but permit remains in effect until application for renewal is issued or denied.
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.)
Brooklyn, New York.-			
Water	Commissioner's Order/ Directive	NYC DEP	May 4, 2000
Air	PA533-73Y	NYC DEP	May 11, 1997
	PA530-93J	NYC DEP	December 17, 1997
	A610000234600A201	NYS DEC	February 1, 1996
	PA528-93N	NYC DEP	December 16, 1997
	PA529-93X	NYC DEP	December 16, 1997
	PA593-83P	NYC DEP	Renewal submitted; awaiting approval
	A610000234600A181	NYS DEC	February 1, 1996
	A610000234600A191	NYS DEC	February 1, 1996
	A61000023460A-121	NYS DEC	February 1, 1996
	PA537-73N	NYC DEP	Renewal submitted; awaiting approval
	PA237-92L	NYC DEP	May 12, 1996
	A610000234600A171	NYS DEC	February 1, 1996
Groton, CT.-			
Water	NPDES Permit # CT0000957	CT DEP	Indefinite. June 1985 permit remains in effect until application for renewal is issued or denied.
	Application for Renewal #85-232	CT DEP	Permit renewal expected prior to June 1, 1995
Air	Conditional Permit to Operate #0081	CT DEP	December 8, 1995
Ringaskiddy, Ireland.-			
Water	License to Discharge Register #W.P. (5) 2/93 (R); Dated August 4, 1993	Cork County Council	No designated expiration date.
Air	Air Emission License Reference Number AP 1/92; Dated August 14, 1992	Cork County Council	No designated expiration date.

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 19,839
Sertraline HCl 50 mg tablets
(Zoloft)
Reviewer: Raman Baweja, Ph.D.

Pfizer, Inc., New York, N.Y. 10017
Submission Dates: March 22, 1996
August 13, 1996
OCPB Receipt Date: August 30, 1996

REVIEW OF TWO DRUG INTERACTION STUDIES

Sertraline 50 mg and 100 mg tablets were appproved in December 1991 for the treatment of depression. In April 1996, a Warning statement was added to the Labelling which mentioned about the coadministration of sertraline with drugs metabolized by cytochrome P450 3A4. The sponsor would now like to insert language in the Precaution section of the labelling for the drug thereby removing the Warning statement (see also Comment 3, below). In this regard, the sponsor has performed two drug-drug interaction studies: (a) one in which terfenadine 60 mg bid was administered for 7 days either alone or with steady state sertraline, 200 mg qd, and (b) where 200 mg of carbamazepine was dosed twice daily either alone or with steady state sertraline, 200 mg qd . The results show that sertraline and terfenadine coadministration within the clinical dosage range do not increase the levels of circulating terfenadine. Also, carbamazepine AUC (0-12) and Cmax were decreased by 14% and 10 % respectively when coadministered with sertraline.

I. Study Report: No: 96-S-0504

Study Title: A Multiple Dose Study to Determine the Potential Interaction of Sertraline 200 mg/day, with Terfenadine in Healthy Subjects

Details of the Study are shown in Attachment I.

Briefly described, this was a 42 day, inpatient, parallel group, placebo controlled study with four treatment groups and a placebo lead-in. Forty normal healthy male volunteers completed the study. The 50 mg tablet of sertraline and the 60 mg marketed terfenadine tablet were used in the study. The focus of this study and the interest of the clinical division is to know the effect of sertraline on the levels of terfenadine, and therefore, the review will not be discussing the terfenadine metabolite levels (fexofenadine), though tables of PK parameters are attached to this review.

A look at the schematic of the study (Attachment I) indicates that the 10 subjects who were placed in Group A of the study did in fact have both terfenadine alone and terfenadine with sertraline treatments administered to them. The other three groups viz., B, C, and D, realistically do not

contribute to the study, and both OCPB and the clinical division had mentioned this earlier to the sponsor when they had requested input for the design of this study. Therefore, the focus for the results will be on the outcome seen for Group A where indeed each subject would serve as their own control.

Results and Discussion: Refer to Attachment I. Table 1 shows the AUC (0-12), Cmax and Tmax for terfenadine for the individual subjects in Group A with the last dose of terfenadine alone (i.e., day 8) and with the last dose of terfenadine with sertraline (i.e., day 40). Table 2 likewise shows the parameter values for fexofenadine (the metabolite of terfenadine). The mean and SD values for terfenadine and the metabolite are shown in Tables 3 and 4. Finally, the mean terfenadine ratios and the 90 % confidence intervals comparing dosing on day 40 to dosing on day 8 are shown in Table 5.

Figure 1 graphically shows terfenadine plasma concentration time plot over the course of day 8 and day 40. Figure 2 is a presentation of fexofenadine.

Table 1 shows that the AUC (0-12) of terfenadine decreased for 9 out of the 10 subjects when terfenadine was administered with sertraline (day 40 versus day 8); similarly, seven out of the 10 subjects showed a decline in their Cmax values upon coadministration.
From Table 3 it is seen that the mean value of AUC (0-12) for terfenadine alone was 30.7 ng*hr/ml and was 18.5 ng*hr/ml upon coadministration; a 40 % decrease.
Table 3 also shows that Cmax decreased by 25 % upon coadministration. Mean Tmaxs are comparable (2 hr).

Electrocardiography: On day 1 (baseline/placebo lead-in), mean (SD) QTc values are 373 (17) msec for Group A. For day 8 which is the steady state terfenadine alone treatment, Group A values are 375 (14) msec, and then for day 40 which is the last day of terfenadine with the last day of sertraline coadministration, the value is 379 (13) msec. These values are comparable.

A check of all the QTc values provided for all the Groups during the full course of this study shows the range to be: 373 (17) to 388 (16) msec.

Conclusion:

AUC (0-12) for terfenadine decreased by 40 % upon coadministration with sertraline; similarly, Cmax decreased by 25 %.

II. Study Report: Protocol No: 050-226

Study Title: A Double Blind, Placebo Controlled, Parallel Group Study To Investigate the Effects of Orally Administered Sertraline on the Plasma Concentration Profile of Carbamazepine and Its Epoxide Metabolite and the Cognitive Effects of These Two Drugs in Healthy Volunteers

Details of the study as well as the study results are presented in Attachment II.

The results show that AUC(0-12) and Cmax for carbamazepine decreased by 14 % and 10 % respectively. For the epoxide there was no change in the pharmacokinetic parameters between treatments (Figures 1 and 2 of Attachment II).

Comments to the Clinical Division:

1. Steady state coadministration of sertraline 200 mg q d decreased AUC (0-12) and Cmax of terfenadine by 40 % and 25 %, respectively.

Mean (SD) QTc values for all Groups during the full course of this study are between 373 (17) to 388 (16) msec. The Medical Officer is requested to verify the electrocardiography results.

2. Sertraline decreased AUC(0-12) and Cmax of carbamazepine by 14 % and 10 % respectively. For the epoxide there was no change in the pharmacokinetic parameters.

3. Reference is made to the Labelling statement from the sponsor regarding these drug interaction studies (see Attachment III of this review). Essentially it states that sertraline coadministration did not increase plasma concentrations of terfenadine or carbamazepine. The statement as written is accurate based on these two in vivo interaction studies. AUC and Cmax of terfenadine decreased by 40 % and 25 %, respectively, upon coadministration with sertraline. The effect of terfenadine or carbamazepine on sertraline was not investigated in these studies.

Recommendation:

Comments 1 - 3 are for the Clinical Division.

Raman Baweja 9/13/96.

Raman Baweja, Ph.D.

RD/FT Initialed by M. Hossain, Ph.D. 9/13/96

cc: NDA 19,839, HFD-120 (Baweja, Hossain, Malinowski), Drug, Chron and Reviewer files (Clarence Bott, HFD-870, Room 13B-31)

Attachment I

Group	Day 1	Day 2-8*	Day 9-10**	Day 11-13**	Day 14-16**	Day 17-19**	Day 20-33**	Day 34-40***
A	T. Placebo 1 tab	Terfen. 60 mg BID	S. Placebo 1 tab	Sert. 1X50 mg	Sert. 2X50 mg	Sert. 3X50 mg	Sert. 4X50 mg	Sert. 4X50 mg + Terfen. 60 mg BID
B	T. Placebo 1 tab	Terfen. 60 mg BID	S. Placebo 1 tab	S. Placebo 1 tab	S. Placebo 2 tabs	S. Placebo 3 tabs	S. Placebo 4 tabs	S. Placebo 4 tabs + Terfen. 60 mg BID
C	T. Placebo 1 tab	Terfen. 60 mg BID	S. Placebo 1 tab	S. Placebo 1 tab	S. Placebo 2 tabs	S. Placebo 3 tabs	S. Placebo 4 tabs	S. Placebo 4 tabs + T. placebo 2 tabs
D	T. Placebo 1 tab	Terfen. 60 mg BID	S. Placebo 1 tab	Sert. 1X50 mg	Sert. 2X50 mg	Sert. 3X50 mg	Sert. 4X50 mg	Sert. 4X50 mg + T. placebo 2 tabs

* Terfenadine on days 2-8, or terfenadine or corresponding placebo (shown as "T. placebo") on days 34-40 was administered at 8 am and 8 p.m.

** Sertraline or corresponding placebo (shown as "S. placebo") was administered at 8 am.

*** The final two study days (days 41-42, not shown in table) were a washout period.

2 Pages

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AM I, Table 3

Table 1: Mean Terfenadine Pharmacokinetic Parameters

		AUC (12 hr) hr.ng/ml			Cmax ng/ml			Tmax hr		
Group	Estimate	Day 8	Day 34	Day 40	Day 8	Day 34	Day 40	Day 8	Day 34	Day 40
A	Mean	30.73	7.08	18.47	3.64	1.54	2.70	2	1	2
	Std	21.85	3.26	10.59	2.30	1.04	1.45	1	1	0
	Min	4.57	2.74	6.67	0.74	0.51	1.08	1	1	1
	Max	70.99	13.28	30.97	7.20	4.24	5.46	3	2	2
	CV%	71.11	46.06	57.37	63.20	67.23	53.75	29	37	28
	N *	10.00	10.00	10.00	10.00	10.00	10.00	10	10	10
B	Mean	19.89	8.46	28.27	2.56	1.17	3.64	2	2	2
	Std	12.75	6.46	22.81	1.63	0.71	2.56	1	2	1
	Min	5.46	2.51	6.08	1.04	0.50	1.45		1	1
	Max	48.70	20.59	74.53	6.52	2.58	8.43	4	6	3
	CV%	64.10	76.34	80.69	63.73	60.42	70.42	42	69	44
	N *	10.00	10.00	10.00	10.00	10.00	10.00	10	10	10
C	Mean	15.19			2.09			1		
	Std	7.20			0.84			1		
	Min	7.05			0.81			1		
	Max	29.50			3.35			2		
	CV%	47.42			40.06			37		
	N *	10.00			10.00			10		
D	Mean	16.36			2.00			2		
	Std	11.07			1.13			1		
	Min	5.48			0.82			1		
	Max	42.77			4.65			4		
	CV%	67.64			56.36			52		
	N *	10.00			10.00			10		

* For Groups A and B N=number of Subjects having terfenadine PK days (i.e., 8, 34 and 40)
  For Groups C and D N=number of Subjects at PK day 8

Group: A (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Sertraline 200 + Terfenadine 60 mg))
Group: B (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Terfenadine 60 mg))
Group: C (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Placebo))
Group: D (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Sertraline 200 mg))

Att. I, Table 4

Table 2: Mean Fexofenadine Pharmacokinetic Parameters

		AUC (12 hr) hr.ng/ml			Cmax ng/ml			Tmax hr		
Group	Estimate	Day 8	Day 34	Day 40	Day 8	Day 34	Day 40	Day 8	Day 34	Day 40
A	Mean	2281.21	1365.32	1793.12	350.66	308.56	335.52	3	2	3
	Std	668.14	319.54	319.84	85.71	87.58	48.19	0	1	0
	Min	1471.10	975.10	1223.10	247.00	215.20	259.40	2	2	2
	Max	3949.60	2027.90	2295.20	540.20	484.00	408.00	3	3	3
	CV%	29.29	23.40	17.84	24.44	28.38	14.36	11	22	18
	N*	10.00	10.00	10.00	10.00	10.00	10.00	10	10	10
B	Mean	2317.77	1410.22	2199.91	384.88	247.16	364.24	3	3	3
	Std	530.99	220.14	304.77	64.83	48.18	41.51	1	1	1
	Min	1772.90	1174.50	1689.20	298.80	193.40	302.40	2	2	2
	Max	3336.20	1768.20	2872.00	492.60	364.80	413.80	4	4	4
	CV%	22.91	15.61	13.85	16.84	19.49	11.40	30	33	28
	N*	10.00	10.00	10.00	10.00	10.00	10.00	10	10	10
C	Mean	2126.95			364.12			2		
	Std	420.62			76.48			0		
	Min	1087.30			192.60			2		
	Max	2530.20			444.60			3		
	CV%	19.78			21.00			19		
	N*	10.00			10.00			10		
D	Mean	2250.57			343.70			3		
	Std	593.04			79.07			1		
	Min	1728.20			227.40			2		
	Max	3355.50			495.80			4		
	CV%	26.35			23.01			30		
	N*	10.00			10.00			10		

* For Groups A and B N=number of Subjects having terfenadine PK days (i.e., 8, 34 and 40)
For Groups C and D N=number of Subjects at PK day 8

Group: A (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Sertraline 200 + Terfenadine 60 mg))
Group: B (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Terfenadine 60 mg))
Group: C (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Placebo))
Group: D (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Sertraline 200 mg))

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Att. I, Table 5

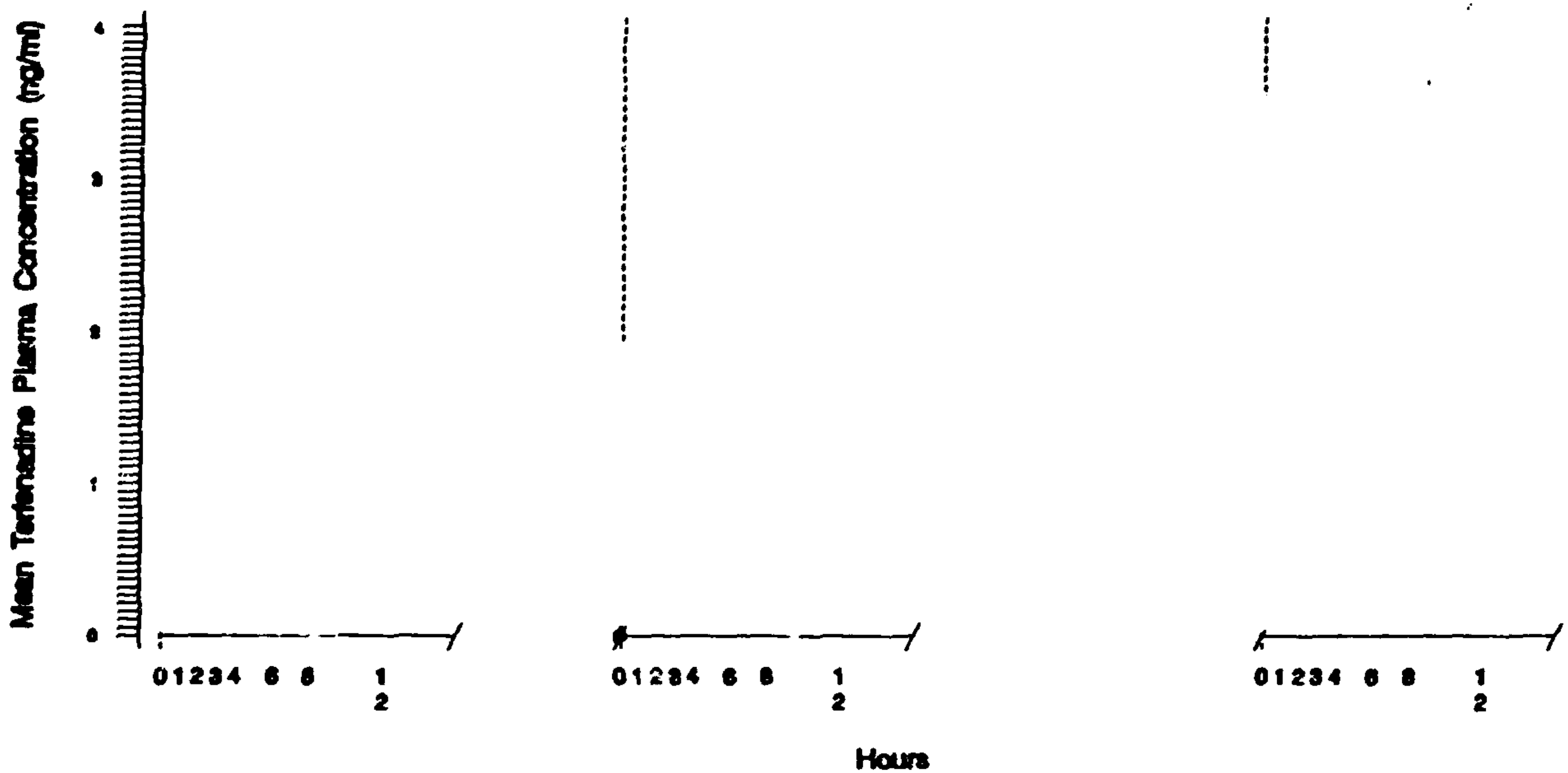
Table 4: Mean Terfenadine Ratios And 90% Confidence Intervals Comparing Dosing On Day 40 To Dosing On Day 8

	90% CI Group A				90% CI Group B			
Parameter	Lower	Lsmean	Upper	P-Value	Lower	Lsmean	Upper	P-Value
RAUC	0.530	0.677	0.863	0.017	1.088	1.342	1.655	0.030
RCmax	0.663	0.814	0.998	0.098	1.163	1.391	1.664	0.008

Group: A (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Sertraline 200 + Terfenadine 60 mg))
Group: B (Day 8 (Terfenadine 60 mg), Days 34 Through 40 (Terfenadine 60 mg))

Att. I, Figure 1

Figure 1: Mean Terfenadine Plasma Concentration



Group: A (Day 8 (Terfenadine 60 mg), Days 34 Trough 40 (Sertraline 200 mg + Terfenadine 60 mg))
Group: B (Day 8 (Terfenadine 60 mg), Days 34 Trough 40 (Terfenadine 60 mg))
Group: C (Day 8 (Terfenadine 60 mg), Days 34 Trough 40 (Placebo))
Group: D (Day 8 (Terfenadine 60 mg), Days 34 Trough 40 (Sertraline 200 mg)

Protocol R0498 A Multiple-Dose Study To Determine The Potential Interaction Of Sertraline,200 mg / day With Terfenadine In Healthy Subjects

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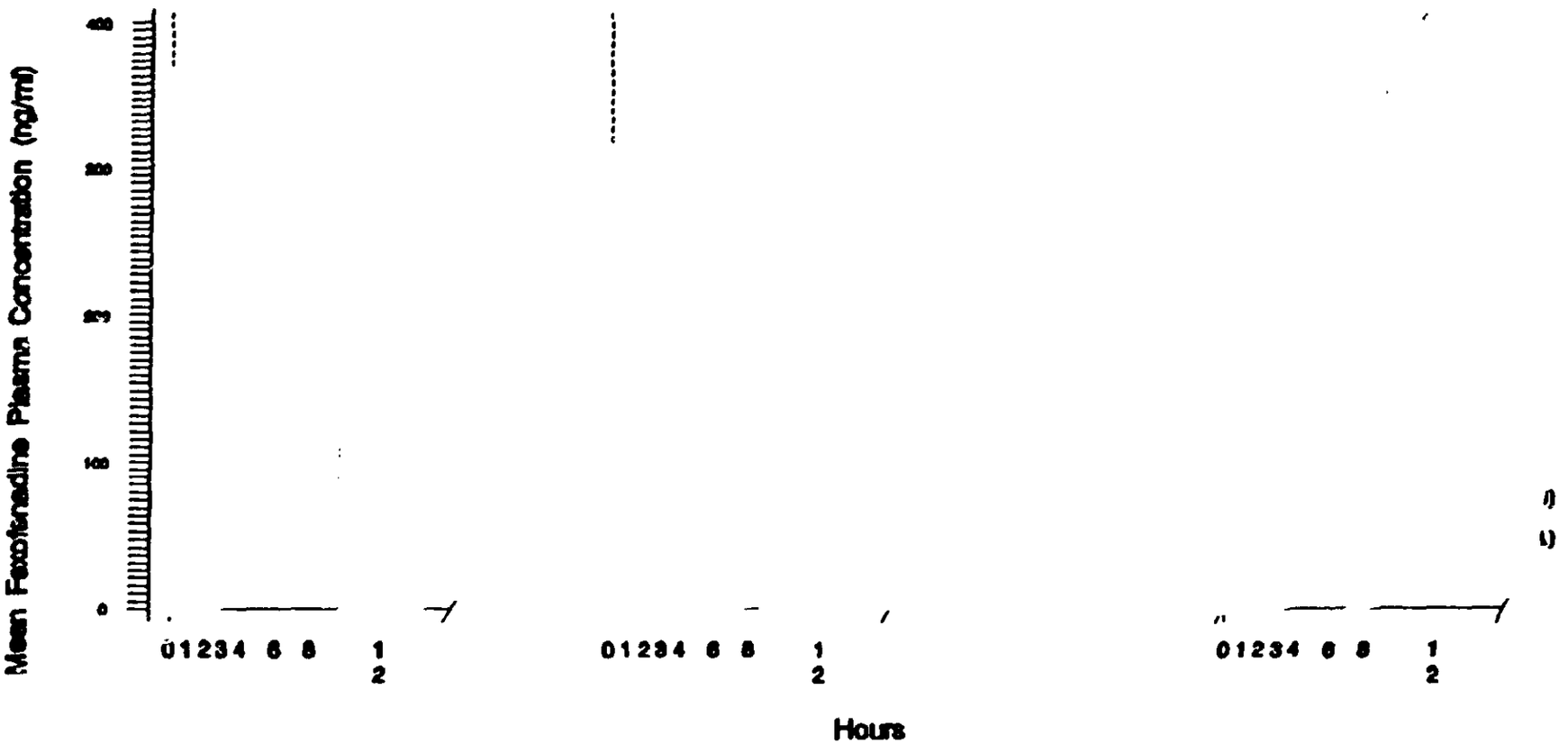
Att I, Figure 2

Figure 2: Mean Fexofenadine Plasma Concentration



Group: A (Day 8 (Terfenadine 60 mg), Days 34 Trough 40 (Sertraline 200 mg + Terfenadine 60 mg))
Group: B (Day 8 (Terfenadine 60 mg), Days 34 Trough 40 (Terfenadine 60 mg))
Group: C (Day 8 (Terfenadine 60 mg), Days 34 Trough 40 (Placebo))
Group: D (Day 8 (Terfenadine 60 mg), Days 34 Trough 40 (Sertraline 200 mg)

Protocol RD498 A Multiple-Dose Study To Determine The Potential Interaction Of Sertraline,200 mg / day With Terfenadine In Healthy Subjects

M:\Project\STL\RD498DB\Programs\Fenember\Programs\Plots\MFIG_TPKSA2

Attachment II

SYNOPSIS

PROTOCOL 050-226: A DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP STUDY TO INVESTIGATE THE EFFECTS OF ORALLY ADMINISTERED SERTRALINE ON THE PLASMA CONCENTRATION PROFILE OF CARBAMAZEPINE AND ITS EPOXIDE METABOLITE AND THE COGNITIVE EFFECTS OF THESE TWO DRUGS IN HEALTHY VOLUNTEERS

Principal Investigator: Dr. P M Dewland

A. STUDY DESIGN:

This was a double-blind, placebo-controlled, parallel-group study. On Days 1 to 32 inclusive, subjects were to receive oral carbamazepine. On Days 16 to 32 inclusive they were also to receive oral sertraline or matching placebo. From Day 13 onwards, blood samples were to be taken prior to each dose of carbamazepine for measurement of trough plasma carbamazepine (CBZ) and carbamazepine-10,11-epoxide (CBZ-E) levels. Samples for plasma concentration profiles were to be taken over 12-hour periods on Days 15 and 32. Psychometric tests were to be performed on Days 1, 15 and 32. Side effect and laboratory safety assessments were to be made at intervals during the study.

B. SUBJECTS:

	Sertraline	Placebo
Entered Study	7	7
Completed Treatment	7	6
Assessed for Pharmacokinetics	7	6
Assessed for Safety	7	7

C. DRUG ADMINISTRATION

Test Product: Sertraline 50mg capsules, lot 529-42, FID JV-80-3.

Reference: Matching placebo capsules, lot 597-46, FID 0006.

Interactant: Carbamazepine 200mg tablets, lot 956-34 (Tegretol, Geigy, lot no. N 585).

All subjects took a single dose of placebo prior to the psychometric tests on Day 1. Carbamazepine 200mg was taken once daily on Days 1 and 2, then twice daily (at 12-hourly intervals) on Days 3 to 31 inclusive and a final single dose on Day 3[illegible]. Sertraline or double-blind placebo was taken once daily on Days 16 to 32 inclusive. Sertraline dosing increased incrementally: 50mg on Day 16, 100mg per day on Days 17 to 19 inclusive, 150mg per day on Days 20 to 22 inclusive and 200mg per day on Days 23 to 32 inclusive.

Att. II

D. RESULTS

1. CBZ Pharmacokinetics	Sertraline Group	Placebo Group
Mean (SD) C_{max} (mcg/ml)		
Day 15 (alone)	6.97 (0.64)	8.06 (0.65)
Day 32 (with Sertraline)	6.24 (1.43)	7.95 (0.79)
Mean Change (Day 32 - Day 15)	-0.73 (1.22)	-0.11 (1.04)
Mean (SD) T_{max} (h)		
Day 15	3.1 (0.9)	2.2 (0.8)
Day 32	3.4 (2.0)	3.0 (1.8)
Mean Change (Day 32 - Day 15)	0.3 (2.2)	0.8 (1.9)
Mean (SD) AUC_{12} (mcg.h/ml)		
Day 15	70.29 (8.92)	82.82 (7.85)
Day 32	60.70 (12.08)	82.14 (6.79)
Mean Change (Day 32 - Day 15)	-9.59 (7.92)	-0.68 (9.50)

2. CBZ-E Pharmacokinetics		
Mean (SD) C_{max} (mcg/ml)		
Day 15	0.752 (0.050)	0.844 (0.121)
Day 32	0.773 (0.212)	0.727 (0.069)
Mean Change (Day 32 - Day 15)	0.022 (0.214)	-0.116 (0.072)
Mean (SD) T_{max} (h)		
Day 15	3.3 (3.1)	3.3 (2.3)
Day 32	4.1 (1.9)	6.0 (3.6)
Mean Change (Day 32 - Day 15)	0.9 (3.4)	2.7 (5.6)
Mean (SD) AUC_{12} (mcg.h/ml)		
Day 15	8.025 (0.637)	8.980 (1.445)
Day 32	7.769 (1.888)	7.828 (0.549)
Mean Change (Day 32 - Day 15)	-0.257 (1.688)	-1.152 (1.059)

3. Pharmacodynamics

Psychometric testing showed that carbamazepine, after 15 and 32 days of dosing, slowed cognitive performance. Simultaneous dosing with sertraline from Day 15 to Day 32 had no measurable effect on cognitive efficiency over and above that produced by carbamazepine.

Att. II

4. Safety

	Sertraline	Placebo
Number of subjects with Treatment-Related*:		
Side Effects	2/7 (0)	2/7 (0)
Laboratory Test Abnormalities	0/7 (0)	1/7 (1)

* Related to Double-Blind Treatment
( ) Resulting in withdrawal from therapy

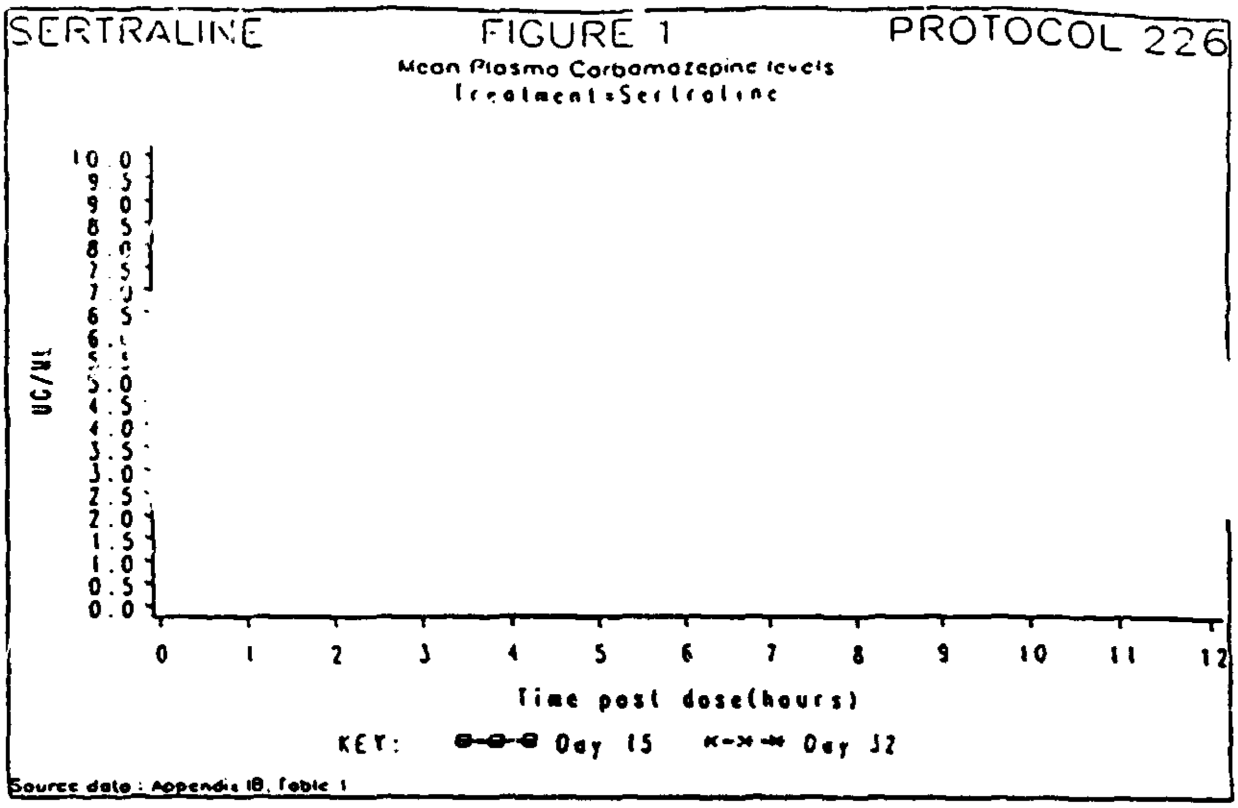
E. SUMMARY AND CONCLUSIONS:

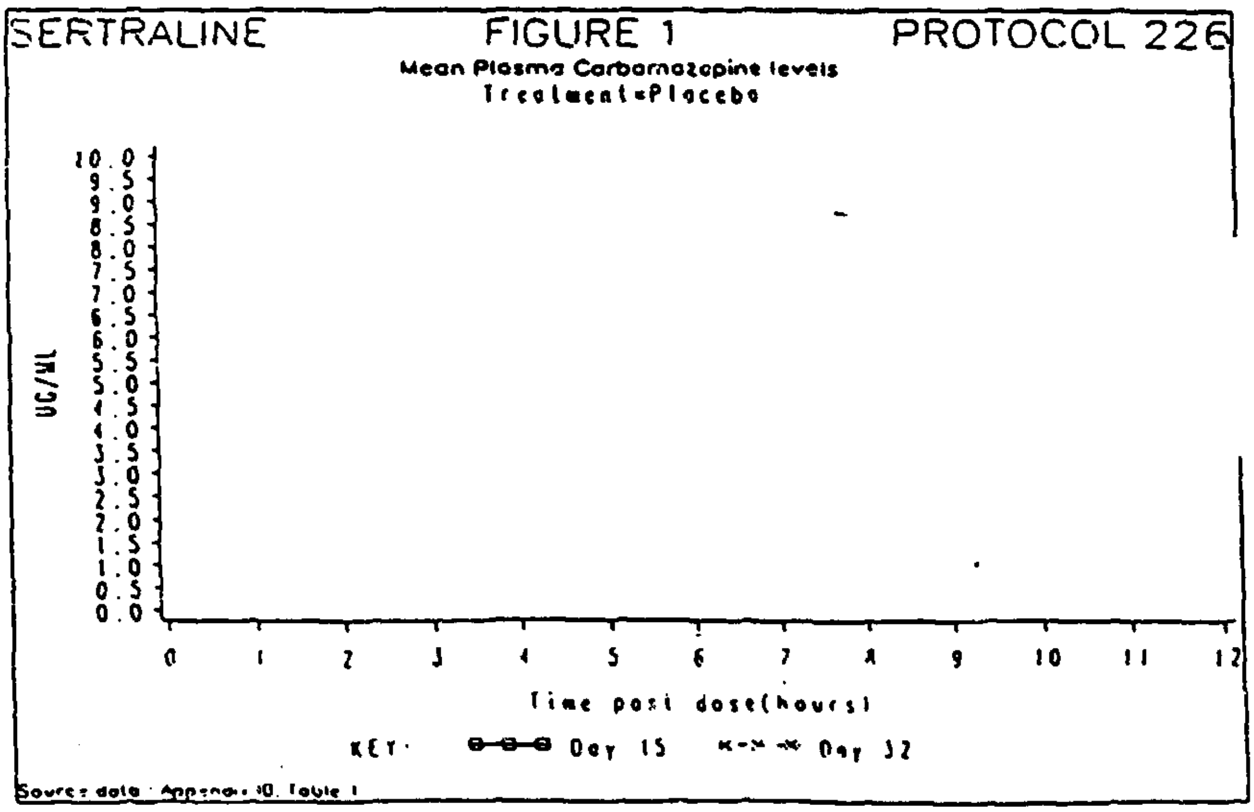
Statistical analysis demonstrated no effect of sertraline on the pharmacokinetics of carbamazepine and carbamazepine-10, 11-epoxide. Although carbamazepine by itself caused some inhibition of cognitive function, the addition of sertraline treatment caused no further detectable effect.

Side effects possibly related to double-blind treatment were reported for 2 of 7 subjects in each treatment group. All such side effects in the sertraline-treated group were mild (abdominal pain and nausea; dizziness, nausea, vomiting, muscle weakness and watering eyes). There were no abnormalities of laboratory tests attributable to treatment in the sertraline-treated group, but one subject in the placebo group was withdrawn from the study because of raised hepatic enzyme levels.

The results of this study show that oral sertraline, has no detectable effect on the pharmacodynamics or pharmacodynamics of carbamazepine in healthy male volunteers.

Att. II

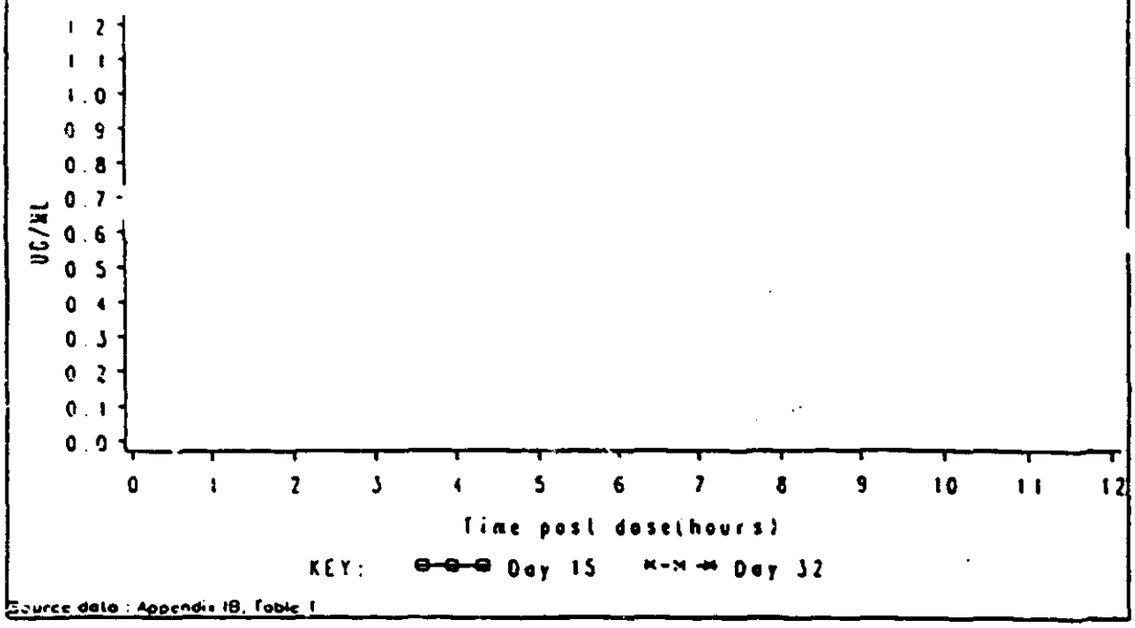

SERTRALINE
FIGURE 1
PROTOCOL 226
Mean Plasma Carbamazepine levels
Treatment=Sertraline
UG/ML
Time post dose(hours)
KEY: Day 15 Day 32
Source data : Appendix 18, Table 1


SERTRALINE
FIGURE 1
PROTOCOL 226
Mean Plasma Carbamazepine levels
Treatment=Placebo
UG/ML
Time post dose(hours)
KEY: Day 15 Day 32
Source data : Appendix 10, Table 1

Att. II

SERTRALINE FIGURE 2 PROTOCOL 226

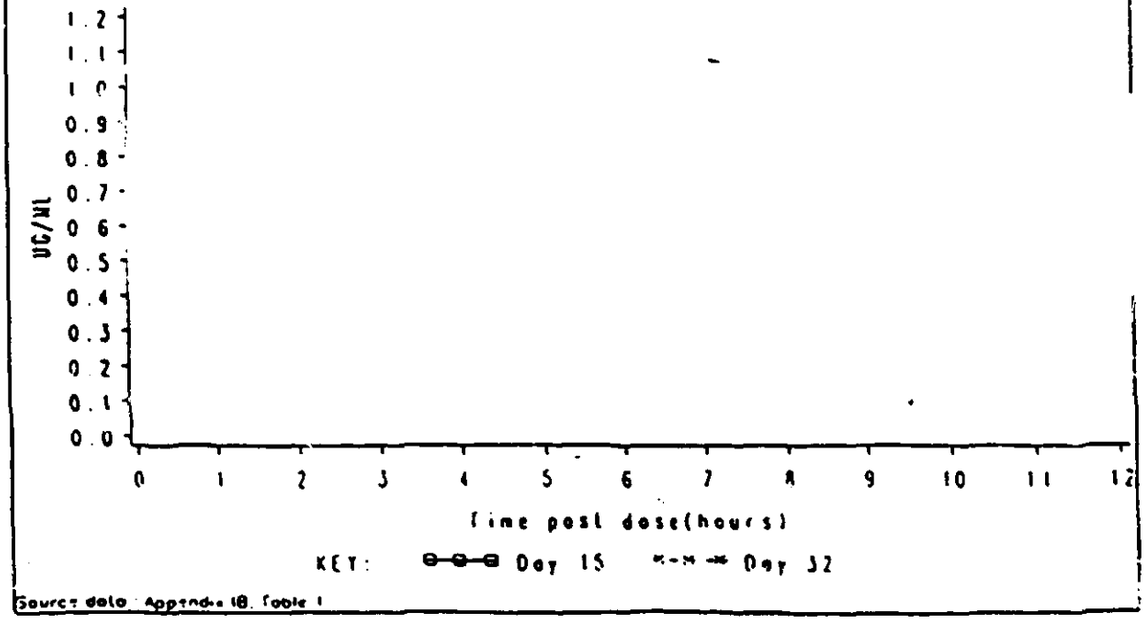
Mean Plasma Carbamazepine-10,11-epoxide levels
Treatment=Sertraline



Source data : Appendix 18, Table 1

SERTRALINE FIGURE 2 PROTOCOL 226

Mean Plasma Carbamazepine-10,11-epoxide levels
Treatment=Placebo



Source data : Appendix 18, Table 1

Sertraline
Labelling

Attachment III

Drugs Metabolized by Cytochrome P4503A4

In two separate *in vivo* interaction studies, sertraline was coadministered with the cytochrome P4503A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline coadministration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P4503A4 activity is not likely to be of clinical significance.

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION

NDA #	19-839, Supplement # 02 Safety Update
Sponsor:	Pfizer, Inc.

DRUG NAME

Generic Name:	Sertraline Hydrochloride
Trade Name:	Zoloft®

DRUG CHARACTERIZATION

Pharmacological Category:	Selective serotonin reuptake inhibitor
Proposed Indication:	Obsessive Compulsive Disorder
Dosage Forms, Strengths & Routes of Administration:	Marketed 50 and 100 mg Tablets

REVIEWER INFORMATION

Clinical Reviewer:	James F. Knudsen, Ph.D., M.D.
Review Completion Date:	March 28,1996

Table of Contents

Tables of Contents (continued)

Table of Contents (continued)

1.0 Material Utilized in Review of Safety Update

1.1 Material from NDA Supplement 002.

The following is a list of specific items reviewed.

VOLUME	DATE SUBMITTED	MATERIAL
60.1	December 7, 1995	Safety Update
60.2	December 7, 1995	Tables
60.3	December 7, 1995	Figures and Spontaneous Reports
60.4	December 7, 1995	World Literature
60.5	December 7, 1995	Foreign Regulatory Update and Labeling
60.6-60.68	December 7, 1995	Case Report Forms

1.2 Related Reviews

NDA #19-839 Sertraline in the treatment of depression

NDA #19-839/S-002 Sertraline in the treatment of obsessive compulsive disorder (OCD)

2.0 Background

Supplement S-002 to NDA 19-839 for Zoloft® (sertraline) tablets in the treatment of OCD was submitted on May 14, 1992 and included data from 2 placebo-controlled studies 371/372 and 237/248 and one uncontrolled study #494. Data from a third placebo-controlled study (protocol 546) were submitted on January 13, 1994. The clinical review of the application was completed on March 1, 1995. An approvable letter was sent on August 1, 1995. The present submission is a safety update report and includes routine clinical data collected from the OCD NDA submitted on May 14, 1992 plus data from an additional group of OCD patients who participated in sertraline studies subsequent to the OCD NDA cut-off date of April 17, 1991 and up through June 30, 1995, the cut-off date for this safety update.

In addition, the sponsor has submitted a separate pediatric/adolescent section which includes safety data collected in completed pediatric/adolescent OCD studies as of the data cut-off of June 30, 1995. For both the adult and pediatric/adolescent studies, serious adverse experiences were in a database that included all completed as well as ongoing studies as of the cut-off date for the safety update of June 30, 1995.

2.1 Indication

Sertraline is a selective serotonin reuptake inhibitor (SSRI) marketed in the United States for the treatment of depression and more recently approved for the treatment of OCD in adults.

2.2 Related INDs and NDAs

Unchanged from those noted in the original OCD NDA submission.

2.3 Administrative History

The following is a brief history.

August 1, 1995	Correspondence stating application for sertraline in treatment of OCD was approvable.
August 10, 1995	Pfizer's letter of intent to file an amendment to S-002.
December 7, 1995	Amendment including safety update to S-002 submitted.

2.4 Proposed Direction for Use

The text from the Division's August 1, 1995 draft of labeling was included in section 1 (volume 1) of this safety update submission and is not repeated in the present review of safety data.

According to the Sponsor, pediatric dosing information is to be submitted at a later date.

2.5 Foreign Marketing

As of September 1, 1995, sertraline has been approved for the treatment of OCD in eleven countries. The product has not been withdrawn form the market in any country.

3.0 Chemistry

Sertraline is a marketed product. There are no chemistry issues to be addressed in this safety supplement.

4.0 Animal Pharmacology

No additional data submitted.

5.0 Description Of Clinical Data Sources

5.1 Safety Update

5.1.1 Study Type and Design/Patient Enumeration

The following table summarizes the total number of patients in the original OCD NDA database plus the additional OCD patients who participated in completed studies after the OCD NDA cut-off date of April 17, 1991. The study types and design of these completed studies as well as the completed pediatric/adolescent studies are summarized in Appendix Tables 5.1.1 and 5.1.2.

There were 7 adult studies and 13 ongoing adult studies as of the June 30, 1995 cut-off date for the safety update.

Table 5.1.1.1
All Completed Adult OCD Studies
(Safety Cut-off Date June 30, 1995)

Study Type	Sertraline	Placebo	Active
Placebo-Controlled			
- Fixed Dose			
371/372	241	84	
- Dose Titration			
237/248	43	44	
546	86	81	
495	87	88	85
336	76	76	
Active-Controlled			
007	86		82
Uncontrolled			
494	8*		
Total	627	373	167

Data Source: Volume 1, P. 10, December 7, 1995. * In original OCD NDA this number was [illegible].

The cumulative sample of 627 sertraline-treated patients noted in the above table includes those 290 OCD patients (from protocol 371/372, 237/248 and 494) whose safety profile was previously described in the integrated safety summary section of the OCD NDA submitted on May 14, 1992, plus an additional 337 (86 from protocol 546 and 251 from the total of the protocols) sertraline-treated patients who participated in studies subsequent to the OCD NDA cut-off date of April 17, 1991 and up through June 30, 1995, the cut-off date for the safety update. The following table presents the total patient numbers in each treatment group for the completed and ongoing adult studies database. For ongoing studies the number of patients in each treatment group was estimated on the basis of the total number randomized and the protocol-specific proportion of patients to be randomized to each treatment group.

My review of the original OCD submission consisted of protocols 371/372, 237/248, 494 which were submitted as part of the integrated safety summary and protocol 546 which was submitted separately. The total number of sertraline-treated patients in these 4 protocols was 376.

	Sertraline	Placebo	Active
Adult Completed	627	373	167
Adult Ongoing	954	53	141
Total	1,581	426	308

Data Source: Adapted from a table in Volume 1, P. 11, December 7, 1995.

In addition to the safety data submitted on the 1,581 sertraline-treated patients in the completed and ongoing adult OCD studies, data from pediatric/adolescent studies were submitted. The following table presents the total patient numbers in each treatment group for the two completed (protocols 498 and 525) and two ongoing (protocols 536, 550) pediatric/adolescent studies database as of June 30, 1995.

All Pediatric Studies
(Cut-Off Date June 30, 1995)

	SERTRALINE	PLACEBO
Completed Studies	153	95
Ongoing Studies	67	0
Total	220	95

The sample includes 92 sertraline-treated patients and 95 placebo-treated patients who participated in study 498, a 12-week double-blind placebo-controlled flexible-dose study and 61 sertraline-treated patients who participated in a 51-day open-label clinical pharmacokinetics study 525. An estimated 67 placebo patients from study 498 were subsequently treated with sertraline in an extension study, protocol 536, bringing the total safety denominator to 220. Study 550 was an open-label extension to 525. This study did not add any newly-exposed patients as all subjects received sertraline in study 525.

5.1.2 Demographics

Table 5.1.2 presents demographic information for adult OCD patients in all completed studies as of the safety update cut-off date of June 30, 1995.

6

Table 5.1.2

OCD Safety Update: COMPLETED STUDIES

	Sertraline			Placebo			Active Control		
	male	female	total	male	female	total	male	female	total
NUMBER OF PATIENTS	328	299	627	219	154	373	70	97	167
RACE									
WHITE	288	233	521	206	146	352	33	43	76
BLACK	1	3	4	2	2	4	1	4	5
OTHER	11	5	16	11	6	17	2	2	4
NOT SPECIFIED*	28	58	86	0	0	0	34	48	82
AGE CATEGORY (YRS)									
15-44	249	202	451	167	119	286	44	70	114
45-64	71	87	158	46	27	73	67	95	162
>=65	8	10	18	6	8	14	70	97	167
MEAN AGE (YRS)	36.6	39.5	38.0	37.5	38.4	37.9	41.4	38.6	39.8
AGE RANGE (YRS)	18-72	18-77	18-77	16-88	19-77	16-88	18-71	18-73	18-73

Pooled data from protocols 237/248, 371/372, 494, 548, 496 338, 007
* STUDY 007 - 168 PATIENTS RACE - NOT SPECIFIED

Patients were predominately Caucasian and less often elderly. More often the patients were males.

The demographic profile for the pediatric/adolescent patients participating in the OCD completed studies is presented in the table which follows.

Table 5.1.2.1
Demographic Profile for Pediatric/Adolescent Studies
in Completed Studies

	SERTRALINE			PLACEBO		
	MALE	FEMALE	TOTAL	MALE	FEMALE	TOTAL
NUMBER OF PATIENTS+	85	68	153	47	48	95
RACE						
WHITE	74	55	129	42	37	79
BLACK	5	4	9	2	6	8
OTHER	6	9	15	3	5	8
AGE CATEGORY (YRS)						
6-12	51	31	82	31	23	54
13-17	34	37	71	16	25	41
MEAN AGE (YRS)	11.8	13.0	12.3	11.7	12.6	12.1
AGE RANGE (YRS)	6-17	6-17	6-17	6-17	7-17	6-17

Data Source: Adapted from table 32, Vol. 2, P. 445.
+ Pooled data from protocols 496 and 525.

The age range was 6-17 years with a mean age of 12 years in both sertraline and placebo-treated patients. Patients were more often males and predominately Caucasian.

5.1.3 Extent of Exposure (dose/duration)

Table 5.1.3 depicts the updated number of patients who were exposed to sertraline by total duration of therapy and maximum daily dose received during treatment in all completed adult OCD studies up through the cut-off date of June 30, 1995. The majority of the patients were exposed to sertraline for 6 months or less. Only 15% (95/627) were exposed to sertraline for more than 6 months. Fifty-two percent (325/627) of sertraline-treated patients received the maximum recommended daily dose of 200 mg. The mean maximum daily dose of sertraline was 148mg.

For completeness, Appendix Table 5.1.3 displays the number of patients exposed to sertraline by total duration of therapy and mean daily dose. The majority of patients received sertraline for 6 months or less. Thirty percent received a mean daily dose of 150-200mg.

Patient (sertraline-treated) exposure years was 255.70.

Table 5.1.3
OCD Safety Update: Completed Adult Studies
Number of Subjects Receiving Sertraline
According to Maximum Daily Dose and Duration of Therapy

	SERTRALINE MAXIMUM DAILY DOSE (MG)[1]					
DURATION OF THERAPY (DAYS)	50	100	150	200	TOTAL NUMBER	%
1	1	0	0	0	1	0.0%
2-10	11	15	0	0	26	4.5%
11-31	19	11	3	9	42	6.7%
32-90	25	43	32	149	249	39.7%
91-180	37	55	19	103	214	34.1%
181-364	6	9	0	10	25	3.9%
>=365	6	6	4	54	70	11.2%
TOTAL	105	139	58	325	627	100%
%	16.7%	22.2%	9.3%	51.8%	100%	

1. PATIENTS ARE COUNTED ONCE ONLY, i.e. EACH PATIENT CONTRIBUTES TO ONLY ONE CELL
Pooled data from protocols 237/248, 371/372, 494, 546, 495, 336, 007
Data Source: Table 3, Vol 2, P. 120

The table below depicts the number of pediatric/adolescent patients who were exposed to sertraline by total duration of therapy and maximum daily dose received. The majority (81%, 124/153), of the patients were exposed to a maximum daily dose of 200mg, in contrast to the adult patients in whom the maximum daily dose was received by 52% (325/627). The mean maximum dose was 185mg/day, higher than the mean maximum daily dose of 148mg in adults. Three percent of the pediatric/adolescent patients received sertraline for more than 6 months.

Pediatric/Adolescent Studies
Pooled Data From Protocols 498 and 525
NUMBER OF SUBJECTS RECEIVING SERTRALINE ACCORDING TO MAXIMUM DAILY DOSE AND DURATION OF THERAPY

	SERTRALINE MAXIMUM DAILY DOSE (MG)[1]								
DURATION OF THERAPY (DAYS)	50	75	100	125	150	175	200	TOTAL NUMBER	%
1	3	0	0	0	0	0	0	3	2.0%
2-10	3	0	0	0	0	0	0	3	2.0%
11-31	0	0	3	1	3	0	3	10	7.0%
32-90	1	1	5	0	4	3	118	132	86.0%
91-180	0	0	0	0	2	0	3	5	3.0
TOTAL NUMBER	7	1	8	1	9	3	124	153	100%
%	4.6%	0.7%	5.2%	0.7%	5.9%	2.0%	81.0%	100%	

1 PATIENTS ARE COUNTED ONCE ONLY, I.E. EACH PATIENT CONTRIBUTES TO ONLY ONE CELL

Appendix Table 5.1.3.1 displays the number of pediatric patients exposed to sertraline by total duration of therapy and mean daily dose. The mean duration of exposure was 58 days. Thirty-seven percent received a mean daily dose of 150-200mg. (Compared with 30% in the adult OCD patients). Patient (sertraline) exposure years was 24.37.

5.2 Secondary Sources

5.2.1 Non-IND Studies

There are no updates to be made in this section.

5.2.2 Post-Marketing Experience

Spontaneous reports (through June 30, 1995) for all OCD patients treated with sertraline were tabulated by body system (WHO dictionary) and presented in volume 3. There were 109 cases and 200 events.

A review of the adverse events in the adult OCD spontaneous reports with or without concomitant medications was similar to the adverse event profile contained within the package insert for the indication of depression.

5.2.3 Literature

The sponsor submitted a world literature update (volume 4). The sponsor provided an update of the world literature pertaining to the use and safety of sertraline in the treatment of OCD patients.

A search of worldwide literature pertaining to the use and safety of sertraline in OCD patients was conducted through DIALOG using four commercial databases: MedLine, EMBASE, Biosis and PsycInfo. The databases were searched for applicable abstracts dated January, 1994 through September, 1995. The last literature review of sertraline safety cases, which was submitted September 28, 1994, cited literature published through June, 1994. All articles previously reviewed were eliminated from the current report. The DIALOG search was conducted by Veronica Plucinski, M.L.S., Assistant Director of Pfizer's Professional Information Department.

The reviewed material consisted of original articles (clinical and preclinical), reviews and meta-analyses, case reports, and new drug updates. Full text articles were submitted for all abstracts, and all foreign language articles were translated

Unpublished abstracts from scientific meetings were also gathered from Pfizer's in-house database and submitted.

After systematic review of the world literature pertaining to the use of sertraline in OCD patients, I have concluded that there were no findings of any adverse event, or any other report, that would adversely affect the conclusions about the safety of sertraline in this population that are presented in the Zoloft NDA (#19-839/S-002 submitted 5/14/92) or the accompanying final safety update. None of the reviewed material reported any side effect or adverse event that was not already included in the product labeling.

6.0 Human Pharmacokinetics

No update of this section was submitted. The pharmacokinetics data from the pediatric study 525 has not been submitted as of 3/26/96.

7.0 Efficacy Results

Not applicable for this safety update review.

8.0 Safety Findings

8.1 Methods

The clinical safety of sertraline was evaluated in a manner similar to that of the original OCD NDA submission. This consisted of analyses of adverse event reports, clinical laboratory analytes, vital signs, body weight and ECGs. The search for serious events included an evaluation of reports of deaths (section 8.2), dropouts due to adverse events (section 8.3) and an evaluation of other events identified as serious by the sponsor (section 8.4) from all completed as well as all ongoing studies which were submitted to this safety update. In addition, routine withdrawal phenomena and abuse potential are discussed in section 8.5.6, available information pertaining to human reproduction experiences is provided in section 8.5.7. Overdose experience in patients exposed to sertraline is discussed in section 8.5.8. Section 8.6 provides a summary of adverse experiences considered to be both important and possibly/probably related to exposure to sertraline. Serious events considered unlikely to be drug-related are mentioned in section 8.7. Drug-demographic, drug-disease, drug-drug interaction are summarized in section 8.8.

Additionally, the safety update data were examined to determine if there were any gender-related differences as well as age and race-related differences in adverse event rates.

Spontaneous reports for sertraline in the treatment of OCD were examined to determine whether or not the profile was similar to the adverse events documented in the package insert.

Case report forms (CRFs) from the pediatric/adolescent patients who discontinued prematurely from the study were examined for additional serious events as well as laboratory and vital sign data.

8.2 Assessment of Deaths

The cut-off date for the assessment of deaths for adult and pediatric/adolescent studies was June 30, 1995. There have been no reports of deaths among any sertraline-treated patients.

In the spontaneous reporting system there was one death reported (December 21, 1993) of a 40YOM who committed suicide during sertraline treatment for two months.

8.3 Assessment of Dropouts

8.3.1 *Overall Pattern of Dropouts*

Dropouts for all reasons in the adult OCD placebo-controlled studies are summarized in updated table 8.3.1 and are categorized on the basis of the investigator's judgement regarding the single most important reason for dropout.

Table 8.3.1
Rates of Dropout by Treatment Groups and Reason in Placebo-Controlled Adult OCD Studies
Safety Update

	Percent Dropping Out	
Reason for Dropout	**Sertraline (N=533)***	**Placebo (N=373)**
Lack of Efficacy	7.9	13.1
Adverse Experience +	12	5.4
All Others ++	9.6	11.5
Total Dropouts	29.5%	30.0%

Adapted from Sponsor's Table 13, Vol. 2, P. 230.
*Pooled studies include 237/248, 371/372 (weeks 1-12), 546, 495, 336
\+ Adverse experience includes intercurrent illnesses and abnormal laboratory results.
++ All others include: refused to continue, protocol violation, lost to follow-up, non-compliance and administrative reasons.

As in the original NDA data, the placebo group had the higher rate of discontinuation for lack of efficacy (13.1% vs 7.9%) while the sertraline-treated group had higher rates of dropouts for adverse experiences (12% vs 5.4%). The fixed-dose study 371/372 was discussed in the original OCD NDA review and is summarized here.

Rate of Discontinuation For Adverse Experiences in Weeks 1-12 and Weeks 1-52 of the fixed Dose Study Protocol 371/372

Treatment Period	Sert. 50mg	Sert. 100mg	Sert. 200mg	Placebo
Number of Patients	80 pts	81 pts	80 pts	84 pts
Weeks 1-12	8%	14%	8%	6%
Weeks 1-52	8%	16%	13%	7%
Weeks 13-52	0%	2%	5%	1%

Sponsor's Table from Vol. 1, P. 20.

The table provides the rate of discontinuation for adverse experiences in Weeks 1-12 and Weeks 1-52 and the difference between the two (Weeks 13-52). In Weeks 13-52, there were six additional sertraline patients who discontinued for adverse experiences compared to 1 placebo patient who discontinued for that reason. Of the six sertraline patients who discontinued: 0 were in the 50mg group, two were in the 100mg group, and four were in the 200mg group. Thus, during the 40-week continuation phase, the rate of discontinuations due to adverse experiences increased with increasing sertraline dose.

Table 8.3.1.1 shows the percentage of dropouts for all reasons in the pediatric/adolescent safety database.

Table 8.3.1.1
Rates of Dropout by Treatment Groups and Reasons in Placebo-Controlled Pediatric/Adolescent OCD Studies

Percent Dropping Out		
Reason for Dropout	**Sertraline (N=92)***	**Placebo (N=95)**
Lack of Efficacy	3.3	2.1
Adverse Experience +	13.0	4.2
All Others ++	3.3	7.4
Total Dropouts	19.6%	13.7%

Adapted from Sponsor's Table 58, Vol. 2, P. 467.
* Protocol 498 was only placebo-controlled study
\+ Adverse experience includes intercurrent illness and abnormal laboratory results.
++ All others include: Protocol violation, lost to follow-up and poor compliance.

Premature dropouts for adverse experiences were approximately three times more frequent in the sertraline than in the placebo treatment group. Slightly more (3.3%) sertraline than placebo-treated (2.1%) discontinued because of lack of efficacy.

The discontinuation rates for adverse experiences in sertraline-treated patients were comparable in adults and pediatric/adolescents (12% and 13%, respectively).

8.3.2 Adverse Events Associated With Dropouts

Adverse events associated with dropouts (in the placebo-controlled OCD trials) in at least 1% of sertraline-treated adult patients and at least twice the placebo rate are displayed in the following table:

Percentage of Patients Dropping out in Adult OCD Placebo-Controlled Trials

	SERTRALINE (N=533)	PLACEBO (N=373)
Psychiatric Disorders		
Insomnia	2.6	0.8
Somnolence	1.9	0.3
Gastro-Intestinal Disorders		
Nausea	2.8	0.3
Diarrhea	2.1	0.8

Adapted from Sponsor's Table 32, Vol. 2, P. 341.
Pooled data from 237/248, 371/372 (weeks 1-12), 546, 495 and 336.

In both the original OCD NDA database and this safety update database, adverse events associated with dropouts in sertraline-treated patients were concentrated mainly in the psychiatric and gastrointestinal systems.

The table which follows displays those adverse events most frequently associated with dropouts (in the placebo-controlled OCD trials) in at least 1% of sertraline-treated patients and at least twice the placebo rate in the pediatric/adolescent OCD database.

Percentage of Patients Dropping Out From Pediatric/Adolescent OCD Placebo-Controlled Trials

	Sertraline (N=92)	Placebo (N=95)
Psychiatric Disorders		
Agitation	3.3	0.0
Insomnia	2.2	1.1
Concentration Impaired	2.2	0.0

Adapted from Sponsor's Table 61, Vol. 2, P. 473.
Data from placebo-controlled study number 498.

The adverse events most frequently associated with dropouts were grouped with psychiatric disorders.

The adverse events associated with discontinuations in the adult OCD database were most frequently reported to be gastrointestinal and psychiatric side effects, whereas, in the pediatric database the most frequently occurring adverse events were psychiatric in nature.

8.4 Other Specific Search Strategies

8.4.1 Serious Adverse Events

As of the OCD safety update cut-off date of June 30, 1995, 1,581 adult patients in completed and ongoing studies had received treatment with sertraline; 426 with placebo and 308 with active control drugs. There were 30 reports (2%) of adverse experiences reported as serious in sertraline-treated patients compared to 11 reports (3%) in the placebo treatment group and 8 (3%) patients in the active-control group and 8 patients on blinded therapy for which the blind had not been broken.

In the completed and ongoing studies of the pediatric/adolescent OCD program, serious adverse experiences were reported in 16 (7.3%) of 220 sertraline-treated patients and none of the 95 placebo-treated patients.

Narrative summaries of drop-outs due to medical events were reviewed for serious adverse events. No additional serious adverse events were located.

Serious adverse events possibly or probably related to sertraline will be discussed under specific subsections of this safety review. Events not related, in my opinion, to sertraline use are tabulated and appear in the table of serious events not considered drug-related (Appendix 8.7).

8.4.2 Search for Emergence of Suicidality

There were no reports of completed suicides in either the adult OCD database (N=1581) or the pediatric/adolescent database (N=220). The table which follows summarizes the incidence of serious adverse experiences associated with suicidality in the adult and pediatric/adolescent database.

Summary of Suicidality in All Adult and Pediatric/Adolescent OCD Studies (cut-off data June 30, 1995)

Protocols	Treatment Groups	N	Attempts	Gesture	Ideation	Total Suicidality (%)
Adult	Sertraline	1581	2	1	6	0.6%
	Placebo	426	0	0	1	0.2%
	Active Control	308	3	0	0	0.1%
Pediatric/Adolescent	Sertraline	220	1	2	3	3.0%
	Placebo	95	0	0	0	0.0%

When results are expressed as percent of patient per treatment group and as a function of exposure to treatment (incidence per patient exposure year) the incidence of suicidality was 0.035/PEY for the adult sertraline-treated group (PEY=225.7) compared to 0.25PEY for the

pediatric/adolescent group (PEY=24.37). The final adult OCD database compares favorably with that of the original OCD NDA report of less than 1% incidence of suicidality in sertraline-treated patients. In the small pediatric/adolescent pooled population of OCD patients, the incidence of suicidality in sertraline-treated patients was five fold greater than the adult OCD sertraline-treated patients. A summary of the medical history of the 6 pediatric/adolescent cases is located in appendix 8.4.2.

Of the 6 cases, 3 occurred in protocol 525, 2 in protocol 536 and 1 in protocol 550. The one placebo reported case occurred in protocol 498. There were 3 males and 3 females. The mean age of the six patients was 14 years (range 8-17 years). Four of the 6 were reported to have a comorbid diagnosis of major depression. Four of the 6 patients had received a maximum dose of 200mg prior to the report of suicidality, which occurred over a wide range of days, (8 to 136 days of sertraline exposure). The one placebo-treated patient (protocol 498) of which there is limited data had a report of suicidal ideation classified as mild in intensity (data from table 60, p. 470 in volume #2).

Suicidal acts or emergence of suicidal thoughts in depressed patients treated with other SSRIs have been discussed and revealed no association with an increased risk (Beasley et al., BMJ 303:685,1991). Obsessive compulsive disorder has a substantial comorbidity with major depression and other anxiety disroders (Weissman et al. J Clin Psychiatry 55:3(Supp.),5:1994) and depression is an important risk factor for suicide. Before receiving sertraline, 4 of the 6 pediatric patients had a comorbid diagnosis of major depression and therefore may have been more suicidal at start of treatment. Similar cases of self-injurious ideation or behavior have been reported in fluoxetine-treated young OCB patients (10 to 17 years old). Four of the 6 had major risks for self-destructive behavior including depression (King et al. J. Am. Acad Child Adolesc Psychiatry 30:179,1991.)

8.5 Other Safety Findings

8.5.1 Adverse Events Incidence Table

Appendix Table 8.5.1.1 is the safety update table which displays the adverse events occurring at a rate of 1% or greater in the adult sertraline-treated OCD patients in the combined placebo-controlled clinical trials. The table is ordered from the system with the most frequently reported adverse experiences to the system with the fewest reports of experiences. Long-term data from the 40-week continuation phase of protocol 371/372 are not included in this table. The incidence of adverse experiences differed only slightly depending on whether the data included weeks 1-12 or weeks 1-52 from this protocol which was discussed in the original OCD NDA.

All adverse experiences whether observed or listed by the investigator or reported by the subject were recorded in CRFs. All adverse experiences were included in this section whether or not the investigator deemed them to be related to the study medication. The adverse experiences were auto encoded from the investigator's term to body system and preferred term using the WHO-AE dictionary. Each adverse experience was only counted once for a given subject, regardless of the number of times a given adverse experience was reported. For patients with more than one treatment-emergent adverse experience with the same preferred term, the events with greater severity or more probable relationship to the medication was chosen.

Adverse events were most frequently associated with either the psychiatric, gastrointestinal or central/peripheral nervous systems and were similar in distribution to that observed in the OCD NDA.

Tables of incidences of adverse experiences in all adult OCD placebo-controlled studies by age (Vol. 2, Table 28), gender (Vol. 2, Table 29) and by race (Vol. 2, Table 30) were provided by the sponsor. The limited sample size in the age category >= 65 years old (17 sertraline and 14 placebo patients) and race category other than Caucasian precludes any valid comparisons of adverse event incidence rates between these two subgroups. The adverse events occurred at about the same rate in men as in women except for the following adverse experiences which were reported more frequently in the sertraline-treated female patients than the sertraline-treated male patients: nervousness, nausea, diarrhea, vomiting, headache, tremor and increased appetite.

Appendix Table 8.5.1.2 displays the adverse events in placebo-controlled trials occurring at a rate of 1% or greater in the pediatric/adolescent sertraline-treated OCD patients. The most frequently reported adverse experiences following sertraline administration were of psychiatric, gastrointestinal and CNS/PNS/ANS origin. The majority of reports occurred within these body systems. Subgroup analysis for gender was not done.

The table which follows compares the commonly observed and possibly drug related adverse experiences associated with the use of sertraline in the safety update for adult OCD patients (incidence of 5% or greater for sertraline and an incidence for sertraline of at least twice that for placebo-treated patients) with data from the depression treated patients (derived from the 1% table, vol. 1., page 14).

Comparison of Commonly and Possibly Sertraline-Related Events in Placebo-Controlled Adult Depression and Adult OCD Patient Groups (Safety Update)

Adverse Experience	Percentage of Patients Reporting			
	OCD		Depression	
	Sertraline (N=533)	Placebo (N=373)	Sertraline (N=861)	Placebo (N=853)
Autonomic Nervous System Disorders				
Sweating Increased	6	1	8	3
Centr. & Periph. Nerv. System Disorders				
Dizziness	17	6	12	7
Tremor	8	1	11	3
Gastrointestinal Disorders				
Nausea	30	11	26	12
Diarrhea/Loose Stools	24	10	18	9
Anorexia	11	2	3	2
Dyspepsia	10	4	6	3
Psychiatric Disorders				
Insomnia	28	12	16	9
Libido Decreased	11	2	<1	<1
+Sexual Dysfunction Male (1)	17	2	16	2
Impotence	5	1	<1	<1

(1) Primarily ejaculatory delay.
+ Corrected for gender

Common and Drug-Related Events

As an indication of which adverse events may be common and likely to be drug-related, those adverse events with an incidence among sertraline-treated patients of 5% or greater and an incidence at least twice that amount in placebo-treated patients were selected from the pooled placebo-controlled adult OCD database. These common and potentially drug-related events are presented in the table that follows. Long-term data from the 40-week continuation phase of protocol 371/372 are not included so that all of the pooled studies are of comparable duration.

Common and Possible Sertraline-Related Adverse Experiences in the Pooled Placebo-Controlled Adult OCD Studies, Safety Update

Adverse Experiences	Sertraline (N=533) %	Placebo (N=373) %
Gastrointestinal		
Nausea	30	11
Diarrhea	24	10
Anorexia	11	2
Dyspepsia	10	4
Psychiatric		
Insomnia	28	12
Libido Decreased	11	2
Sexual Dysfunction+	17	2
Impotence	5	1
Central and Peripheral Nervous Systems		
Dizziness*	17	6
Tremor	8	0.5
Skin and Appendages		
Sweating Increased	6	1

* This term is an additional adverse experience which was not listed in the original OCD NDA database.
+ Ejaculation failure based on male patients only: sertraline 17% (N=296) and placebo 2% (N=219).

The incidence of adverse experiences in placebo-controlled studies differed only slightly (minor increases in small number) when the long-term data of 371/372 were included. Headache and dizziness occurred with greater frequency during long-term treatment than other adverse experiences.

Those events with an incidence among sertraline-treated pediatric/adolescent OCD patients of 5% or greater and an incidence at least twice that amount in placebo-treated patients in placebo-controlled studies are listed in the table which follows.

Common and Possible Sertraline-Related Adverse Experiences in Placebo-Controlled Pediatric/Adolescent OCD Studies (Protocol 498)

Adverse Experiences	Sertraline (N=92) %	Placebo (N=95) %
Psychiatric		
Insomnia	37	13
Nervousness	15	6
Agitation	13	2
Central and Peripheral Nervous Systems		
Dizziness	12	6
Hyperkinesia	9	4
Tremor	6	0
Gastro-Intestinal		
Nausea	17	7
Anorexia	13	5
Body As A Whole		
Fatigue	8	2
Skin and Appendages		
Rash	5	1

Commonly occurring adverse experiences in the sertraline pediatric/adolescent treatment group not reported at a comparable rate in the adult OCD group were: nervousness, agitation, hyperkinesia, fatigue and rash. Whereas, in the adult OCD's sertraline treatment group the commonly occurring adverse experiences not reported at a comparable rate in the pediatric/adolescent treatment group were: decreased libido, ejaculatory failure, diarrhea, dyspepsia, and increased sweating.

Evidence of Dose-Relatedness to Certain Adverse Experiences

The multi center outpatient study 371/372 was a fixed-dose study (50,100 or 200mg/day or placebo) and included a 12-week treatment phase followed by an additional 40 weeks of double-blind treatment for responders. These data were discussed in the original OCD NDA. To summarize, 4 adverse experiences showed a statistically significant dose-related increase in incidence. These were: ejaculation failure, tremor, dyspepsia and yawning. The adverse experience profile during the long-term treatment phase of this protocol (1-52 weeks) was similar to that of the 1-12 week exposure. In addition to the 4 adverse experiences (ejaculation failure, tremor, dyspepsia and yawning) which showed a statistically significant dose-related increase in incidence during weeks 1-12, two other adverse expeirences showed a dose-related increase during weeks 1-52, namely an increase in weight and sweating.

8.5.2 Laboratory Findings

In the OCD safety update the sponsor has provided updated incidence tables of clinically significant laboratory abnormalities in all placebo-controlled OCD adult studies (studies 237/248, 371/372, 546, 495 and 336). These data are displayed in appendix 8.5.2.1 of this review. No laboratory data were collected in protocol 007, the active-controlled study. The three methods used in the original OCD NDA database to evaluate abnormal laboratory data were used in the OCD adult NDA safety update database, and pediatric/adolescent OCD data. The data from the latter are displayed in appendix table 8.5.2.2 of this review.

Mean baseline and mean change from baseline to final visit in laboratory test values for the adult and pediatric/adolescent placebo-controlled databases are displayed in appendices 8.5.2.3 and 8.5.2.4, respectively.

8.5.2.1 Blood Chemistry

Appendix table 8.5.2.1 displays the proportion of patients in the placebo-controlled adult OCD studies with values of potential clinical concern at some time on assigned treatment. There were no statistically significant differences between sertraline and placebo-treated groups for any analyte, ($p>0.05$ Fisher's Exact Test). These findings compare with those of the original OCD NDA data.

Appendix table 8.5.2.2 displays the proportion of pediatric patients in the placebo-controlled OCD study (protocol 498) with clinically significant laboratory abnormalities. There were no statistically significant sertraline-placebo differences for any analyte, $p>0.05$ (Fisher's Exact Test).

Mean Change from Baseline-Adult OCD Safety Update

Changes from baseline to final visit for blood chemistry analytes in the placebo-controlled adult OCD studies were examined in this safety update and presented in appendix table 8.5.2.3. A comparison of the mean change from baseline to final visit for laboratory analytes between sertraline and placebo treatment groups using the Wilcoxon Rank Sum test revealed a statistically significant difference between group differences in the change from baseline to final visit for 5 analytes: SGPT, alkaline phosphatase, total bilirubin, uric acid and cholesterol. These data are summarized in the table below. In each case the mean changes from baseline were within normal ranges.

Mean Change and Percent Change From Baseline in Chemistry Analytes In OCD Safety Update For Placebo-Controlled Adult Studies

	Sertraline		Placebo	
Laboratory Analytes	N	Change from Baseline (% Change)	N	Change from Baseline (% Change)
SGPT (U/l)	489	2.9 (13%)	353	0.4 (2%)
ALK Phos (U/L)	490	3.2 (5%)	353	0.3 (0.4%)
Total Bilirubin (mg/dl)	489	-0.01 (2%)	356	0.03 (6%)
Cholesterol (mg/dl)	490	7.7 (4%)	352	-3.1 (2%)
Uric Acid (mg/dl)	422	-0.2 (4%)	288	0.1 (2%)

Pooled data for studies 237/248, 371/372, 546, 495 and 336 from patients yielding data at baseline and final visit.
Data Source: Adapted from Table 41, Vol. 2, P. 408.
Note: Comparison of change using Wilcoxon Rank Sum Test was statistically significant for the five analytes.

SGPT values showed a statistically significant increase from baseline for final visit with an average of 2.9 units (13%) in sertraline-treated patients compared to 0.4 units (2%) in the placebo group. There was no statistically significant dose response relationship in the fixed-dose study, 371/372.

Mean total cholesterol increased from baseline an average of 7.7mg/dl (4%) in the sertraline group compared with a mean decrease of 3.1mg/dl (2%) in the placebo group, a statistically significant difference. In the fixed-dose study 371/372 dose-response analysis of the mean changes in cholesterol treatment indicated elevations in cholesterol were confined to the maximum dose of 200mg. There was no statistically significant difference from placebo with the 50mg and 100mg doses of sertraline.

Uric acid values decreased from a baseline 0.2mg/dl(-4%) in sertraline-treated paitents compared with an increase of 0.1mg/dl(2%) in placebo-treated patients, a statistically significant difference.

There were two laboratory analytes whose mean change from baseline was significantly different in sertraline vs placebo in the adult OCD NDA safety update but not in the original OCD NDA. These analytes were: total bilirubin and alkaline phosphatase. Total serum bilirubin decreased from baseline an average of 0.01mg/dl(-2.0%) in the sertraline-treated group compared to a mean increase of 0.03mg/dl(6%) in the placebo-treated group, a statistically significant difference. Alkaline phosphatase values showed a statistically significant mean increase from baseline of 3.2 units (5%) in the sertraline-treated group compared to a mean increase of 0.3 units (0.4%) in the placebo-treated group. The clinical significance of these changes is uncertain.

Mean Change from Baseline Pediatric/Adolescent OCD Studies

Appendix table 8.5.2.4 summarizes the mean change from baseline data. There was a statistically significant between-group difference (Wilcoxon Rank Sum Test) in the mean change from baseline to final visit for the following analytes: SGOT, total cholesterol and uric acid. These data are summarized in the table which follows.

Mean Change and Percent Change from Baseline in Chemistry Analytes
OCD Pediatric/Adolescent Placebo-Controlled Study (Protocol 498)

	Sertraline		Placebo	
Laboratory Analytes	N	Change From Baseline (% change)	N	Change From Baseline (% change)
SGOT (U/L)	92	0.92 (4%)	91	-0.62 (3%)
Cholesterol (mg/dl)	92	6.53 (4%)	91	-6.67 (4%)
Uric Acid (mg/dl)	92	-0.67 (15%)	91	0.09 (2%)

Data Source: Adapted from Table 67, Vol. 2, P. 491.

For comparison purposes, in the adult OCD database the SGOT level increased from baseline an average of 2.2 units (11%) in the sertraline-treated group compared to a mean increase from baseline of 1.6 units (7%) in the placebo-treated group. This difference was not statistically significant.

The mean changes from baseline for blood cholesterol in the pediatric/adolescent database were similar to that of the adult mean changes from baseline whereas the uric acid changes relative to baseline in the former group of patients were several orders of magnitude greater than that of the adult sertraline-treated patients.

Dropouts - Adult OCD Safety Update

Four additional cases of premature discontinuations involving clinical chemistry laboratory findings were reported in the safety update, bringing the total to 5/533 (0.9%) sertraline-treated vs 1/373 (0.3%) placebo treated in placebo-controlled OCD adult studies.

Of the 5 sertraline-treated patients who dropped out, 4 (0.8%) were due to elevation of serum transaminases (in protocol 371/372 patient #7, protocol 495, patients #158 and 358 and protocol 336 patient #0132) and one due to elevated blood glucose (patient #37 from protocol 495) compared with one placebo-treated patient who dropped out because of elevated serum transaminases (patient #283, protocol 495). Line listings as well as CRFs were supplied by the sponsor and reviewed by the medical reviewer. The six cases are summarized in and presented in the table on the following page.

Appendix Table 8.5.2.1.2
Summary of Patients Discontinuing Treatment Because of Clinically Significant Chemistry Laboratory Abnormalities.

STUDY	PATIENT	SEX	AGE (YRS)	DOSE AT TIME OF WITH-DRAWAL (MG/DAY)	DURATION OF THERAPY (DAYS)	COMMENTS
336	0132	F	36	50	7	Patient had abnormal labs (SGOT 41 U/L, SGPT 85 u/L) at screening which were not discovered until 1 week after randomization. Patient took Thorazine 150 mg/day as a concomitant medication (which had been taken regularly for more than 2 years). Repeat SGOT and SGPT were within normal limits one month after discontinuation of sertraline
495	158	M	41	50	104	In this 60kg oriental there was an asymptomatic increase in SGPT and SGOT to 106 U/L and 63 U/L, respectively. After 104 days of sertraline (50mg/d) from baseline of 18 and 24, respectively. Four weeks later, the SGOT and SGPT values were 34 U/L and 39 U/L, respectively. No h/o ethanol or drug use. PT had h/o irritable bowel syndrome.
495	37	M	53	100	57	Patient entered study with high but not clinically significant blood glucose (195 mg/dL) and urine glucose. At the end of week 4, blood and urine glucose had risen to 233 mg/dL, respectively. Patient was removed from the study to be followed by an internist.
495	358	F	40	200	43	This 5'7" patient (wt.=85kg) had elevated SGPT (401 U/L) and SGOT (128/U/L) from baseline of 33 U/L and 27 U/L, respectively. Improved 10 days later to SGPT 137 U/L and SGOT 53 U/L; seventeen days later SGPT (63 U/L) and SGOT (28 U/L). No h/o ethanol or drug use.
371/372	7	M	27	100	196	Asymptomatic elevation of liver enzymes SGOT (246 U/L). SGPT 172 U/L). Decrease to 36 U/L and 54 U/L, respectively 10 days after discontinuation with complete normalization 30 days after cessation of treatment.
495	283	M	44	0 (placebo)	108	Elevated SGPT (115 U/L) and SGOT (69 U/L). Seven weeks later, SGPT and SGOT still elevated (133 and 64 U/L, respectively). Eight-month history of hypertension and 10-year history of chronic allergies.

Dropouts Pediatric/Adolescent OCD Studies

In the placebo-controlled pediatric/adolescent OCD study (protocol 498) one placebo (1/95) and no sertraline-treated patients (0/92) dropped out due to laboratory tests abnormalities. The one placebo-treated patient #509 dropped out due to asymptomatic elevations of serum transaminases (SGPT 186 μ/L and SGOT = 95 μ/L) after 30 days of placebo treatment. There have not been reports of dropouts in the other protocols (525, 536 and 550).

The findings in the pediatric/adolescent are consistent with the adult trials and the current product labeling for depression, with respect to laboratory test abnormalities although the mean change from baseline uric acid levels in the sertraline-treated pediatric/adolescent group is several orders of magnitude greater than that of the adult patients, (placebo groups were similar).

8.5.2.2 Hematology

The appendix table 8.5.2.1 displays the number of patients with hematologic analytes of potential clinical concern in the 5 placebo-controlled adult OCD studies. Overall, the number of patients flagged for values of clinical concern was small and similar to the original OCD NDA database. There were no statistically significant differences, $p>0.05$ (Fisher's Exact Test) between the sertaline and placebo groups.

The appendix table 8.5.2.2 displays the number of patients with hematologic analytes or potential clinical concern in the one placebo-controlled pediatric/adolescent study (protocol 498). There were no statistically significant differences between sertraline-placebo treatment groups in the incidence of clinically significant laboratory abnormalities for any analyte, $p>0.05$ (Fisher's Exact Test).

Mean Change from Baseline-Adult OCD Study Update

Appendix Table 8.5.2.4 summarizes the mean change from baseline. Statistically significant mean changes from baseline (sertraline vs placebo) were seen in one hematologic analyte, white blood cell count. White blood cell count increased from baseline an average of 30 cells/mm^3 (0.4%) in sertraline-treated patients compared to a mean decrease of 190 cells/mm^3 (3%) in placebo-treated patients. The mean change was small and within the normal ranges ($\leq 2.8x10^3/mm^3$ or $\geq 16x10^3/mm^3$). There were no significant differences reported between sertraline vs placebo in the original OCD NDA.

Mean Change from Baseline-Pediatric/Adolescent OCD Studies

Appendix table 8.5.2.4 summarizes the mean change from baseline. Statistically significant mean changes from baseline (sertraline vs placebo) were seen in one hematologic analyte, eosinophils. The percentage of eosinophils increased from baseline an average of 0.56% in the sertraline group compared to an average decrease of 0.14% in the placebo group. Similar changes were not noted in the adult OCD database.

Examining individual patient data, the measurement with respect to baseline values was that in a 15YOM (patient #818, study 92N0054) who had a baseline eosinophil of 3.4% and 13% on day 9 of treatment. The final value was 3% while on sertraline. There were no serious events reported with incremental change in eosinophils.

There were similar patterns noted in the placebo-treated groups ascertained from the scattergram of eosinophils in figure 35 supplied by the sponsor (vol. 3, p. 537).

Although the most comon cause of elevated eosinophils is probably allergic reactions to drugs, there was no evidence for such an association in the existing database.

Dropouts-Adult OCD Safety Update

The only hematologic analyte that resulted in discontinuation from an OCD study was a decreased white blood cell count in one sertraline patient, (a 22 YOM (study 371/372, patient #14) who had asymptomatic transient leukopenia. The WBC did not fall below 3.1. This patient was discussed in the original OCD NDA submission. No additional reports of discontinuation have been incorporated into the safety update.

Dropouts-Pediatric/Adolescent OCD Database

No sertraline-treated patients discontinued from a study due to hematologic test abnormalities in any pediatric/adolescent protocol.

8.5.2.3 Urinalyses

The appendix table 8.5.2.1 provides a summary table of patients with urinalysis values of potential clinical concern in placebo-controlled adult OCD studies. As was the case in the original OCD NDA database, there were no statistically significant or clinically meaningful differences between the sertraline and placebo-treated patients.

The appendix table 8.5.2.2 shows the incidence of clinically significant urinalysis abnormalities in the placebo-controlled pediatric/adolescent studies. There were no statistically significant or clinically meaningful sertraline-placebo differences.

Mean change from Baseline-Adult OCD Safety Update

A table was not provided by sponsor. In the original OCD NDA there was no statistically significant differences between sertraline and placebo group.

Mean Change from Baseline Pediatric/Adolescent OCD Studies

There were no statistically significant differences in sertraline vs placebo patients for any urinalysis analyte.

Dropouts-Adult OCD Safety Update

There were no dropouts in the final safety update.

Dropouts-Pediatric/Adolescent Safety Update

There were no dropouts due to urinalyses analytes.

8.5.3 Vital Signs and Body Weight

Abnormalities in vital signs were identified by the following criteria: heart rate ≥120 bpm or ≤50 bpm; systolic blood pressure (standing or supine) ≥180 mmHg or ≤90 mmHg; diastolic blood pressure (standing or supine) ≥105 mmHg or ≤50 mmHg. Additionally, changes from baseline were required to be greater than or equal to: 15 bpm for heart rate, 20 mmHg for systolic blood pressure, and 15 mmHg for diastolic blood pressure. Values were flagged if one or more of the vital signs were outside the pre-determined reference range or if a change from baseline exceeded the predetermined range; either value was of potential clinical concerns. A similar approach was used for the pediatric/adolescent database.

Line listings and CRFs of all patients who discontinued because of abnormalities in vital signs were reviewed for vital sign abnormalities.

Tables of reference age specific percentiles of blood pressure measurements in the 1-18 year old range, as well as heart rate are provided in appendix 8.5.3.1.

Proportion of Adult Patients in Placebo-Controlled Studies Having Potentially Clinically Significant Change in Vital Signs

Appendix Table 8.5.3.2 displays the number of patients in the safety update with vital sign abnormalities in all placebo-controlled adult OCD patients. The predominant vital sign abnormality in both treatment groups was decreased blood pressure, most notably in the standing and supine systolic blood pressure measurements. Thirteen of 518 (2.5%) sertraline-treated patients and 14/357 (3.9%) placebo-treated patients had at least one clinically significantly decreased systolic reading upon standing. There were no statistically significant differences in the incidence of clinically significant abnormalities in vital sign measurements between the treatment groups. These findings are consistent with the original OCD NDA database.

Proportion of Pediatric/Adolescent Patients Having Potentially Clinically Significant Changes in Vital Signs in the Placebo-Controlled Study (Protocol 498)

Appendix Table 8.5.3.3 shows the number of pediatric/adolescent patients with vital sign abnormalities in the placebo-controlled study. The predominant vital sign abnormality was decreased supine diastolic blood pressure. Seventeen percent of sertraline-treated patients and 13% of placebo-treated patients had at least one significantly decreased supine diastolic reading and 7% of sertraline-treated and 3% of placebo-treated patients had a decreased standing diastolic blood pressure reading. For both sertraline and placebo-treated patients, the incidence of vital sign abnormalities was higher than in the adult studies.

A list of patients with clinically significant vital sign abnormalities was provided by the sponsor (Vol. 2, P. 494, Table 70). The most abnormal value in the supine diastolic blood pressure reading occurred in a 15 YOF (patient #221) who had an abnormal baseline reported at 112 mmHg. On day 57 of treatment, the reading was 50mmHg. In patients with normal baseline readings the maximum decrease from baseline was 43 mmHg, recorded after 15 days of treatment, in a 12 YOM (patient #17) whose baseline supine diastolic reading was 80 mmHg. There were no reports of serious events associated with vital sign changes in these patients.

Mean Change From Baseline in Placebo-Controlled Studies-Adult OCD Safety Update

Mean baseline values and mean changes from baseline to final visit, in vital signs for sertraline and placebo-treated patients are displayed in Appendix Table 8.5.3.4. Pairwise comparisons revealed statistically significant changes with respect to the vital signs displayed in the following table.

OCD Safety Update: Adult Placebo-Controlled Studies
Mean Change From Baseline in Vital Signs

Vital Sign	Sertraline Change From Baseline (%)	Placebo Change From Baseline (%)
Standing SBP	-1.41 mmHg (0.65%)	0.23 mmHg (0.47%)
Standing DBP	-0.78 mmHg (0.18%)	0.48 mmHg (1.29%)
Standing Heart Rate	-1.37 bpm (0.76%)	0.80 bpm (2.25%)

SBP= Systolic Blood Pressure DBP= Diastolic Blood Pressure HR = Heart Rate
Adapted from Sponsor's Table 43, Vol. 2, P. 419; pooled data from protocols 237/248, 371/372, 494, 546, 336.

The mean changes from baseline to final visit in vital signs in the pooled data set are small, however, these changes may not adequately reflect outliers.

Mean Change from Baseline in Placebo-Controlled Study (protocol 498)-Pediatric/Adolescent OCD Database

Comparisons of mean changes and mean changes from baseline to last visit of vital sign measurements are displayed in Appendix Table 8.5.3.5. Mean change scores in the sertraline group did not differ significantly from mean change scores in the placebo group for any vital sign measurement.

Dropouts, Adult and Pediatric OCD Studies

There were no dropouts for vital sign abnormalities in either the adult safety update or pediatric OCD placebo-controlled studies.

Body Weight

Body weight was measured at ev y visit. The proportion of patients having clinically significant weight changes occurring in the adult placebo-controlled studies in the safety update is presented below.

OCD Safety Update: Placebo-Controlled Studies
Incidence of Clinically Significant Changes From Baseline in Body Weight
(>=7% Increase or Decrease From Baseline)

	Number of Patients with Clinically Significant Change in Body Weight (%)	
	Sertraline (N=523)	**Placebo (N=368)**
Increase (>=7% Above Baseline)	**28 (5.4%)***	**6 (1.6%)**
Decrease (>=7% Below Baseline)	**26 (5.0%)***	**9 (2.4%)**

*p<=0.05 compared with placebo using Fisher's Exact Test.
Adapted from sponsor's Table 46, Vol. 2, P. 431, pooled data for protocols 237/248, 371/372, 546, 495 and 336.

On the basis of the threshold criteria statistically significant weight changes were noted in the sertraline-treated patients compared to placebo. There were no consistent unidirectional changes.

In the pediatric/adolescent database, body weight was measured at every visit. The proportion of patients having clinically significant weight changes occurring in the placebo-controlled study (protocol 498) is presented in the table which follows.

Pediatric/Adolescent Placebo-Controlled Study
Incidence of Clinically Significant Changes From Baseline
in Body Weight (>=7% Increase or Decrease From Baseline).

	Number of Patients with Clinically Significant Change in Body Weight (%)	
	Sertraline (N=92)	**Placebo (N=94)**
Increase (>=7% above baseline)	8 (8.7%)	10 (10.6%)
Decrease (>=7% below baseline)	5 (5.4%)*	0 (0.0%)

* p<=0.05 compared with placebo using Fisher's Exact Test.
Adapted from Sponsor's Table 71, Vol. 2, Page 498.

Five (5.4%) of the sertraline-treated adult patients and no placebo-treated patients were reported to have experienced a clinically significant decrease in body weight, a statistically significant difference. The range of values was -6 to -12 pounds over 17 to 48 days of sertraline exposure. There were two (final value relative to baseline -10 pounds for both patients) additional reports in

the non-placebo controlled studies (protocol 525).

There were no serious adverse experiences reported to have occurred with body weight changes.

Mean Change From Baseline-Adult OCD Safety Update

The mean change in weight from baseline to final visit in the pooled placebo-controlled studies was 0.39 pounds among the sertraline and 0.02 pounds among the placebo-treated patients. These changes were not statistically significant.

Mean Change From Baseline-Pediatric/Adolescent OCD Studies

The mean change in weight from baseline to final visit in the placebo-controlled OCD study (protocol 498) was an increase of 0.58 pounds among the sertraline and 2.52 pounds among the placebo-treated patients. These changes were statistically significant.

Droputs, Adult and Pediatric OCD Studies

In placebo-controlled adult studies, 0.2% (1/533) sertraline-treated and no placebo-treated (N=373) discontinued because of a decrease in body weight. This one patient was described in the original OCD NDA review. There were no differences in the incidence rates when long-term data from protocol 371/372 were included in the data pool.

In completed (N=153) and ongoing (N=67) pediatric/adolescent sertraline studies no sertraline-treated patients discontinued because of a decrease in body weight.

8.5.4 Electrocardiograms

ECGs were analyzed and reported in a manner similar to that of the original OCD NDA.

The table which follows presents the incidence of clinically significant ECG abnormalities in all placebo controlled studies in the OCD NDA safety update.

OCD Final Safety Update
All Placebo-Controlled Studies
Incidence of Clinically Significant ECGs

	Number of Patients (%)	
	Sertraline (N=445)	**Placebo (N=288)**
Clinically Significant	0 (0.0%)	1 (0.3%)

NOTE: Incidences for all visits were summarized.
Patient required a baseline ECG and at least one additional ECG in order to be included in the summary.
ECG data not available for study 336.
Adapted from Sponsor's Table 48, Vol. 2, P. 441.

In the safety update as was the case in the original OCD NDA submission, there was no clinically significant treatment-emergent ECG abnormality recorded among the sertraline-treated patients.

The incidence of changes from baseline ECG measurement is provided in appendix table 8.5.4.1. There were no statistically significant differences between the groups.

The incidence of clinically significant ECG changes by treatment group in the placebo-controlled pediatric OCD study (Protocol 498) is shown in the table which follows. There were no clinically significant treatment-emergent ECG abnormalities recorded. One patient (Protocol 498, study #90-N-0241, patient #76), however, was considered by the investigator to have a clinically significant change from baseline in the ECG tracing at the end of week 12, although the ECG itself was not felt to be clinically significant. This sertraline-treated patient's ECG was noted to be normal at Day 1 of washout and at the end of weeks 1 and 4. The week 12 ECG was read as abnormal, but not clinically significant. The change from baseline, however, was determined to be significant in that the patient had developed P-wave changes and sinus tachycardia. The investigator noted that this change in the tracing may have been related to a concomitant medication (Ventolin syrup for asthma) that the patient had taken for two days immediately prior to the week 12 ECG. No follow-up ECG was obtained.

Pediatric/Adolescent Placebo-Controlled Study
(Protocol 498)
Incidence of Clinically Significant ECG Abnormalities

	Number of Patients (%)	
	Sertraline (N=91)	**Placebo (N=95)**
Clinically Significant	0 (0.0%)	0 (0.0%)

Note: Incidences for all visits were summarized.
Patient required a baseline ECG and at least one additional ECG in order to be included in the summary.

The incidence of changes from baseline ECG measurements is displayed in appendix table 8.5.4.2. There were no statistically significant differences between the groups.

There were no patients in any study who discontinued due to ECG readings considered abnormal in either the adult or pediatric/adolescent databases.

8.5.5 Special Studies

There were no special studies submitted with the safety update.

8.5.6 Withdrawal Phenomena/Abuse Potential

There is no additional information in the safety update.

8.5.7 Human Reproduction Data

In the adult OCD NDA safety update, three pregnancies were reported (one from the initial OCD NDA submission, patient #36 (study 88NO179, protocol 371/372) and two additional patients from protocol 371/372, patient 38 (study 88NO179) and patient #36 (study 88NO173). Patient #38, a 36 YOF had an ectopic pregnancy with surgical evacuation. Patient #36 is to be followed pre and postnatally. There were no reports of pregnancy in the pediatric/adolescent database. There is no additional information in this safety update with respect to human reproduction data.

8.5.8 Overdose Experience

As of the cut-off date of June 30, 1995 for this safety update, there have been 2 reported cases of overdose in the world-wide OCD database in sertraline-treated patients. One of the sertraline overdose cases was described in the original OCD NDA. The second case is summarized here.

Patient STL-NY-91-007-0118 was a 33 year old female who intentionally ingested 45 X 50mg capsules (i.e. 2250 mg) of sertraline in a suicide attempt after 64 days of sertraline treatment. Concomitant medications included piroxicam and thiocolchicoside for lumbago. The patient's symptoms upon admission to the hospital were somnolence and mutism. The patient was given ipecac and activated charcoal at which time she showed restlessness, excitation, hands/feet tremor, clonic closing of her eyelids and sharp osteotendinous reflexes. Blood screen was positive for alcohol (1.05 g/L). She improved and was discharged the following day after receiving psychiatric counseling.

In the pediatric/adolescent database there were 2 reported cases of overdose.

Patient #225 from protocol 525 (study #92-N-0058) was a 14 year old male with major depression who had been receiving 200 mg/day sertraline. He was hospitalized overnight on the 35th day of the study for a suicide gesture in which he ingested 400 mg of sertraline, 10 mg of lorazepam and an unknown amount or organophosphate insecticide. The patient was continued in the study.

Patient #217 from protocol 536 (study #91-N-0242) was a 17-year old female with OCD. She was admitted to the hospital for two nights after taking an intentional overdose of antihistamines. The patient had been in the study for 136 days, and at a dose of 200 mg/day sertraline for 55 days. The patient was discontinued from the study, but continued taking Zoloft 200 mg/day. Three weeks later, the patient ingested an unknown type of pill in another suicide gesture, and was readmitted to the hospital. No further outcome information is available.

Symptoms of overdose with sertraline as well as the management of overdose are discussed in the existing product labeling.

8.6 Summary of Potentially Important Adverse Events Considered Possibly or Probably Drug Related

8.6.1 Seizures

In the original OCD NDA database there were 4 reports of seizures (as of 10/10/94). Of these 4 reports, one occurred in the completed placebo-controlled studies and 3 in the ongoing or not yet completed pediatric/adolescent studies (protocols 536 and 498). Available information on these cases was summarized previously in the review of the OCD NDA database. There are no additional reports of seizures in this safety update of which the OCD NDA database is a subset and which includes safety data from the above mentioned pediatric/adolescent studies in addition to data from all ongoing studies. Therefore, 4 reports of seizures out of 1801 sertraline-treated patients [1581 patients in completed (N=627) and ongoing (N=954) adult studies and 220 patients in completed (N=153) and ongoing (N=67) pediatric/adolescent studies] represents a crude incidence of 0.2% compared to 0% for placebo (N=521) and 0.3% for active control (N=308).
The 3 pediatric/adolescent reports of seizure (3/220=1.4%) were summarized from the available information at the time in the original OCD/NDA review and are summarized in table 8.6.1 incorporating any additional information from the CRFs submitted.

In the pediatric/adolescent database there was no apparent correlation between the reported event and either duration of treatment (or withdrawal of drug) or dose of sertraline given prior to the seizure (range 0.6 to 3.8 mg/kg bwt. Incidentally, in a hypothetical adult male OCD patient who weighs 75kg and is 5'10" in height (body surface area of 1.91m^2) a 200mg daily dose of sertraline

would be approximately 2.7mg/kg bwt, or 105mg/m^2 compared to 3.8mg/kg bwt (body surface area of 1.54m^2) or 130mg/m^2 in the pediatric patient #222 and 1.4mg/kg bwt (body surface area of 1.72m^2) or 58mg/m^2 in patient #223. There is insufficient data for the third pediatric patient #823.

Table 8.6.1
Patients Experiencing Seizure in Pediatric/Adolescent Studies

PROTOCOL	PATIENT/ STUDY NO.	AGE	SEX	DURATION OF TREATMENT (DAYS)	DOSE (mg/ kgBW)	BODY WEIGHT (kg) Height (cm)	COMMENTS
498	222/90-N-0242	14	F	58	200 (3.8)	53kg (160cm)	1. Pt. had no seizure hx, but pos. family hx. No concomit Rx 2. Brief, witnessed clonic seizure. In the M.D.'s judgement cause of seizure was study drug. Not hospitalized. 3. Pt. Rx with carbamazepine and sertraline re-initiated and titrated up to 200mg/day.
536	223/91-N-0242	15	F	15*	100 (1.4)	75 (152cm)	1. Pt. and family had no seizure hx. No concomit. Rx. 2. Witnessed Grand mal seizure. Not hospitalized. In the M.D.'s judgement, the cause of seizure was sertraline. 3. Pt. Rx with carbamazepine. Sertraline restarted and switched to paroxetine. Another seizure report occurred.
536	823/92-N-0055	15	M	4	50 (0.6)	88 kg (N/A)	1. Pt. had two seizures, but no family hx. No concomit. Rx. 2. Pt. had comorbid dx of autism. 3. Pt. had grand mal seizure. In M.D.'s judgement, cause of seizure uncertain. After D/C, pt. Dx by neurologist with complex partial epilepsy and Rx with felbatol.

* Patient did not take medications on study day 12, 14 or 15.

Two of the three pediatric patients (patients 222 and 223) for whom I have laboratory data did show decreases relative to baseline values in total serum protein and serum albumin levels days prior to the seizure. This may or may not be clinically meaningful with respect to the relationship between bound and unbound drug in plasma and subsequent risk of toxicity. Intrinsic clearance may also vary.

The incidence of seizures among the sertraline-treated pediatric OCD patients (3/220; 1.4%) was higher than the incidence of seizures reported in the adult OCD trials (1/1581; 0.01%). In general, the incidence of seizures is reported to be higher among pediatric patients. The incidence in patients 10 to 19 years old ranges form 37 to 58 per 100,000 per year and drops to 12 to 37 per 100,000 in the age group 40 to 59.

Finally, in world-wide reports of overdoses of sertraline alone (as of November, 1992 = 28) in reported doses from 500mg to 6000mg seizures have not been reported.

Seizures are a labeled event in the PRECAUTIONS section of the package insert.

8.6.2 Suicidality

The incidence of suicidality among patients in the final safety update in OCD studies has been discussed in section 8.4.2 of this review.

8.6.3 Activation of Mania/Hypomania

There were no reports of mania/hypomania in the adult sertraline-treated OCD patients in controlled studies (N=627) and one report out of 373 (0.3%) in placebo-treated patients. In the ongoing adult studies, there were three reports of mania/hypomania, two of which occurred in sertraline-treated patients and one of which in a patient who had been in blinded therapy. All three patients discontinued treatment. Therefore, in all adult OCD studies (completed and ongoing) the incidence of mania/hypomania was 0.1% (2/1581) compared to 0.2% (1/426) in placebo-treated patients.

In the completed pediatric/adolescent database, there were 3 reports (3/153 = 2.0%) of manic reaction in sertraline and no reports in placebo-treated patients. The reactions were not considered serious and patients continued treatment. There were no reports of mania/hypomania in ongoing studies. Therefore in all pediatric/adolescent OCD studies (completed and ongoing) the incidence of mania/hypomania was 1.4% (3/220) and 0% (N=95) in placebo treated.

These data suggest that the risk of precipitating manic reactions with sertraline in either adult or podiatric patients is small.

Mania and hypomania are mentioned in the package insert.

8.6.4 Weight Loss

Findings regarding weight loss have been discussed in the section entitled, "Vital Signs". The adverse experience was reported as either mild or moderate in severity. As reported previously in the original OCD NDA, one sertraline patient and no placebo-treated patients discontinued because of weight loss.

In the pediatric/adolescent placebo-controlled OCD study (protocol 498) the incidence of the adverse experience weight loss was 5% (5/92) in sertraline-treated and 0% (N=95) in the placebo-treated patients. The severity was mild to moderate. No patients discontinued from the placebo-controlled studies because of weight loss.

Weight loss is mentioned in the PRECAUTIONS (General) section of package insert.

8.6.5 Increased Serum Transaminase Levels

In the safety update in all of the adult OCD pooled studies 237/248, 371/372, 494, 546, 495, 336 (according to the sponsor letter dated March 6, 1996, there was no laboratory data collected for protocol 007 sertraline-treated patients, N=86) there have been 7 sertraline-treated patients who showed clinically significant elevations of transaminases. Six of these reports were submitted previously to the OCD NDA. 3 placebo-treated patients (0.4%) had transaminase elevations. Briefly of the seven sertraline-treated patients:

4 patients (patient # 18, 29 49 and 151) exhibited an isolated elevation in the SGPT test (probably most sensitive indicator of liver injury).

2 patients (patient # 7 and 358) exhibited elevation of both liver tests.

1 patient (patient # 3) exhibited an isolated elevation of the SGOT test.

The mean time from the first dose to the most abnormal transaminase value was 77 days (range from day 43-196). Four patients, #3, 18, 49 and 358 of the seven patients had clinically significant elevations in either SGPT or SGOT levels on days 43-45.

The range of SGOT levels was 128 to 246 U/L. The range of SGPT levels was 134 to 401 U/L.

Moderate elevations in SGOT levels (3-8x ULN) occurred in one patient (patient # 7). Moderate elevations in SGPT levels occurred in two patients (patient # 49 and 358). There were no marked SGOT elevations (> 8x ULN). There was one marked SGPT elevation (>8 x μLN in patient #358). Patient #358 (protocol 90CE21-0495) was a 40YOF (Caucasian, 5'7"/187lbs) college graduate, married, no children, and employed selling cosmetics. She had no history of ethanol or drug abuse. She used spermicide for birth control. She took multiple vitamins. No other medications noted. Patient dosed at 200mg/day until September 1. Data for this patient are presented in the table on the next page.

The following adverse experiences were reported by the patient beginning on 7/21 and were "ongoing": decreased appetite (end of week 4 weight had decreased from 187 to 184 pounds), blurry vision, decreased libido, headaches and anorgasmia. Ibuprophen (200mg pd) was taken on 8/26, 8/29 and 8/31. No other medications reported. The case demonstrates the following:

1. Rapidity of onset of hepatic effects
2. No prodrome of distinguishing symptoms
3. Possible increase in hepatic injury (persistent and worsening SGPT) between transaminase measurements.
4. Reduction in transaminase levels when sertraline was discontinued.
5. No evidence of hypersensitivity reaction.

Data from Patient #358 Which Demonstrates Association of Sertraline and Hepatic Injury (Drug Stopped on 9/1)

Date of visit Collection Date (Blood)	Baseline (7/14)	Week 2 (8/3)	Week 4 (8/17)	Week 6 (8/31)	Termination (9/4)	Follow-up (9/18)
Analyte (Normal Range)						
Total Bilirubin (0.2-1.2mg/dl)	0.5	0.2	0.3	0.4	0.5	not available
Alkaline Phosph. (31-110U/L)	88	89	120	120	111	not available
SGPT (6-34U/L)	33	33	113	401	249	63
SGOT (9-34 U/L)	27	22	68	128	87	28
Albumin (3.3-4.9g/dl)	4.2	3.8	4.1	4.0	4.1	not available

None of the 7 sertraline-treated patients developed jaundice. This is consistent with the observation that the highest total bilirubin value among these 7 patients never exceeded 1.5 mg/dl. Jaundice is not normally observed until the total serum bilirubin exceeds 2-2.5 mg/dl.

Adverse events of each patient were reviewed in an attempt to determine whether prodromal signs/symptoms preceded the appearance of the abnormal hepatic values. Three of the 7 patients (patient #3, 151, and 49) experienced no adverse events. A review of the four remaining patients (patient #29, 7, 18, and 358) did not suggest the presence of prodromal symptoms or symptom clusters with respect to impending liver toxicity.

None of the elevations was accompanied by clinical symptoms indicative of a hypersensitivity reaction.

8.6.6 Increased Serum Cholesterol

In the safety update, there were 3 additional reports of clinically significant cholesterol abnormalities in sertraline adult-treated patients (one from protocol 546 and two from protocol 495) for an incidence of 3.0% (13/490) compared to placebo of 1% (3/352). The difference was not statistically significant. For all placebo-controlled studies, mean total cholesterol increased form baseline an average of 8mg/dl (4%) in the sertraline group which compared to a mean decrease of 3.0 dl (2%) in the placebo group. This difference was statistically significant.

In the pediatric/adolescent placebo-controlled study (study 498) there were no reports of clinically significant cholesterol abnormalities in either the sertraline or placebo-treated patients. However, the mean total cholesterol increased from baseline an average of 7mg/dl (4%) in the sertraline group compared to a mean decrease of 7mg/d (5%) in the placebo-treated group, a statistically significant difference ($p<0.0001$).

What if any is the clinical meaning of these statistically significant findings? Higher serum cholesterol levels in children have been associated with aortic atherosclerosis at autopsy in adolescent and young men (Newman etal. N. Engl. J Med. 314: 138,1986). Findings in a recent study (Klag etal N. Engl. J. Med. 328:313, 1993) indicate a strong association between serum cholesterol levels measured early in life and total morbidity and mortality due to cardiovascular disease. In adults the risk of death from cardiovascular disease increases in a parabolic fashion with increases in the level of total serum cholesterol.

8.6.7 Decrease in Serum Uric Acid Levels

Sertraline is associated with a weak uricosuric effect in both adult and pediatric/adolescent sertraline-treated OCD patients. In the premarketing clinical trials for depression, sertraline was associated with a mean decrease in serum uric acid levels of approximately 7% and is noted as such in the PRECAUTIONS section of the package insert. This hypouricemic effect isnot well characterized with regards to: dose-relatedness, time of onset, reversibility of event, influence of age, gender, or mechanism of action (enhanced renal clearance?, interference with tubular reabsorption?). Reports in the literature have noted that serum uric acid concentrations are inversely related to renal blood flow (Frohlich JAMA 270:378,1993) and that hypouricemia is seen with hyponatremia related to SIADH and increased renal clearance of uric acid (Decaux et al Nephron 39:164,1985). Neither fluoxetine or paroxetine have been reported to have a uricosuric effect.

8.6.8 Search For Other Significant Events Alleged to Occur in Other members of the Drug Class

The table which follows displays the incidence of insomnia for all placebo-controlled adult OCD studies as well as for the pediatric/adolescent OCD placebo-controlled study (study 498).

Safety Update Table for All Placebo-Controlled (Adult and Pediatric/Adolescent) OCD studies

Adverse Experience	Adult % of Patients*		Pediatric/Adolescent % of Patients	
	Sertraline N=533	Placebo N=373	Sertraline N=92	Placebo N=95
Insomnia	30% (30%)*	24% (13%)	37%	13%

* protocols 237/248, 371/372 (1-12 weeks), 495, 546, 336
The pediatric/adolescent placebo-controlled study was study 498.

Relative to placebo, insomnia as an adverse experience was reported more frequently by the pediatric/adolescent OCD population, compared to the adult OCD patients.

Safety Update Table for All Placebo-Controlled
Adult and Pediatric/Adolescent OCD Studies
Incidence of Discontinuation Associated with Insomnia

Adverse Experience	Adult* % of Patients		Pediatric/Adolescent % of Patients	
	Sertraline N=533	Placebo N=373	Sertraline N=92	Placebo N=95
Insomnia	3%	1%	2%	1%

* protocols 237/248, 371/372 (1-12 weeks), 495, 546, 336

Of the 14 adult sertraline-treated patients who discontinued because of insomnia the intensity was recorded as severe by 7 patients, moderate by 6 patients and mild by the last patient. Whereas, of the 3 placebo-treated patients who discontinued, the level of intensity was either mild, moderate or severe in one of the 3 patients.

Of the 2 pediatric/adolescent patients who discontinued because of insomnia, one episode was recorded as mild and the other as severe. Whereas the intensity was mild in the only placebo-treated patient.

The incidence of insomnia in the adult treated patients in the safety update was comparable to the incidence of insomnia reported in the original OCD NDA database.

8.6.8.2 Anxiety

The table which follows displays the incidence of anxiety in the safety update for all placebo-controlled adult and pediatric/adolescent OCD studies.

Safety Update Table for All Placebo-Controlled
(Adult and Pediatric/Adolescent) OCD Studies

Adverse Experience	Adult* % of Patients		Pediatric/Adolescent % of Patients	
	Sertraline N=533	Placebo N=373	Sertraline N=92	Placebo N=95
Anxiety	8%	6%	2%	1%

* protocols 237/248, 371/372 (1-12 weeks), 495, 546, 336

The pediatric/adolescent placebo-controlled study was study 498.

Safety Update Table for All Placebo-Controlled (Adult and Pediatric/Adolescent) OCD Studies Incidence of Discontinuation Associated with Anxiety

Adverse Experience	Adult* % of Patients		Pediatric/Adolescent % of Patients	
	Sertraline N=533	Placebo N=373	Sertraline N=92	Placebo N=95
Anxiety	2%	1%	0%	0%

* protocols 237/248, 371/372 (1-12 weeks), 495, 546, 336

The pediatric/adolescent placebo-controlled study was study 498.

The incidence of anxiety in the adult treated patients in the safety update was comparable to the incidence of anxiety in the original OCD NDA database.

8.6.8.3 Rash and Possible Allergic Events

In the safety update for all adult placebo-controlled OCD studies, the incidence of skin rash (regardless of long-term exposure) was 2% (12/533) and 1% (5/373) in the sertraline and placebo-treated groups, respectively, somewhat less than the original NDA OCD database. In the pediatric/adolescent placebo-controlled study, the incidence of skin rash was 5% (5/92) and 1% (1/95), respectively (differences not statistically significant). These were described as mild in intensity. One sertraline-treated patient in the adult placebo-controlled studies (regardless of long-term exposure) discontinued because of a skin rash (intensity described as moderate). No placebo-treated patients dropped out.

One sertraline-treated patient was reported to have dropped out in the original OCD NDA because of a rash characterized as contact dermatitis.

In the pediatric/adolescent placebo-controlled study, one sertraline and no placebo-treated patients dropped out due to skin rash. The patient was a 14YOF (patient #251, protocol 90NO247), 114 pounds (5'4" in height) with a post-medical history positive for hypothyroid, Rx with synthroid for 8 years. She developed a generalized body rash (moderate in severity) on day 28 of sertraline treatment (100mg/day). Rash treated with diphenhydramine and hydrocortisone cream. Rash diminished in severity two days after discontinuation.

8.6.8.4 Zimelidine Syndrome

This hypersensitivity reaction resembling influenza was mentioned in the original adult OCD NDA review at which time it was noted that there were no reports of such a hypersensitivity like reaction.

In the safety update (adult and pediatric) there was no evidence of a clustering of those events which characterized the influenza-like events associated with zimelidine use.

8.6.8.5 Platelet Function

There were no additional reports of purpura in the adult placebo-controlled studies submitted to the safety update. Therefore the incidence of purpura in the adult OCD placebo-controlled studies is 1% (5/533) and 0% for placebo.

In the pediatric/adolescent placebo-controlled study (#498) there were 2 reports (2%) in the sertraline and one report (1%) in the placebo-treated groups. There were no dropouts due to purpura.

There were no reports of bleeding or ecchymoses in either the adult or pediatric/adolescent database.

8.6.8.6 Extrapyramidal Side Effects

The incidence of rigors in the adult OCD safety database was 1% (4/533) for sertraline-treated patients and 0% in the placebo-treated patients. There were no differences when the long-term data (1-52 weeks) from protocol 371/372 was pooled with the other studies. One sertraline-treated patient (0.2%) dropped out due to rigors. The patient #32 (study 88N0173), protocol 371/372 was a 48YOM who withdrew after 5 days of sertraline due to anxiety, faintness, diarrhea, headache and rigors of one day duration. The dose at time of withdrawal was 100mg.

Additionally one sertraline-treated 50YOF patient (#10-study 88N0172) from protocol 371/372 dropped out because of akathisia and insomnia. The experiences occurred after 96 days of sertraline exposure at 100mg/day.

One 70YOM patient #20 (study 88N0179, protocol 371/372) dropped out after 232 days of sertraline exposure at a dose of 200mg/day because of mandibular dystonia in addition to mouth chewing and moderate agitation. All resolved 18 days after discontinuation.

There were no reports of extrapyramidal type reactions in the pediatric/adolescent protocol.
The issue of extrapyramidal reactions associated with SSRIs including sertraline, has been addressed by the Agency.

8.6.7.8 Sexual Dysfunction

The incidence of ejaculation failure, impotence and changes in libido in adult OCD placebo-controlled studies is displayed in the following Safety Update table. The data are similar to the original OCD NDA data.

Incidence of Adverse Experiences Associated with Sexual Dysfunction in Adult OCD Placebo-Controlled Studies - Safety Update*

	(Percent of Patients)	
Adverse Experience	**Sertraline N=533**	**Placebo N=373**
Ejaculation Failure+	9%	1%
Impotence+	3%	1%
Libido Change	11%	2%

* Pooled studies 237/248, 371/372, 546, 336
There were no differences when long-term data (1-52 weeks) from protocol 371/372 were pooled.
+ Ejaculation delay based on male patients only: sertraline = 17% (N=296)
and placebo = 2% (N=219)
+ Impotence - % based on male patients only: sertraline = 5% (N=296)
and placebo = 1% (N=219).

The majority of sertraline-treated patients considered ejaculatory failure and impotence as mild to moderate with respect to level of intensity. No placebo-treated patient considered these dysfunctions as severe in the level of intensity.

Of the 60 sertraline-treated patients who noted a change in libido, only 6 considered the experience as severe. None of the 9 placebo-treated patients considered the experience as severe.

From the original OCD NDA submission, the incidence of ejaculation failure showed a statistically significant dose-related increase.

The table which follows displays the incidence of patients who discontinued due to sexual dysfunction.

Incidence of Adverse Experience Associated with Sexual Dysfunction and Discontinuation in Adult OCD Placebo-Controlled Studies - Safety Update

	(Percent of Patients)	
Adverse Experience	**Sertraline (N=533)**	**Placebo (N=373)**
Ejaculation Failure	1%	0%
Libido Change	1%	0.3%

Each tabulated regardless of gender.

No pediatric/adolescent patients complained of sexual dysfunction.

8.7 Summary of Other Serious Events Considered Unlikely to be Drug-Related

The search strategy described in section 8.4 (Safety Findings Discovered With Other Specific Search Strategies) identified a total of 57 patients in the adult OCD safety update pooled database with serious adverse events. Among the 57 patients, 30 were in the sertraline group, 11 in the placebo, 8 in comparator gorup and 8 were on blinded therapy. In the pediatric/adolescent pooled database, a total of 16 patients (all sertraline-treated) with serious adverse events were identified. Events considered by the undersigned reviewer to be unrelated to sertraline treatment, comparator drug and placebo are listed in appendix 8.7.

8.8 Drug Interactions

8.8.1 Drug-Demographic Interactions

Analysis for age, gender and race effects on adverse event incidence were conducted for the adult OCD database, and are found in Appendix 8.8.1.

Age

A greater proportion of discontinuations due to adverse experiences occurred in the elderly: 18% (3/17) vs 10% (50/516) in those <65 years of age. Of possible concern, may be adverse experiences such as dizziness (and therefore resultant unsteady gait). The incidence was 29% (5/17) vs 16% (84/546) in sertraline-treated patients for >=65 and <65 years of age, respectively. In the placebo group the incidence was 9% for the patient <65 years of age and 7% for >=65 years of age.

However, the sample of sertraline and placebo-treated elderly-treated patients is too small to enable conclusions regarding the safety of sertraline in this population.

Gender

A greater proportion of sertraline-treated females (12% 29/237) discontinued treatment because of adverse experiences compared to males (8% 24/296). There was no difference between the placebo-treated groups (4% vs 4%). Overall, female and male paitents had a similar adverse

experience profile, with the exception of ejaculation failure and impotence.

Race

The limited size in the non-Caucasian race categories does not permit comparisons of adverse experience incidence rates between the sub-groups.

8.8.2 Drug-Disease Interactions

Drug-Disease interactions were not specifically compared in either the original OCD NDA or the safety update. Post-studies and current labeling indicate that sertraline clearance is reduced in patients with hepatic impairment.

8.8.3 Drug-Drug Interactions

There were no formal drug-drug interaction studies specifically addressed in either the original OCD NDA or the safety update.

Drug-drug interaction studies are discussed in the present labeling for sertraline in the treatment of depression.

9.0 Labeling Review

The draft labeling submitted to NDA 19-839/S-002 on December 7, 1995 by the sponsor, with the safety update is based upon the draft labeling contained in the Division's letter of August 1, 1995.

10.0 Conclusions

The safety profile of sertraline in the safety update compares favorably with the safety profile previously established in the OCD NDA for the daily dose range 50 to 200. The majority of side effects in clinical trials were psychiatric and gastrointestinal in nature, transitory and mild or moderate in severity.

The safety profile of sertraline in pediatric OCD patients was similar to the safety profile in the adult OCD patients with some exceptions. Adverse events associated with discontinuations in the pediatric database were most frequently psychiatric in nature and included agitation, insomnia, concentration impairment and nervousness. In the adult OCD database discontinuations were associated with, for the most part, different psychiatric adverse events than the pediatric patients (insomnia, somnolence and anxiety) and in addition, gastrointestinal side-effects (nausea, diarrhea). Dose reduction in these children may have ameliorated some of the behavioral side-effects.

The incidence of suicidality was higher in the pediatric/adolescent database than the adult OCD database and may be a result of psychiatric/neurologic comorbidity (major depression) in the former group. The incidence of seizures was higher in the pediatric/adolescent group than adult OCD group and with the data available does not appear causally related to the sertraline use. The incidences of clinically significant laboratory abnormalities (transaminase, cholesterol, uric acid analytes) were similar in the pediatric/adolescent and adult OCD groups and consistent with the current product labeling.

The overall incidence of clinically significant vital sign measurements was similar in the pediatric and adult databases. Although the incidence of vital sign abnormalities, particularly decreased diastolic blood pressure measurements, was higher in the pediatric database. There were no serious adverse experiences associated with the decreased blood pressure.

11. Recommendations

There are no safety issues that would preclude approval of this safety update.

James F. Knudsen

James F. Knudsen, M.D., Ph.D.

cc: Original NDA 19-839
Div. File HFD-120/
/CSO/PDavid/
/Tlaughren/
/JKnudsen/

4-2-96

I agree that we can now proceed with the approval of this supplement. However, there are some labeling issues that still need resolution. See my memo to the file for more detailed comments.

James P. Laughren, MD
GL, PDP

Appendices

Appendices (continued)

TABLE 1: OCD FINAL SAFETY UPDATE

List of All Controlled Studies: COMPLETED

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 Randomized	Completed Study		M	F			
Protocol 86CE21-237/248											
Chouinard Goodman Greist Jenike Rasmussen White	86-N-0172 86-N-0171 86-N-0173 86-N-0174 86-N-0175 86-N-0176	Capsules 50 mg 50 mg QD to 200 mg QD	Placebo	87	71	37	74	13	Double-Blind Parallel Flexible Dose	8 Weeks (+ 2 weeks down titration)	To compare the efficacy and safety of sertraline and placebo in the treatment of non-depressed outpatients with obsessive compulsive disorder.
Protocol 88CE21-371/372											
Chouinard DuBoff Greist Halaris Kim Koran Liebowitz Lydiard Mendels Rasmussen White	88-N-0170 88-N-0179 88-N-0171 88-N-0180 88-N-0177 88-N-0178 88-N-0175 88-N-0173 88-N-0174 88-N-0176 88-N-0172	Capsules 50 mg 50 mg QD 100 mg QD 200 mg QD	Placebo	325	87	39	191	134	Double-Blind Parallel Fixed Dose	52 Weeks (12 weeks with 40 week continuation)	To compare the efficacy and safety of 50 mg/day, 100 mg/day, and 200 mg/day sertraline with placebo in the treatment of obsessive compulsive disorder.

APPENDIX 5.1.1

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: COMPLETED

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 Randomized	Completed Study		M	F			
Protocol 90CE21-0495											
Cutler	90-N-0119	Capsules	Placebo	260	141	38	125	135	Double-Blind Parallel	18 Weeks	To evaluate the comparative safety and efficacy of sertraline, clomipramine and of placebo in patients with obsessive compulsive disorder.
Dominguez	90-N-0122	25 mg, 50 mg									
Dupont	90-N-0120										
Fawcett	90-N-0121										
Greist*	90-N-0123	50-200 mg	25-250 mg								
Ferguson	92-N-0005	Sertraline	Clomipramine								
Halaris	90-N-0135										
Kiev	90-N-0124										
Kim	90-N-0125										
Koran	90-N-0126										
Linden	90-N-0127										
Lydiard	90-N-0128										
Mendels	90-N-0129										
Nakra	90-N-0130										
Neziroglu	90-N-0131										
Riesenberg	92-N-0032										
Stahl	90-N-0133										
Winstead	90-N-0134										

** 0 patients entered.*

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: COMPLETED

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 Randomized	Completed Study		M	F			
Protocol 90CF21-0498											
Cutler	90-N-0241	Capsules	Placebo	187	156	12	99	88	Double-Blind Parallel	12 Weeks	To evaluate the safety and efficacy of sertraline compared to placebo in children and adolescents with obsessive compulsive disorder.
Biederman	90-N-0242	25 mg, 50 mg									
March	90-N-0243										
Steiner	90-N-0244										
Dominguez	90-N-0245	25-200 mg									
Ferguson	90-N-0246	Sertraline									
Rosenthal	90-N-0247										
Cook	90-N-0033										
Riesenberg	92-N-0008										
Muller	92-N-0047										
Kolewicz*	92-N-0049										
Wagner	92-N-0052										
Sallee	92-N-0054										

* 0 patients entered.

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: COMPLETED

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 Randomized	Completed Study		M	F			
Protocol 91CE21-0546											
Apter Asnis Bystritsky Carlton* Curtis Ferguson Kronig Landbloom Munjack Riesenberg Roy-Byrne	91-N-0046 91-N-0056 91-N-0047 91-N-0048 91-N-0049 91-N-0050 91-N-0051 91-N-0052 91-N-0053 91-N-0054 91-N-0055	Tablets 50 mg 50-200 mg Sertraline	Placebo	167	117	37	92	75	Double-Blind Parallel Flexible Dose	12 Weeks	To determine the safety and efficacy of sertraline compared to placebo in the treatment of outpatients with obsessive compulsive disorder.

** 0 patients entered.*

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: COMPLETED

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 Randomized	Completed Study		M	F			
Protocol STL-NY-91-007											
Moffaert	001	Capsules 50 mg	Capsules 50 mg	168	110	40	62	106	Double-Blind Parallel Dose Titration	18 Weeks (16 weeks + 2 weeks down titration)	To evaluate the safety and efficacy of sertraline in comparison to clomipramine in outpatients with obsessive compulsive disorder.
Ansart	002										
Bisserbe	003										
Danan	004	50-200 mg Sertraline	50-200 mg Clomipramine								
Faure	005										
Flament	006										
Guilbert	007										
Hantouche	008										
Goubey	009										
Lenouene	010										
Durand	011										
Mondragon	012										
Deroche	015										
Leclercq	016										
Blanwblomme	017										
Denis	018										
Singer	019										
Vallee	023										
Menyard	024										

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: COMPLETED

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 Randomized	Completed Study		M	F			
Protocol 050-336											
Mullin	015	Capsules 50 mg	Placebo	152	110	40	69	83	Double-Blind Parallel	12 Weeks	To compare the safety and efficacy of sertraline and placebo in patients with obsessive compulsive disorder.
Montgomery	178										
Casey	179										
Drummond	180										
Dinan	181	50-200 mg Sertraline									
Carney	182										
O'Sullivan	183										
Judd	186										
Bowman	187										
Ghadiali	188										
Master	189										
Edwards	190										
Ahmad	191										
Matthew	192										
Rao	193										
Salen	194										
Plowman	195										
Goodhead	196										
Caplan	197										
Nugent	198										
Morgan	199										
Clare	200										
Hajioff	201										
Mehta	202										
McGuffin	203										

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: COMPLETED

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 Randomized	Completed Study		M	F			
Protocol 050-336 *(continued)*		–	–	–	–	–	–	–	–	–	–
Connolly	204										
Habib	205										
Khan	206										
Chattree	207										
Jilani	208										
Lodge	209										
Quraishy	210										
Paykel	211										
Szulecka	212										
Bennie	213										
McGuffin	214										
Langmuir	215										
Majid	216										
Olive	217										
Edwards	218										
Salva	219										
Mousawi	220										
Lynch	221										
Kelly	222										
Jauhar	223										
Freeman	224										
Ghosh	225										
Shrestha	226										

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: ONGOING

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 Randomized	Completed Study		M	F			
Protocol R-0234											
Hoehn-Saric	91-S-0720	Capsules	Capsules	148	95	38	n/a	n/a	Comparative Dose Titration	12 Weeks (+1 week down titration)	To compare the safety and efficacy of sertraline and desipramine in outpatients with concurrent DSM III-R major depression and obsessive compulsive disorder.
Lydiard	91-S-0721	50 mg	50 mg, 100 mg								
Winstead	91-S-0722										
Ninan	91-S-0723	Sertraline	Desipramine								
McElroy	91-S-0724	50-200 mg	50-300 mg								
Stahl	91-S-0725										
Black	91-S-0726										
Foa	91-S-0727										
Robinson	91-S-0728										
Liebowitz	91-S-0729										
McDougle	91-S-0730										
Zajecka	91-S-0731										
Mavissakalian	91-S-0732										
Greist	91-S-0733										
Rasmussen	91-S-0734										
Jenike*	91-S-0735										
Londborg*	91-S-0737										

** 0 patients entered.*

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

***List of All Controlled Studies:* ONGOING**

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 Randomized	Completed Study		M	F			
Protocol R-0241											
Hoehn-Saric	92-S-0720	Capsules	Capsules	31	15	35	n/a	n/a	Double-Blind	20 Weeks	To compare the
Lydiard	92-S-0721	50 mg	50 mg, 100 mg							(+ 1 week	long-term safety and
McDougle	92-S-0730									down titration)	efficacy of sertraline
Rasmussen	92-S-0734										and desipramine in
Stahl	92-S-0725	50-200 mg	50-300 mg								patients with
Winstead	92-S-0722	Sertraline	Desipramine								concurrent major
Zajecka	92-S-0731										depression and
Black	92-S-0726										obsessive compulsive
Foa	92-S-0727										disorder who have
Greist	92-S-0733										completed and
Liebowitz	92-S-0729										shown a clinical
McElroy	92-S-0724										response in a 12-
Ninan	92-S-0723										week double-blind
Robinson	92-S-0728										trial (Protocol 234).

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: ONGOING

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 Randomized	Completed Study		M	F			
Protocol 93CE21-0615											
Apter	93-N-7101	Tablets 50 mg	Placebo (Weeks 53 - 80)	606	0	n/a	n/a	n/a	Single-Blind (Weeks 1 - 52)	80 Weeks	To evaluate the long-term safety of sertraline in patients with obsessive compulsive disorder and its long-term efficacy compared to placebo in the prevention of relapse.
Davidson	93-N-7102										
Nakra	93-N-7103										
Dupont	93-N-7104										
Goodman	93-N-7105	50-200 mg Sertraline							Double-Blind Parallel (Weeks 53-80)		
Kiev	93-N-7106										
Ferguson	93-N-7107										
Koran	93-N-7108										
Bielski	93-N-7109										
Londborg	93-N-7110										
Lydiard	93-N-7111										
Munjack	93-N-7112										
Ninan	93-N-7113										
Pigott	93-N-7114										
Rasmussen	93-N-7115										
Robinson	93-N-7116										
Simon	93-N-7117										
Smith	93-N-7118										
Stahl	93-N-7119										
Zajecka	93-N-7120										
Houck	93-N-7121										

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: ONGOING

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 Randomized	Completed Study		M	F			
Protocol 93CE21-0643											
Apter	94-N-7101	Tablets	none	54	33	n/a	n/a	n/a	Study Continuation Double-Blind Parallel	12 Weeks	To evaluate the comparative efficacy and safety of 250-400 mg sertraline relative to a 200 mg fixed dose in outpatients with obsessive compulsive disorder who have failed to respond to 10 weeks of single-blind treatment with sertraline titrated to a dose of 200 mg.
Davidson	94-N-7102	50 mg, 100 mg									
Nakra	94-N-7103										
Dupont	94-N-7104	200 mg									
Goodman	94-N-7105	Sertraline									
Kiev	94-N-7106	v									
Ferguson	94-N-7107	250-400 mg									
Koran	94-N-7108	Sertraline									
Bielski	94-N-7109										
Londborg	94-N-7110										
Lydiard	94-N-7111										
Munjack	94-N-7112										
Ninan	94-N-7113										
Doyle	94-N-7114										
Rasmussen	94-N-7115										
Robinson	94-N-7116										
Simon	94-N-7117										
Smith	94-N-7118										
Stahl	94-N-7119										
Zajecka	94-N-7120										
Houck	94-N-7121										

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: ONGOING

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 Randomized	Completed Study		M	F			
Protocol STL-NY-94-002 Lambert Ansseau, E.A. Lopez Cottraux Cassano Griez Silverstone Naukkarinene Berk Freeman	n/a n/a n/a n/a n/a n/a n/a n/a n/a n/a	Capsules 50 mg 50-200 mg Sertraline	Capsules 20 mg 20-80 mg Fluoxetine	134	38	n/a	n/a	n/a	Double-Blind, Parallel Comparative Dose Titration	16 Weeks	To evaluate the efficacy, safety and toleration of sertraline in comparison to fluoxetine in outpatients with obsessive compulsive disorder, with or without concurrent depression.

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Controlled Studies: ONGOING

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 Randomized	Completed Study		M	F			
Protocol STL-BRA-94-004 Gentil Versiani	 n/a n/a	 Capsules 50 mg 50-200 mg Sertraline	 Placebo	 58	 48	 n/a	 n/a	 n/a	 Double-Blind Parallel Dose Titration Outpatients	 14 Weeks	 To evaluate the efficacy, safety and tolerability of sertraline compared to placebo in outpatients with obsessive compulsive disorder.
Protocol STL-JP-94-601 Dr. Kamijima, K.	 n/a	 Tablets 25 mg, 50 mg Sertraline 25 mg - 100 mg 50 mg - 200 mg	 Placebo	 70	 14	 n/a	 n/a	 n/a	 Double-Blind Parallel Flexible Dose	 8 Weeks	 To evaluate the efficacy, safety and clinical usefulness of sertraline in the treatment of patients with obsessive compulsive disorder and to determine the optimal dosage.

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Uncontrolled Studies: COMPLETED

Principal Investigators	Study No.	Sertraline Formulation and Dosage	Number of Patients		Mean Age (yrs)	Sex		Study Design	Duration of Study	Study Objective
			Total Enrolled	Completed Study		M	F			
Protocol 90CE21-0494										
Chouinard*	90-N-0176	Capsules	59	44	40	35	24	Open Label	52 Weeks	To evaluate the long-term safety of 50-200 mg/day of sertraline in the treatment of outpatients with long-term obsessive compulsive disorder who have responded to 52 weeks of double-blind treatment in Protocol 371/372.
DuBoff	90-N-0179	50 mg								
Greist	90-N-0171									
Halaris	90-N-0180	50 mg QD								
Kim	90-N-0177									
Koran	90-N-0178	to								
Liebowitz	90-N-0175									
Lydiard	90-N-0173	200 mg QD								
Mendels	90-N-0174									
Rasmussen	90-N-0176									
Mallya	90-N-0172									

** 0 patients entered.*

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Uncontrolled Studies: COMPLETED

Principal Investigators	Study No.	Sertraline Formulation and Dosage	Number of Patients		Mean Age (yrs)	Sex		Study Design	Duration of Study	Study Objective
			Total Enrolled	Completed Study		M	F			
Protocol 90CK21-0525										
Biederman*	90-N-0222	Capsules	61	53	13	33	28	Open Label Parallel Dose Escalation	51 Days	Tolerance and pharmacokinetics of two sertraline dosing regimens after single and multiple dosing in children and adolescents with OCD or depression.
Johnston	91-N-0068	25 mg, 50 mg								
Sood*	91-N-0135									
Livingston	92-N-0060									
Sallee	92-N-0058	Sertraline								
Blumer	92-N-0062	25-200 mg								
Ferguson	92-N-0068	50-200 mg								
Kirkwood*	91-N-0135									
Rosenthal	92-N-0070									

** 0 patients entered.*

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Uncontrolled Studies: ONGOING

Principal Investigators	Study No.	Sertraline Formulation and Dosage	Number of Patients		Mean Age (yrs)	Sex		Study Design	Duration of Study	Study Objective
			Total Enrolled	Completed Study		M	F			
Protocol 90CE21-0533										
Wong	90-N-0226	Capsules 50 mg 50-200 mg Sertraline	8	6	34	1	7	Open Label	12 weeks	To study the effects of sertraline on serotonin re aptor occupancy as determined by positron emission tomography (PET) of patients with obsessive compulsive disorder.
Protocol 91CE21-0536										
Cutler Biederman March Steiner Dominguez Ferguson Rosenthal Cook Riesenberg Sallee Wagner Kopiewicz* Muller	91-N-0241 91-N-0242 91-N-0243 91-N-0244 91-N-0245 91-N-0246 91-N-0247 91-N-0037 92-N-0026 92-N-0055 92-N-0053 92-N-0048 92-N-0049	Capsules 25 mg, 50 mg 25-200 mg Sertraline (Ages 6 to 12) 50-200 mg Sertraline (Ages 13 to 17)	133	64	13	n/a	n/a	Open Label Flexible Dose	52 Weeks	To evaluate the long-term safety and efficacy of sertraline in children and adolescents with obsessive compulsive disorder who have completed a 12-week double-blind study (Protocol 498).

*0 patients entered.

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Uncontrolled Studies: ONGOING

Principal Investigators	Study No.	Sertraline Formulation and Dosage	Number of Patients		Mean Age (yrs)	Sex		Study Design	Duration of Study	Study Objective
			Total Enrolled	Completed Study		M	F			
Protocol 91CK21-0550										
Biederman*	90-N-0222	Capsules 25 mg, 50 mg	43	22	13	25	16	Open Label Flexible Dose	24 Weeks	To evaluate the long-term safety and efficacy of sertraline in children and adolescents with obsessive compulsive disorder or depression who have completed the 51-day multiple dose pharmacokinetic (PK) study of sertraline (Protocol 525).
Saline	92-N-0059									
Johnston	91-N-0069									
Sood*	91-N-0165	50-200 mg Sertraline								
Livingston*	92-N-0061									
Blumer*	92-N-0063									
Kirkwood*	92-N-0065									
Ferguson	92-N-0069									
Rosenthal	92-N-0071									
Protocol STL-AR-94-002										
Cia	n/a	Capsules 50 mg	49	10	n/a	n/a	n/a	Open Label Dose Titration	16 Weeks	To evaluate the efficacy, safety and toleration of sertraline in outpatients with obsessive compulsive disorder.
		50-200 mg Sertraline								

** 0 patients entered.*

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Uncontrolled Studies: ONGOING

Principal Investigators	Study No.	Sertraline Formulation and Dosage	Number of Patients		Mean Age (yrs)	Sex		Study Design	Duration of Study	Study Objective
			Total Enrolled	Completed Study		M	F			
Protocol STL-EG-95-003 Ahmed Okashr	n/a n/a	Tablets 50 mg 50-200 mg Sertraline	27	12	n/a	n/a	n/a	Open Label	12 Weeks	To evaluate the efficacy, safety and toleration of sertraline in outpatients with obsessive compulsive disorder, with or without concurrent depression.
Protocol STL-JP-92-004 Kamishima, K.	n/a	Tablets 25 mg, 50 mg 25-200 mg Sertraline	36	19	n/a	n/a	n/a	Open Label	8 Weeks	To investigate the safety and efficacy of sertraline in patients with obsessive compulsive disorder.

TABLE 1: OCD FINAL SAFETY UPDATE *(continued)*

List of All Uncontrolled Studies: ONGOING

Principal Investigators	Study No.	Sertraline Formulation and Dosage	Number of Patients		Mean Age (yrs)	Sex		Study Design	Duration of Study	Study Objective
			Total Enrolled	Completed Study		M	F			
Protocol STI-JP-94-602 Dr. Kamijima, K.	n/a	Tablets 25 mg, 50 mg 25-200 mg Sertraline	10	1	n/a	n/a	n/a	Open Label Flexible Dose	26 Weeks	To evaluate the long-term safety and efficacy of sertraline in obsessive compulsive disorder.
Protocol STL-COL-95-001 Leon Sanchez	n/a n/a	Tablets 50 mg 50 mg Sertraline	2	0	n/a	n/a	n/a	Open-Label Fixed Dose	26 Weeks	To evaluate the efficacy and safety of a fixed dose of sertraline in the management of outpatients with obsessive compulsive disorder, with or without concurrent depression.

PEDIATRIC OCD STUDIES

Protocol #	Design	Sertraline Formulation & Dosage	Control Agent	Number of Sertraline-Treated Patients	Mean Age (years)	Duration of Study	Study Objective
90CE21-0498	double-blind parallel multicenter randomized flexible dose	25 and 50 mg capsules --- 6-12 y.o.: 25 - 200 mg QD 13-17 y.o.: 50 -200 mg QD	Placebo	92 6-12 y.o.: 53 13-17 y.o.: 39	12	12 weeks	Compare the safety & efficacy of sertraline & placebo in pediatric patients with OCD
90CK21-0525	open-label parallel multicenter single dose followed by multiple dose PK study	25 and 50 mg capsules --- 50 mg 25 - 200 mg QD or 50 -200 mg QD	None	61 6-12 y.o.: 29 13-17 y.o.: 32	13	51 days	Determine the PK and tolerance of single & multiple dose sertraline administration in pediatric patients with OCD or depression
91CE21-0536	open-label multicenter flexible dose (extension to Protocol 498)	25 and 50 mg capsules 6-12 y.o.: 25 - 200 mg QD 13-17 y.o.: 50 -200 mg QD	None	133	---	52 weeks	Determine the long-term safety & efficacy of sertraline in pediatric patients with OCD
91CK21-0550	open-label multicenter flexible-dose (extension to Protocol 525)	50 mg capsules 50-200 mg QD	None	43	---	24 weeks	Determine the long-term safety & efficacy of sertraline in pediatric patients with OCD or depression

APPENDIX 5.1.3

. OCD FINAL SAFETY UPDATE: ALL STUDIES

PROTOCOLS 237/248,371/372,494,546,495,336,887

NUMBERS (%) OF ALL SUBJECTS RECEIVING SERTRALINE ACCORDING TO MEAN DAILY DOSE AND DURATION OF THERAPY.

	SERTRALINE MEAN DAILY DOSE (MG/DAY)[1]				
DURATION OF THERAPY (DAYS)	1-49	50-99	100-149	150-200	TOTAL
1	0	1	0	0	1
2-10	2	24	0	0	26
11-31	0	38	11	1	42
32-90	0	98	87	72	249
91-180	2	97	36	79	214
181-364	0	15	0	10	25
>=365	0	19	23	28	70
TOTAL	4	276	157	190	627
%	0.6%	44.0%	25.0%	30.3%	100%
TOTAL EXPOSURE (SUBJECTS-YEARS)					255.70

1, SUBJECTS ARE COUNTED ONCE ONLY, I.E. EACH PATIENT CONTRIBUTES TO ONLY ONE CELL

APPENDIX 5.1.3.1

. OCD FINAL SAFETY UPDATE: ALL PEDIATRIC/ADOLESCENT STUDIES

PROTOCOLS 490,525

NUMBERS (%) OF ALL SUBJECTS RECEIVING SERTRALINE ACCORDING TO MEAN DAILY DOSE AND DURATION OF THERAPY.

	SERTRALINE MEAN DAILY DOSE (MG/DAY)[1]				
DURATION OF THERAPY (DAYS)	1-49	50-99	100-149	150-200	TOTAL
1	0	3	0	0	3
2-10	3	0	0	0	3
11-31	0	7	3	0	10
32-90	2	7	70	53	132
91-180	0	0	2	3	5
TOTAL	5	17	75	56	153
%	3.3%	11.1%	49.0%	36.6%	100%
TOTAL EXPOSURE (SUBJECTS-YEARS)					24.37

[1]PATIENTS ARE COUNTED ONCE ONLY, I.E. EACH PATIENT CONTRIBUTES TO ONLY ONE CELL

APPENDIX 8.4.2

Summary of Pediatric Patients with Reports of Suicidality

Protocol 525:

Patient #225 (study #92-N-0058) was a 14-year-old male with major depression who had been receiving 200 mg/day sertraline. He was hospitalized overnight on the 35th day of the study for a moderate suicide gesture in which he ingested 400 mg of sertraline, 10 mg of lorazepam and an unknown amount of organophosphate insecticide. The suicidal ideation was thought to have resolved within one day and the patient was not discontinued. The following day the patient ingested 8 grams of chloral hydrate. Nevertheless, the investigator continued the patient in the sertraline study and the patient completed the study five days later, apparently without further sequelae. The patient's history was significant for a diagnosis of conduct disorder, which was ongoing at study start. Methylphenidate 40 mg qd was discontinued immediately prior to entering the study.

Patient #4 (study #92-N-0062) was an 8-year old male with major depression who had been receiving 200 mg/day sertraline. He was hospitalized on the 36th day of the study for a suicide gesture, and dropped from the study. The patient mutilated himself by cutting his feet with a razor blade and tying a tie around his neck. There was no previous history of self-mutilation or suicidality, although family history was significant for affective disorder (mother, maternal uncle) and suicide (maternal uncle).

Patient #218 (study #92-N-0070) was a 13 year old male with major depression who was receiving 150 mg/day sertraline. He was discontinued and hospitalized after 22 days of irritability, agitation, and suicidal ideation. The patient had a prior history of several hospitalizations for depression, child abuse, attention deficit, hyperactivity disorder, and other episodes of agitation and irritability. He was treated with psychotherapy (individual and family) and desipramine. The adverse events resolved within three weeks after discontinuation.

Protocol 550:

Patient #229 (study #92-N-0059) was a 17-year old female who was

APPENDIX 8.4.2

(Continued)

hospitalized for suicidal ideation related to her major depression. The patient had a pre-study history of two suicide attempts. She had been on sertraline 50 mg/day for 8 days prior to the onset of the event. The patient was discontinued from the study five days after the event. Further outcome information is not available.

Protocol 536:

Patient #217 (study #91-N-0242) was a 17-year old female with severe OCD. She was admitted to the hospital for two nights after taking an intentional overdose of antihistamines. The patient had been in the study for 136 days, and at a dose of 200 mg/day sertraline for 55 days. Life stressors may have precipitated the event. The patient was discontinued from the study, but continued taking Zoloft 200 mg/day. Three weeks later, the patient ingested an unknown type of pill in another suicide gesture, and was readmitted to the hospital. No further outcome information is available.

Patient #221 (study #91-N-0242), a 15-year old female with co-morbid post-traumatic stress disorder, was hospitalized for suicidal ideation brought on by memories of rape. The patient had been on sertraline 200 mg/day for 74 days prior to the event. The patient continued in the study without interruption of study medication.

OCD Safety Update
Events Occurring at a Rate of 1% or Greater in Sertraline-Treated Adult Patients*

	SERTRALINE (N=533)	PLACEBO (N=373)
ADVERSE EXPERIENCE	**%**	**%**
PSYCHIATRIC DISORDERS		
INSOMNIA	28	12
SOMNOLENCE	15	8
LIBIDO DECREASED	11	2
ANXIETY	8	6
NERVOUSNESS	7	6
AGITATION	6	3
DEPRESSION	3	3
DEPERSONALIZATION	3	1
PARANOIA	2	1
AMNESIA	2	2
CONCENTRATION IMPAIRED	2	2
YAWNING	2	0.3
APATHY	1	0
THINKING ABNORMAL	1	0
TEETH-GRINDING	1	0
GASTRO-INTESTINAL DISORDERS		
NAUSEA	30	11
DIARRHEA	24	10
DYSPEPSIA	10	4
CONSTIPATION	6	4
ABDOMINAL PAIN	5	5
FLATULENCE	4	1
VOMITING	3	1
TOOTH CARIES AGGRAVATED	1	1

APPENDIX 8.5.1.1

APPENDIX 8.5.1.1 (Continued)		
	SERTRALINE (N=533)	PLACEBO (N=373)
ADVERSE EXPERIENCES	**%**	**%**
CENTR. & PERIPH. NERV. SYST. DISORDERS		
HEADACHE	30	24
DIZZINESS	17	9
TREMOR	8	1
PARESTHESIA	3	1
HYPERTONIA	2	1
URINARY RETENTION	2	0.3
TWITCHING	1	1
CONVULSIONS	1	0
HYPERKINESIA	1	0
AUTONOMIC NERVOUS SYSTEM DISORDERS		
MOUTH DRY	14	9
ANOREXIA	11	2
EJACULATION FAILURE	9	1
APPETITE INCREASED	3	1
IMPOTENCE	3	1
FLUSHING	1	0.3

APPENDIX B.C.1 1 (Continued)		
	SERTRALINE (N=533)	PLACEBO (N=373)
ADVERSE EXPERIENCES	**%**	**%**
BODY AS A WHOLE-GENERAL DISORDERS		
FATIGUE	14	10
CHEST PAIN	3	2
PAIN	3	1
HOT FLUSHES	2	1
BACK PAIN	2	1
FEVER	2	1
ASTHENIA	1	1
MALAISE	1	1
RIGORS	1	1
SKIN AND APPENDAGES DISORDERS		
SWEATING INCREASED	6	1
RASH	2	1
PRURITUS	1	1
ACNE	1	1
URTICARIA	1	0
SKIN DRY	1	0
RESPIRATORY SYSTEM DISORDERS		
RESPIRATORY DISORDER	4	4
PHARYNGITIS	4	2
DYSPNEA	2	1
COUGHING	1	1
RHINITIS	1	1
EPISTAXIS	1	0.3

APPENDIX 8.5.1.1 (Continued)		
	SERTRALINE (N=533)	PLACEBO (N=373)
ADVERSE EXPERIENCES	**%**	**%**
METABOLIC AND NUTRITIONAL DISORDERS		
WEIGHT INCREASE	3	0.3
WEIGHT DECREASE	1	1.0
THIRST	1	0
EDEMA PERIORBITAL	1	0
VISION DISORDERS		
VISION ABNORMAL	4	2
CONJUNCTIVITIS	1	0
EYE ABNORMALITY	1	1
MUSCULO-SKELETAL SYSTEM DISORDERS		
MYALGIA	2	4
ARTHRALGIA	2	1
ARTHROSIS	1	0.3
HEART RATE AND RHYTHM DISORDERS		
PALPITATION	3	2
URINARY SYSTEM DISORDERS		
POLYURIA	2	1.0
SPECIAL SENSES OTHER, DISORDERS		
TASTE PERVERSION	3	1.0

APPENDIX 8.5.1.1 (Continued)		
	SERTRALINE (N=533)	**PLACEBO (N=373)**
ADVERSE EXPERIENCES	**%**	**%**
REPRODUCTIVE DISORDERS, FEMALE		
DYSMENORRHEA	1	1
HEARING AND VESTIBULAR DISORDERS		
EARACHE	1	1
TINNITUS	1	1
VASCULAR (EXTRA CARDIAC) DISORDERS		
PURPURA	1	0

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT AND THE MOST SEVERE OCCURRENCE IS SHOWN.

*Pooled date from placebo-controlled studies 237/248, 371/372 (weeks 1-12), 546, 495 and 336.
Adapted from Sponsor's Table 27, Vol. 2, P. 295.

APPENDIX 8.5.1.2
Events Occurring at a Rate of 1% or Greater in Sertraline-Treated Pediatric/Adolescent Patients*

	SERTRALINE (N=92)	PLACEBO (N=95)
ADVERSE EXPERIENCE	**%**	**%**
PSYCHIATRIC DISORDERS		
INSOMNIA	37	13
NERVOUSNESS	15	6
SOMNOLENCE	13	11
AGITATION	13	2
AGGRESSIVE REACTION	4	3
PARANOIA	3	3
CONCENTRATION IMPAIRED	3	0
MANIC REACTION	3	0
ANXIETY	2	1
EMOTIONAL LABILITY	2	1
THINKING ABNORMAL	1	0
SOMNAMBULISM	1	1
DEPRESSION	1	0
HALLUCINATIONS	1	0

APPENDIX 8.5.1.2 (Continued)		
	SERTRALINE (N=92)	PLACEBO (N=95)
ADVERSE EXPERIENCE	**%**	**%**
CENTR. & PERIPH. NERV. SYST. DISORDERS		
HEADACHE	36	24
DIZZINESS	12	6
HYPERKINESIA	9	4
TREMOR	7	0
URINARY INCONTINENCE	3	2
TWITCHING	2	0
PARESTHESIA	1	1
CONVULSIONS	1	0
DYSPHONIA	1	0
GASTRO-INTESTINAL DISORDERS		
NAUSEA	17	7
DIARRHEA	13	12
ABDOMINAL PAIN	12	17
DYSPEPSIA	7	7
VOMITING	5	5
FLATULENCE	4	4
AUTONOMIC NERVOUS SYSTEM DISORDERS		
ANOREXIA	13	5
APPETITE INCREASED	3	4
MOUTH DRY	1	3
SYNCOPE	1	1
FLUSHING	1	0

APPENDIX 8.5.1.2 (Continued)		
	SERTRALINE (N=92)	PLACEBO (N=95)
ADVERSE EXPERIENCE	**%**	**%**
BODY AS A WHOLE - GENERAL DISORDERS		
FATIGUE	8	2
CHEST PAIN	4	1
FEVER	3	1
MALAISE	2	0
BACK PAIN	1	0
SKIN AND APPENDAGES DISORDERS		
RASH	5	1
SKIN DISORDER	2	0
RASH ERYTHEMATOUS	1	2
SWEATING INCREASED	1	2
PRURITUS	1	1
ACNE	1	0
ALOPECIA	1	0
RASH PUSTULAR	1	0
SKIN ODOR ABNORMAL	1	0
URTICARIA	1	0

APPENDIX 8.5.1.2 (Continued)		
	SERTRALINE (N=92)	PLACEBO (N=95)
ADVERSE EXPERIENCE	**%**	**%**
RESPIRATORY SYSTEM DISORDERS		
PHARYNGITIS	3	5
RESPIRATORY DISORDER	2	4
EPISTAXIS	2	0
COUGHING	1	4
HYPERVENTILATING	1	0
RHINITIS	1	0
BRONCHOSPASM	0	2
METABOLIC AND NUTRITIONAL DISORDERS		
WEIGHT DECREASE	3	0
WEIGHT INCREASE	1	3
REPRODUCTIVE DISORDERS, FEMALE		
DYSMENORRHEA	1	1
BREAST PAIN FEMALE	1	0
MENSTRUAL DISORDER	1	0
VISION DISORDERS		
EYE ABNORMALITY	1	0
MYDRIASIS	1	0
VISION ABNORMAL	1	0
VASCULAR (EXTRA CARDIAC) DISORDERS		
PURPURA	2	1

APPENDIX 8.5.1.2 (Continued)		
	SERTRALINE (N=92)	PLACEBO (N=95)
ADVERSE EXPERIENCE	**%**	**%**
MUSCULO-SKELETAL SYSTEM DISORDERS		
MYALGIA	1	1
URINARY SYSTEM DISORDERS		
CYSITIS	1	0
HEARING AND VESTIBULAR DISORDERS		
EARACHE	1	0
RESISTANCE MECHANISM DISORDERS		
HERPES SIMPLEX	1	0

EACH ADVERSE EXPERIENCE WAS TABULATED ONCE PER PATIENT REGARDLESS OF THE NUMBER OF TIMES IT WAS REPORTED BY THAT PATIENT, THE MOST SEVERE OCCURRENCE IS SHOWN.

*Data from placebo-controlled study 498 adapted from Sponsor's Table 60, Vol. 2, P. 469.

OCD FINAL SAFETY UPDATE: ALL PLACEBO CONTROLLED STUDIES
PROTOCOLS 237/240,371/372,546,495,536

INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES: SERTRALINE COMPARED WITH PLACEBO

				Sertraline			Placebo		
				ALL PTS	ABN PTS	% PTS	ALL PTS	ABN PTS	% PTS
GROUP	PARAMETER	UNITS	CRITERIA						
HEMATOLOGY									
	WBC (WHITE BLOOD COUNT)	X10E3	<= 2.8	485	2	0.4	355	1	0.3
			>= 16	485	0	0.0	355	0	0.0
	EOSINOPHILS	%	>= 10	486	4	0.8	356	8	2.2
	NEUTROPHILS	%	<= 15	486	1	0.2	355	0	0.0
	RBC (RED BLOOD CELLS)	X10E6	<= 3	485	0	0.0	355	0	0.0
			>= 6	485	7	1.4	355	4	1.1
	PLATELETS	X10E3	<= 75	484	1	0.2	354	1	0.3
			>= 700	484	0	0.0	354	0	0.0
	HGB(HEMOGLOBIN)	G/DL	<= 9.5(F) 11.5(M)	485	0	0.0	355	1	0.3
	HCT(HEMATOCRIT)	%	<= 32(F) 37(M)	485	14	2.9	354	8	2.3
URINE ANALYSIS									
	PROTEIN:URINE	UNITS	>= 2	418	7	1.7	291	3	1.0
	GLUCOSE:URINE	UNITS	>= 2	419	2	0.5	291	1	0.3
	CASTS	UNITS	>= 2	418	5	1.2	291	0	0.0
LIVER FUNCTION TESTS									
	T/PROTEIN	G/DL	<= 4.5	490	0	0.0	355	0	0.0
			>= 9	490	0	0.0	355	0	0.0
	ALBUMIN	G/DL	<= 3.5	490	13	2.7	353	12	3.4
			>= 6.5	490	0	0.0	353	0	0.0
	T/BILIRUBIN	MG/DL	>= 2	489	2	0.4	356	4	1.1
	ALK PHOSPHATASE	U/L	>= 3.0 X ULN	490	0	0.0	353	0	0.0
	SGOT UNITS	U/L	>= 3.0 X ULN	484	3	0.6	352	5	0.9
	SGPT UNITS	U/L	>= 3.0 X ULN	489	6	1.2	353	1	0.3
	LDH	U/L	>= 3.0 X ULN	336	0	0.0	212	0	0.0
RENAL FUNCTION TESTS									
	BUN	MG/DL	>= 30	490	2	0.4	355	1	0.3
	CREATININE	MG/DL	>= 2	489	1	0.2	355	0	0.0
	URIC ACID	MG/DL	>= 8.5(F) 10.5(M)	422	1	0.2	288	2	0.7
OTHER									
	CHOLESTEROL	MG/DL	>= 350	490	13	2.7	352	3	0.9
	TRIGLYCERIDES	MG/DL	>= 340	69	2	2.9	64	3	4.7
	RANDOM GLUCOSE	MG/DL	>= 140	422	19	4.5	289	6	2.1

NO STATISTICALLY SIGNIFICANT DIFFERENCES NOTED, P>0.05 (FISHER'S EXACT TEST).
ONLY TWO PATIENTS IN PROTOCOL 237 HAD GLOBULIN MEASURED (BOTH NORMAL) THIS PARAMETER IS NOT BEING TABULATIED

. OCD FINAL SAFETY UPDATE: PEDIATRIC/ADOLESCENT PLACEBO-CONTROLLED STUDY

PROTOCOL 498
INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES: SERTRALINE COMPARED WITH PLACEBO

LABORATORY PARAMETER	CRITERIA FOR ABNORMALITY		ABNORMALITY	SERTRALINE NUMBER TESTED	SERTRALINE NUMBER AND % ABNORMAL		PLACEBO NUMBER TESTED	PLACEBO NUMBER AND % ABNORMAL	
HEMATOLOGY									
WBC (WHITE BLOOD COUNT)	<= 2.0, >= 16	X10E3/MM3	LOW	92	0	0.0%	92	1	1.1%
			HIGH	92	0	0.0%	92	1	1.1%
EOSINOPHILS	>= 10	%	HIGH	92	8	8.7%	92	9	9.8%
NEUTROPHILS	<= 15	%	LOW	92	1	1.1%	92	0	0.0%
RBC (RED BLOOD CELLS)	<= 3, >= 6	X10E6/MM3	LOW	92	0	0.0%	92	0	0.0%
			HIGH	92	1	1.1%	92	0	0.0%
PLATELETS	<= 75, >= 700	X10E3/MM3	LOW	92	0	0.0%	92	0	0.0%
			HIGH	92	0	0.0%	92	0	0.0%
HGB(HEMOGLOBIN)	<= 9.5(F) 11.5(M)	G/DL	LOW	92	4	4.3%	92	2	2.2%
HCT(HEMATOCRIT)	<= 32(F) 37(M)	%	LOW	92	33	35.9%	92	31	33.7%
URINALYSIS									
PROTEIN:URINE	>= 2	UNITS	HIGH	92	5	5.3%	92	5	5.3%
GLUCOSE:URINE	2	UNITS	HIGH	92	0	0.0%	92	1	1.1%
HYALINE CASTS LPF URINE	> 2	UNITS	HIGH	92	1	1.1%	92	0	0.0%
LIVER FUNCTION TESTS									
T/PROTEIN	<= 4.5, >= 9	G/DL	LOW	92	0	0.0%	92	0	0.0%
			HIGH	92	0	0.0%	92	0	0.0%
ALBUMIN	<= 3.5, >= 6.5	G/DL	LOW	92	2	2.2%	92	1	1.1%
			HIGH	92	0	0.0%	92	0	0.0%
T/BILIRUBIN	>= 2	MG/DL	HIGH	92	0	0.0%	92	0	0.0%
ALK PHOSPHATASE	>= 5.0 X ULN	U/L	HIGH	92	0	0.0%	92	0	0.0%
SGOT UNITS	>= 3.0 X ULN	U/L	HIGH	92	1	1.1%	92	0	0.0%
SGPT UNITS	>= 3.0 X ULN	U/L	HIGH	92	1	1.1%	92	1	1.1%
LDH	>= 3.0 X ULN	U/L	HIGH	92	0	0.0%	92	0	0.0%
RENAL FUNCTION TESTS									
BUN	>= 30	MG/DL	HIGH	92	0	0.0%	92	0	0.0%
CREATININE	>= 2	MG/DL	HIGH	92	0	0.0%	92	0	0.0%
URIC ACID	>= 8.5(F) 10.5(M)	MG/DL	HIGH	92	1	1.1%	92	0	0.0%
OTHER									
CHOLESTEROL	>= 330	MG/DL	HIGH	92	0	0.0%	92	0	0.0%
RANDOM GLUCOSE	>= 140	MG/DL	HIGH	92	6	6.5%	92	5	5.4%

APPENDIX 8.5.2.2

OCD FINAL SAFETY UPDATE: ALL PLACEBO-CONTROLLED STUDIES
PROTOCOLS 237/248,371/372,546,495,336

MEAN BASELINE AND MEAN CHANGE FROM BASELINE IN LABORATORY TEST VALUES

	SERTRALINE				PLACEBO				P-VALUES
LABORATORY TEST	N	MEAN BASELINE	CHANGE FROM BASE MEAN	S.E.	N	MEAN BASELINE	CHANGE FROM BASE MEAN	S.E.	OF GROUP COMPARISONS
HEMATOLOGY									
WBC (WHITE BLOOD COUNT)	485	6.80	0.03	0.07	355	6.85	-0.19	0.08	0.044
EOSINOPHILS	486	.94	6.22	0.06	356	2.21	0.15	0.08	0.471
NEUTROPHILS	486	61.09	0.55	0.35	355	61.26	3.17	2.56	0.312
RBC (RED BLOOD CELLS)	485	4.79	-0.03	0.01	355	4.84	-0.02	0.01	0.689
PLATELETS	484	276.73	-4.22	1.86	354	270.84	-2.21	2.38	0.497
HGB(HEMOGLOBIN)	485	14.44	-0.13	0.04	355	14.52	-0.09	0.04	0.521
HCT(HEMATOCRIT)	485	42.86	-0.44	0.14	354	43.24	-0.21	0.16	0.279
LIVER FUNCTION TESTS									
T/PROTEIN	490	7.14	-0.06	0.02	355	7.17	-0.08	0.02	0.406
ALBUMIN	490	4.57	-0.07	0.01	353	4.36	-0.06	0.01	0.868
T/BILIRUBIN	489	0.56	-0.01	0.01	356	0.54	0.03	0.01	0.007
ALK PHOSPHATASE	490	65.68	3.17	0.55	353	66.57	0.29	0.56	0.000
SGPT UNITS	489	22.20	2.93	0.69	353	23.42	0.36	0.66	0.007
LDH	336	152.86	5.29	1.44	212	151.26	-0.30	1.61	0.098
SGOT UNITS	484	20.64	2.23	0.55	352	21.65	1.56	0.94	0.538
RENAL FUNCTION TESTS									
BUN	490	13.99	0.18	0.16	355	13.68	0.05	0.17	0.589
CREATININE	489	1.02	-0.01	0.01	355	1.03	-0.00	0.01	0.282
URIC ACID	422	4.94	-0.25	0.04	288	4.98	0.09	0.04	0.000
OTHER									
CHOLESTEROL	490	204.59	7.69	1.40	352	198.33	-3.10	1.28	0.000
TRIGLYCERIDES	60	136.65	-11.6	11.02	64	129.32	16.05	19.43	0.217
RANDOM GLUCOSE	422	91.78	0.93	0.86	289	91.46	1.34	1.12	0.775

CHANGE OF FINAL VISIT FROM BASELINE WAS CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

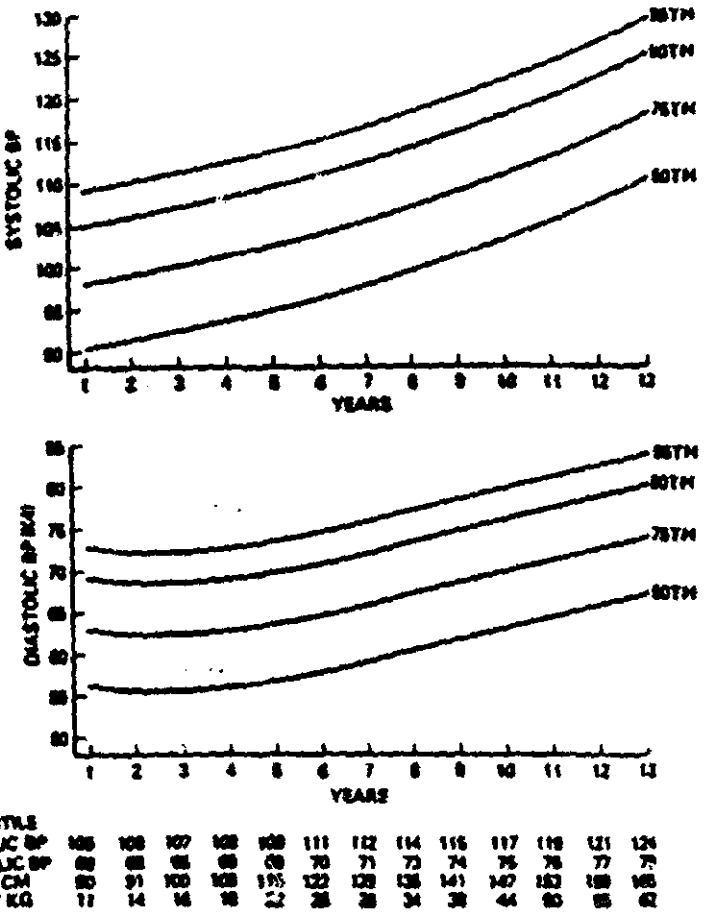
OCD FINAL SAFETY UPDATE: PEDIATRIC/ADOLESCENT PLACEBO-CONTROLLED STUDY
STUDY 498

MEAN BASELINE AND MEAN CHANGE FROM BASELINE IN LABORATORY TEST VALUES: SERTRALINE COMPARED WITH PLACEBO PATIENTS.

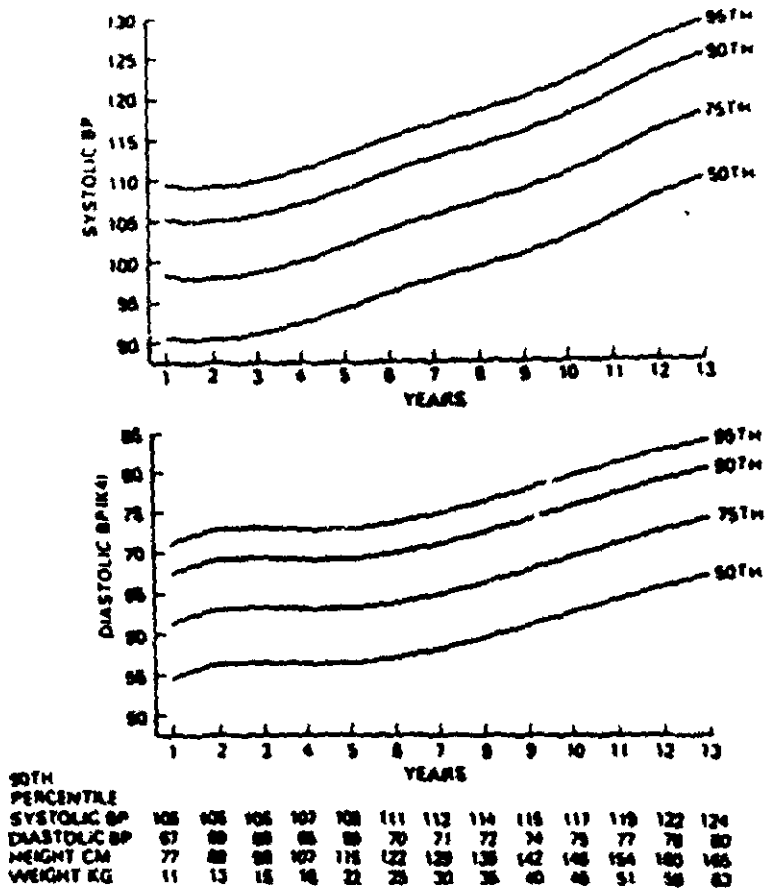
	SERTRALINE				PLACEBO				
LABORATORY TEST	N[1]	BASE MEAN	CHANGE FROM BASE MEAN	S.D.	N[1]	BASE MEAN	CHANGE FROM BASE MEAN	S.D.	P-VALUE[2]
HEMATOLOGY									
WBC (WHITE BLOOD COUNT)	90	7.21	-0.06	1.95	91	6.90	-0.15	1.64	0.8138
EOSINOPHILS	90	2.60	0.56	1.74	91	3.02	-0.14	1.66	0.0035
NEUTROPHILS	90	55.20	1.54	9.73	91	53.27	1.54	9.15	0.8615
RBC (RED BLOOD CELLS)	90	4.71	-0.14	0.27	91	4.72	-0.15	0.25	0.7476
PLATELETS	90	307.93	-5.77	54.95	91	302.91	-5.25	40.57	0.9085
HGB(HEMOGLOBIN)	90	13.68	-0.39	0.80	91	13.56	-0.35	0.71	0.6984
HCT(HEMATOCRIT)	90	40.04	-1.38	3.40	90	39.81	-1.52	2.74	0.9072
URINALYSIS									
PROTEIN:URINE	91	0.05	0.05	0.40	91	0.10	-0.01	0.35	0.2378
GLUCOSE:URINE	91	0.00	0.01	0.10	91	0.01	0.00	0.15	0.5702
LIVER FUNCTION TESTS									
T/PROTEIN	92	7.22	-0.12	0.41	91	7.22	-0.22	0.42	0.0897
ALBUMIN	91	4.34	-0.08	0.33	91	4.35	-0.17	0.25	0.0924
T/BILIRUBIN	91	0.45	-0.04	0.18	91	0.47	0.00	0.18	0.0967
ALK PHOSPHATASE	92	205.97	-10.03	54.35	91	198.04	-5.45	32.58	0.4723
SGOT UNITS	92	23.73	0.92	4.42	91	22.08	-0.62	4.52	0.0273
SGPT UNITS	92	17.36	1.77	8.69	91	14.64	0.95	11.57	0.2528
LDH	91	198.99	-2.31	32.16	90	188.96	-6.09	22.28	0.2229
RENAL FUNCTION TESTS									
BUN	92	12.18	0.27	3.51	91	11.14	0.54	3.28	0.7344
CREATININE	92	0.85	0.00	0.10	91	0.83	-0.01	0.09	0.1558
URIC ACID	92	4.37	-0.67	0.80	91	4.22	0.09	0.72	0.0000
OTHER									
CHOLESTEROL	92	164.24	6.53	25.06	91	162.79	-6.67	17.83	0.0001
RANDOM GLUCOSE	91	86.98	0.22	10.81	91	87.97	-0.15	16.15	0.7805

[1] TOTAL NUMBER OF PATIENTS FOR WHOM EACH LABORATORY TEST'S ASSESSMENT WAS AVAILABLE AT BASELINE AND AT LEAST ONE FOLLOW UP TIME.
[2] COMPARISON OF CHANGE FROM BASELINE USING WILCOXON RANK SUM TEST.
NOTE: CHANGE FROM BASELINE TO FINAL VALUE AND % CHANGE FROM BASELINE VALUE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

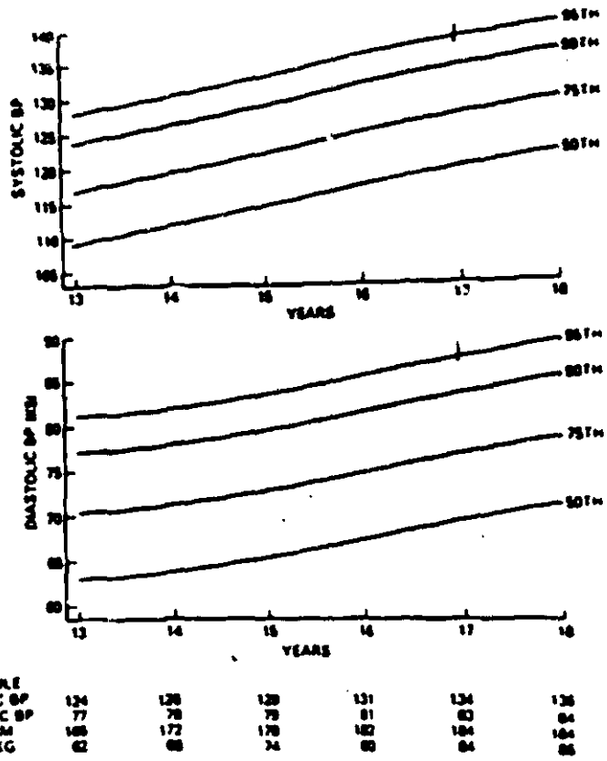
APPENDIX 8.5.3.1



... Age-specific percentiles for BP measurements in boys—1 to 13 yr of age: Korotkoff phase IV (K4) used for diastolic BP. (From National Heart, Lung, and Blood Institute, Bethesda, MD: Report of the second task force on blood pressure control in children—1987. Reproduced by permission of Pediatrics. Vol 79, p 1. Copyright © 1987.)

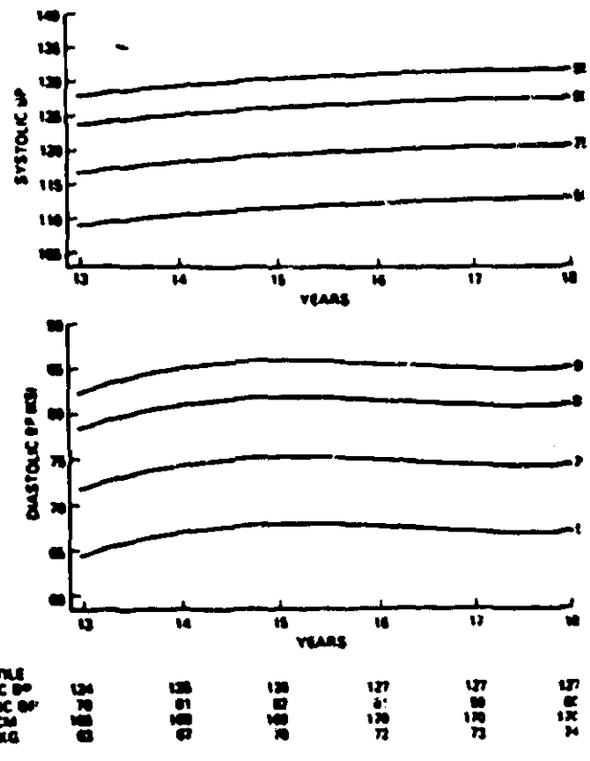


... Age-specific percentiles of BP measurements in girls—1 to 13 yr of age: Korotkoff phase IV (K4) used for diastolic BP. (From National Heart, Lung, and Blood Institute, Bethesda, MD: Report of the second task force on blood pressure control in children—1987. Reproduced by permission of Pediatrics. Vol 79, p 1. Copyright © 1987.)



50TH PERCENTILE						
SYSTOLIC BP	124	126	128	131	134	136
DIASTOLIC BP	77	78	79	81	83	84
HEIGHT CM	165	172	178	182	184	184
WEIGHT KG	62	66	74	80	84	86

. . . . Age-specific percentiles of BP measurements in boys—13 to 18 yr of age; Korotkoff phase V (K5) used for diastolic BP. (From National Heart, Lung, and Blood Institute, Bethesda, MD: Report of the second task force on blood pressure control in children—1987. Reproduced by permission of Pediatrics. Vol 79, p 1. Copyright © 1987.)



50TH PERCENTILE						
SYSTOLIC BP	124	125	126	127	127	127
DIASTOLIC BP	70	71	72	73	73	73
HEIGHT CM	165	168	169	170	170	170
WEIGHT KG	63	67	70	72	73	74

. . . . Age-specific percentiles of BP measurements in girls—13 to 18 yr of age; Korotkoff phase V (K5) used for diastolic BP. (From National Heart, Lung, and Blood Institute, Bethesda, MD: Report of the second task force on blood pressure control in children—1987. Reproduced by permission of Pediatrics. Vol 79, p 1. Copyright © 1987.)

APPENDIX 8.5.3.1
(Continued)

Pulse Rates at Rest

Age	Lower Limits of Normal		Average		Upper Limits of Normal	
Newborn	70/min		125/min		190/min	
1–11 mo	80		120		160	
2 yr	80		110		130	
4 yr	80		100		120	
6 yr	7[illegible]		100		115	
8 yr			90		110	
10 yr	70		90		110	
	Girls	*Boys*	*Girls*	*Boys*	*Girls*	*Boys*
12 yr	70	65	90	85	110	105
14 yr	65	60	85	80	105	100
16 yr	60	55	80	75	100	95
18 yr	55	50	75	70	95	90

Behrman, RE. (ed) Nelsons Textbook of Pediatrics, p1127, 1996

OCD FINAL SAFETY UPDATE: ALL PLACEBO-CONTROLLED STUDIES

PROTOCOLS 237/248, 371/372, 546, 495, 336

INCIDENCE OF CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS IN SERTRALINE COMPARED WITH PLACEBO PATIENTS.

Parameter	Criterion Value	Change Relative to Baseline	Number Tested (1)		Number and % of Patients with Specified Change (2)			
			Sertraline	Placebo	Sertraline		Placebo	
STANDING HEART RATE	120 bpm	increase >=15	517	354	8	1.6%	2	0.6%
	50 bpm	decrease >=15	517	354	3	0.6%	2	0.6%
STANDING SYSTOLIC BP	180 mmHg	increase >=20	518	357	0	0.0%	1	0.2%
	90 mmHg	decrease >=20	518	357	13	2.5%	14	3.9%
STANDING DIASTOLIC BP	105 mmHg	increase >=15	518	357	10	1.9%	3	0.8%
	50 mmHg	decrease >=15	518	357	5	0.9%	3	0.8%
SUPINE HEART RATE	120 bpm	increase >=15	520	360	1	0.1%	0	0.0%
	50 bpm	decrease >=15	520	360	6	1.1%	3	0.8%
SUPINE SYSTOLIC BP	180 mmHg	increase >=20	520	360	1	0.1%	1	0.2%
	90 mmHg	decrease >=20	520	360	12	2.3%	13	3.6%
SUPINE DIASTOLIC BP	105 mmHg	increase >=15	520	360	2	0.3%	1	0.2%
	50 mmHg	decrease >=15	520	360	5	0.9%	6	1.6%

1 - Total number of patients for whom each vital signs assessment was available at baseline and at least one follow up time

2 - Number and percentage of patients for whom one or more follow up value meets the criterion for being "Clinically Significant".

Note: In order to be identified as being potentially clinically significantly abnormal, an ondrug value would need to meet the criterion value, and also represent a change of at least the magnitude noted in the change column.

OCD FINAL SAFETY UPDATE: PEDIATRIC/ADOLESCENT PLACEBO-CONTROLLED STUDY

PROTOCOL 498

INCIDENCE OF CLINICALLY SIGNIFICANT CHANGES IN VITAL SIGNS IN SERTRALINE COMPARED WITH PLACEBO PATIENTS.

Parameter	Criterion Value	Change Relative to Baseline	Number Tested (1)		Number and % of Patients with Specified Change (2)			
			Sertraline	Placebo	Sertraline		Placebo	
STANDING HEART RATE	120 bpm	increase >=15	92	94	1	1.0%	5	5.1%
	50 bpm	decrease >=15	92	94	1	1.0%	0	0.0%
STANDING SYSTOLIC BP	160 mmHg	increase >=20	92	94	0	0.0%	0	0.0%
	90 mmHg	decrease >=20	92	94	3	3.2%	6	6.3%
STANDING DIASTOLIC BP	105 mmHg	increase >=15	92	94	1	1.0%	0	0.0%
	50 mmHg	decrease >=15	92	94	6	6.5%	3	3.1%
SUPINE HEART RATE	120 bpm	increase >=15	92	94	2	2.1%	1	1.0%
	50 bpm	decrease >=15	92	94	1	1.0%	1	1.0%
SUPINE SYSTOLIC BP	160 mmHg	increase >=20	92	94	0	0.0%	0	0.0%
	90 mmHg	decrease >=20	92	94	7	7.6%	6	6.3%
SUPINE DIASTOLIC BP	105 mmHg	increase >=15	92	94	0	0.0%	0	0.0%
	50 mmHg	decrease >=15	92	94	16	17.3%	12	12.7%

1 - Total number of patients for whom each vital signs assessment was available at baseline and at least one follow up time

2 - Number and percentage of patients for whom one or more follow up value meets the criterion for being "Clinically Significant".

Note: In order to be identified as being potentially clinically significantly abnormal, an ondrug value would need to meet the criterion value, and also represent a change of at least the magnitude noted in the change column.

OCD FINAL SAFETY UPDATE: ALL PLACEBO-CONTROLLED STUDIES

PROTOCOLS 237/248, 371/372, 546, 495, 336

MEAN BASELINE AND MEAN CHANGE FROM BASELINE IN VITAL SIGNS AND BODY WEIGHT IN SERTRALINE COMPARED WITH PLACEBO PATIENTS.

	SERTRALINE							PLACEBO							P-VALUE	P-VALUE
		MEAN	---CHANGE FROM BASE ---				MEAN %		MEAN	---CHANGE FROM BASE ---				MEAN %	OF MEAN	OF MEAN
VITAL SIGN	N	BASELINE	MEAN	S.D.	MIN	MAX	CHANGE	N	BASELINE	MEAN	S.D.	MIN	MAX	CHANGE	BASELINE	CHANGES
SUPINE SYSTOLIC BP mmHg	520	119.89	-.802	12.25	-46	74	-.099	360	119.39	-.483	11.29	-34	47	-.048	0.6126	0.6955
SUPINE DIASTOLIC BP mmHg	520	75.31	.4154	9.56	-30	50	1.715	360	75.03	0.875	8.87	-20	26	2.097	0.6828	0.4704
SUPINE HEART RATE bpm	520	73.52	-1.07	9.82	-36	36	-.583	360	72.87	0.175	9.45	-34	30	1.137	0.3716	0.0616
STANDING SYSTOLIC BP mmHg	518	120.09	-1.41	12.84	-60	61	-.649	357	118.54	.2269	10.58	-26	30	.4705	0.1077	0.0472
STANDING DIASTOLIC BP mmHg	518	78.57	-.784	9.77	-30	34	-.182	357	77.63	.4762	8.65	-38	32	1.29	0.1531	0.0499
STANDING HEART RATE bpm	517	78.79	-1.37	11.25	-34	44	-.756	354	77.86	.8023	11.45	-40	40	2.251	0.2402	0.0857
BODY WEIGHT lb.	523	151.61	.3884	7.25	-24	54	.3458	368	144.19	.0174	4.42	-21	19	.0115	0.0312	0.3822

CHANGE AT FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

APPENDIX 8.5.3.4

OCD FINAL SAFETY UPDATE: PEDIATRIC/ADOLESCENT PLACEBO-CONTROLLED STUDY

PROTOCOL 498

MEAN BASELINE AND MEAN CHANGE FROM BASELINE IN VITAL SIGNS AND BODY WEIGHT IN SERTRALINE COMPARED WITH PLACEBO PATIENTS.

	SERTRALINE						PLACEBO						P-VALUE	P-VALUE
		MEAN	---CHANGE FROM BASE---			MEAN %		MEAN	---CHANGE FROM BASE---			MEAN %	OF MEAN	OF MEAN
VITAL SIGN	N	BASELINE	MEAN	S.D.	MIN	MAX	CHANGE	N	BASELINE	MEAN	S.D.	MIN	MAX	CHANGE	BASELINE	CHANGES
SUPINE SYSTOLIC BP mmHg	92	108.15	-.837	9.63	-34	30	-.391	94	106.78	0.766	9.82	-28	24	1.191	0.3925	0.2626
SUPINE DIASTOLIC BP mmHg	92	64.75	-1.27	12.78	-40	42	-.028	94	63.70	.0638	9.35	-22	26	1.741	0.4929	0.4164
SUPINE HEART RATE bpm	92	77.08	-.228	11.82	-30	24	1.397	94	77.07	1.064	10.82	-26	32	2.22	0.9993	0.4377
STANDING SYSTOLIC BP mmHg	92	108.11	-1.34	10.05	-24	20	-.731	94	107.34	-.234	10.79	-26	26	.2479	0.6395	0.4718
STANDING DIASTOLIC BP mmHg	92	67.32	1.087	12.28	-31	32	3.704	94	67.62	-.596	9.87	-27	22	.5199	0.8378	0.3048
STANDING HEART RATE bpm	92	84.96	-1.35	12.95	-36	24	.0878	94	83.73	2.447	14.33	-34	58	4.546	0.5823	0.0599
BODY WEIGHT lb.	92	105.44	.5815	4.15	-11	12.5	.9263	94	105.15	2.524	3.37	-6	13	2.605	0.9598	0.0006

CHANGE OF FINAL VISIT FROM BASELINE AND % CHANGE FROM BASELINE WERE CALCULATED FOR EACH PATIENT AND THE MEANS OF THESE CHANGES DETERMINED.

TABLE 49: OCD FINAL SAFETY UPDATE. ALL PLACEBO-CONTROLLED STUDIES.
PROTOCOLS 237/248, 371/372, 546, 495

INCIDENCE OF CHANGES FROM BASELINE IN ECG.

BASELINE/VISIT	NUMBER OF PATIENTS (%)		P-VALUE[1]
	SERTRALINE	PLACEBO	SERTRALINE VS PLACEBO
	(N=445)	(N=288)	
NORMAL /NORMAL	259 (58.2%)	178 (61.8%)	
NORMAL /ABNORMAL	70 (15.7%)	39 (13.5%)	0.382
ABNORMAL/NORMAL	23 (5.2%)	13 (4.5%)	
ABNORMAL/ABNORMAL	93 (20.9%)	58 (20.1%)	

NOTE: INCIDENCES FOR ALL VISITS WERE SUMMARIZED.
PATIENT REQUIRED A BASELINE ECG AND AT LEAST ONE ADDITIONAL ECG IN ORDER TO BE INCLUDED IN THE SUMMARY.
ECG DATA NOT AVAILABLE FOR STUDY 336.

[1] FISHER'S EXACT TEST (TWO-TAILED) WAS USED TO COMPARE THE PROPORTION OF PATIENTS WHO HAD AT LEAST ONE ABNORMAL ECG DURING THE TRIAL, GIVEN THAT EACH BASELINE ECG WAS NORMAL.

PROGRAM: SOCDEKG IN C.MM
DATE : 26OCT95 TIME:14:50

TABLE 74: OCD FINAL SAFETY UPDATE: PEDIATRIC/ADOLESCENT PLACEBO-CONTROLLED STUDY.
PROTOCOL 498

INCIDENCE OF CHANGES FROM BASELINE IN ECG.

	NUMBER OF PATIENTS (%)			
BASELINE/VISIT	SERTRALINE		PLACEBO	
	(N=91)		(N=95)	
NORMAL /NORMAL	61	(67.0%)	67	(70.5%)
NORMAL /ABNORMAL	15	(16.5%)	13	(13.7%)
ABNORMAL/NORMAL	5	(5.5%)	7	(7.4%)
ABNORMAL/ABNORMAL	10	(11.0%)	8	(8.4%)

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

THE CONDITIONAL TEST COMPARING THE PROPORTION OF PATIENTS WHO HAD A NORMAL BASELINE ECG AND AT LEAST ONE ABNORMAL FOLLOW-UP ECG RESULTED IN A P-VALUE OF 0.677 (USING FISHER'S EXACT TEST).

PROGRAM: S498EKG IN CJML
DATE : 13JUN95 TIME:15:28

Appendix 8.7
(Safety Update)
Summary of Serious Adverse Events Occurring in Sertraline Treated Patients and Considered Unlikely to be Drug Related

Treatment: Sertraline

Patient Identifier (PID)	Serious Adverse Experience	Day of Onset (From first dose of study medication)	Dose at Onset	Comment
#13(88N0177)	Fracture	68	100	Fell and fractured right ankle, remained in study
#091 (STL-NY-91007-OU)	Carpal Tunnel	95	200	Continued Sertraline
#9006 (93N7105-615)	S. Ideation	88	200	Suicidal ideation 15d after D/C sertraline (D/C due to depression
#9003 (93N7106-615)	Breast Cancer	15	50	D/C
#9013 (93N7111-615)	Cholecystitis	79	200	Pre-existing cholelithiasis Continued in study
#9007 (93N7119-615)	Fracture	112	50	Lost to follow-up
#9005 (93N7113-615)	Auditory Hallucinations Muscle twitch	80	200	D/C
#9012 (93N7107-615)	Fracture	264	200	Fracture to cheek bone after Roller blading, remained in study
#9015 (93N7113-615)	Renal Calculus	10	50	Procedures, patient remained in study
#9005 (93N7110-615)	Fibroids	330	200	Remained in study
#9045 (93N71009-615)	Ulcers	27	50	Endos copic procedure Remained in study
#9023 (93N7121-615)	Renal Colic	106	200	Remained in study
#9040 (93N7105-615)	Laminx	196	200	Remained in study
#9033 (93N7102-615)	Rectocele	28	50	D/C due to protocol violation
#9035 (93N7102-615)	S. Ideation	264	200	D/C

#253(STLNY 94-002)	OCD	76	200	Pt d/c study on his own due to worsening OCD
#5201-2 (STL JP 92004)	Panic	3	25	O.D on unspecified drug D/C
#12(88N0171-371/372)	GI Bleed	79	50	No active bleeding site found D/C
#28 (88N0171-371/372)	Right Calf Pain	31	100	Thrombophlebitis ruled out D/C
#38(88N0179-371/372)	Pregnancy	362	100	D/C
#9(88N0174-371/372)	S. Ideation	86	200	Secondary to depression Resolved after 1 day
#33(88N1079-371/372)	Seizure	146	200	H/O seizures not hospitalized D/C
#L-14 (90N0171-494)	O.D.	415	-	Took 1000 mg of sertraline H/O suicidal gesture
#5(90N0171-494)	Hemorrhoidx	215	50	D/C
#118(007)	O.D.	68	-	Took 2250 mg of sertraline D/C
#0135(336)	S. Ideation	22	50	H/O mood swings Rx with carbamazepine
#524(92-N0054-498)	Attention Deficit disorder	32	200	Exacerbation of ADD D/C
#14(92N0058-525)	Oppositional Behavior	35	200	Pre-existing Dx
#21(91N0242-536)	Cervical	206	200	Wrestling injury D/C
#511(92N0053-536)	Mono Nucleosis	43	75	D/C
#211(92N0071-550)	Motor vehicle Accident	N/A	200	Continuod

Appendix 8.7 (Continued)
(Safety Update)
Summary of Serious Adverse Events Occurring in Comparator Treated Patients and Considered Unlikely to be Drug Related

Treatment: Comparator

Patient Identifier	Serious Adverse Experience	Day of Onset	Dose at Onset	Comment
#268(90N0131)	Appendicitis	94	250	Hospitalized for Appendectomy Remained in study
#360(STL-NY-91007-19)	Lingual Tumor	15	N/A	Glossectomy, remained in study
#027(91-50723-234)	Seizure	61	N/A	No neurological Sequelae D/C
#306(STL-NY-002)	Depression Anxiety	8	20 mg/d	D/C
#105(007-5)	Suicide Attempt	36	50	Took 750 mg of Clomipramine No H/O suicidality
#112(007-5)	Suicide Attempt	101	50	Family H/O depression D/C
#984(007-9)	Suicide Attempt	46	150	H/O suicide attempts X2
#084(007-4)	Vomiting Anxiety	1	50	Appendicular Peritonitis D/C

Appendix 8.7
(Safety Update)
Summary of Serious Adverse Events Occurring in Placebo Treated Patients and Considered Unlikely to be Drug Related

Treatment: Placebo

Patient Identifier	Serious Adverse Experience	Day of Onset	Dose at Onset	Comments
#8(88N0172)	Hernia	46	0	Remained in study
#24(88N0176)	OCD	13	0	Insufficient clinical Response D/C study
#41(88N0179)	Abd pain Low HCT	260	0	No pathology found Continued study
#190 (91N0055)	Right ductal Cancer	28	0	Lumpectomy Outcome not known
#0024 (336-200)	OCD	17	0	Insufficient clinical Response D/C
#0172 (336-216)	OCD	13	0	Insufficient clinical Response D/C
#0199 (336-186)	OCD	78	0	Insufficient clinical Response D/C
#0018 (336-198)	Anxiety	64	0	D/C
#0152 (336-216)	OCD	21	0	D/C
#0007 (336-183)	OCD	41	0	D/C
#2(88N0171-371/372)	Insomnia Moderate Stimulation	51	0	History of insomnia
#131(336)	Insomnia Agitation Anxiety	3	0	D/C

David

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION

NDA #	19-839, Supplement # 02
Sponsor:	Pfizer
Clock Date:	May 15, 1992

DRUG NAME

Generic Name:	Sertraline Hydrochloride
Trade Name:	Zoloft®

DRUG CHARACTERIZATION

Pharmacological Category:	Selective serotonin reuptake inhibitor
Proposed Indication:	Obsessive Compulsive Disorder
Dosage Forms, Strengths & Routes of Administration:	Marketed 50 and 100 mg Tablets

REVIEWER INFORMATION

Clinical Reviewer:	James F. Knudsen, Ph.D., M.D.
Review Completion Date:	March, 1995

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1.0 Material Utilized in Review

1.1 Material from NDA

The following is a list of specific items reviewed.

VOLUME	DATESUBMITTED	MATERIAL
21.1	May 14, 1992	Application summary
21.3-5	May 14, 1992	Human PK and individual reports
21.6-10	May 14, 1992	Clinical data
21.11	May 14, 1992	Integrated summary of safety information
31.1	December 21, 1993	Report for protocol 371/372 cumulative data of patients in continuation phase
32.1	January 13, 1994	Final report for protocol 546
32.2-3	January 13, 1994	Patient data listings of protocol 546
1	May 13, 1992	Periodic adverse experience report (12/91-3/92)
1	July 31, 1992	Periodic adverse experience report (3/92-6/92)
25.1	May 6, 1993	Periodic adverse experience report (10/92-12/92)
36.1	April 26, 1994	Periodic adverse experience report (7/93-9/93)
38.1	June 14, 1994	Periodic adverse experience report (10/93-12/93)
39.1	June 23, 1994	Annual report 1/93-12/93
41.1-5	July 26, 1994	Report for protocol 495

(CONTINUED)		
VOLUME	DATE SUBMITTED	MATERIAL
N/A	July 15, 1994	Response to a request of June 8, 1994 - completed tables of safety data.
N/A	August 17, 1994	Response to request for a table of adverse events occurring at 1% with the 3 placebo-controlled trials, 237/248, 371/372 and 546.
N/A	September 28, 1994	Response to a request for literature review for safety information related to sertraline.
N/A	October 19, 1994	Response to a request of a list of serious adverse events occurring in completed and ongoing OCD studies.
N/A	October 25, 1994	Response to a request for a list of countries where Zoloft is approved & for additional safety information.

(CONTINUED		
VOLUME	DATE SUBMITTED	ERIAL
N/A	October 27, 1994	Response to a request for tables illustrating patient distribution by duration and mean daily dose; numbers of patients completed or discontinued.
N/A	November 23, 1994	Response to a request for a summary of four cases (previously submitted Oct. 19. 1994) of seizure with an estimated denominator of this event, and a list of countries where Zoloft is approved.
N/A	February 14, 1995	Response to a request for a chronological list of submissions and an updated annotated package insert.

1.2 Related Reviews

NDA #19-839 (Sertraline for depression)

1.3 Other Resources

The Zoloft® Summary Basis of Approval (12/4/91), Supervisory overview for Zoloft® (August 9, 1991) the Division file, the Periodic Adverse Experience Reports for Zoloft® (for depression) and Annual Reports for Zoloft® for depression were consulted for this review.

2.0 Background

2.1 Indication

Obsessive compulsive disorder (OCD), until recently, was considered rare and difficult to treat. The National Epidemiology Catchment Area (ECA) survey estimated the prevalence of OCD to be as high as 2.5%. It is now generally agreed that OCD is a common psychiatric disorder, with a prevalence exceeding that of schizophrenia (DeVeaugh - Geiss,J. Annu Rev. Med. 44:53,1993).

A number of biological markers point to a defect in serotonergic neurotransmission in patients with OCD. This seems to be supported by the responsiveness, in some cases, of OCD symptoms to modulation of serotonin transmission, more specifically, by the serotonin reuptake inhibitors.

Currently, clomipramine, fluoxetine and fluvoxamine are approved for the treatment of OCD in the United States.

Sertraline (Zoloft®) is marketed in the United States as an antidepressant. Sertraline, a selective serotonin reuptake inhibitor, is structurally dissimilar from the tricyclics, tetracyclics or other currently marketed drugs with antiobsessive/antidepressant properties and hence, devoid of some of the adverse effects commonly reported to occur in patients treated with these drugs. Sertraline does not produce orthostatic decreases in blood pressure, tachycardia, or changes in the electrocardiogram. The incidence of anticholinergic side effects is not significantly different from placebo.

2.2 Related INDs and NDAs

IND
IND
IND

2.3 Administrative History

The NDA for sertraline tablets in the treatment of depression was approved December 30, 1991. The OCD supplement was submitted by Pfizer on May 14, 1992. Data from two placebo-controlled clinical studies (protocols 237/248 and 371/372) were submitted. Data from a third study (protocol 546) were submitted January 13, 1994.

The Agency requested submission to the NDA of a recently completed study, protocol 495 entitled "Double-Blind Comparison of Sertraline, Clomipramine and Placebo in OCD".

At a meeting with the firm on March 1, 1990 general agreement was reached that the depression datasbase could be used to support safety for an OCD NDA submission. At that time it was indicated that as far as patient numbers were concerned, two well controlled studies would suffice (about 300-400 patients).

2.4 Directions for Use

Under INDICATIONS AND USAGE of the proposed labeling, the sponsor notes that the efficacy of sertraline in the treatment of OCD has been established in 8-12 week double-controlled trials. However, OCD patients have been treated in a double-blind fashion for an additional 40 weeks and have had a higher rate of sustained response than placebo. There are no new precautions specific for OCD therapy. With respect to dosage, the proposed labeling advises a maximum dose not greater than 200 mg/day for any indication.The starting dose is 50 mg once daily. Effectiveness of sertraline for any indication has been demonstrated in the dose range of 50-200 mg/day.

2.5 Foreign Marketing

As of October 25, 1994, sertraline has not been approved for use in OCD in foreign countries. Sertraline has been approved for use in major depressive disorders in several countries.

3.0 Chemistry

This is a marketed product. There are no chemistry manufacturing and control issues to be addressed for this NDA supplement.

4.0 Animal Pharmacology

Sertraline inhibits presynaptic reuptake of serotonin without detectable antagonism of norepinephrine or dopamine uptake. The drug has little affinity for cholinergic, histaminergic, GABA or adrenergic receptors. Animal toxicologic studies have demonstrated anorexia, CNS stimulation, convulsions (at higher doses), increased locomotor activity, and some mild liver toxicity. No teratogenicity was attributed

to sertraline in animal studies. The carcinogenicity studies did not reveal any definitive signals of oncogenic potential.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

The primary clinical development program for sertraline in the treatment of OCD consisted of 3 placebo-controlled clinical studies performed under 3 protocols and one active control comparison study with clomipramine and placebo. The study designs are summarized in the following table.

Placebo and Active-Controlled Studies

Protocol 371/372 and 494	DB, parallel group, 11 center, 12 week fixed-dose trial, sertraline v. placebo, outpatients, OCD (n=approx. 80 in each of four treatment groups); sertraline 50mg, 100mg, 200mg qd and placebo responders could continue double-blind therapy for an additional 40 weeks; Protocol 494, open, 11 center, 52 week, flexible-dose trial, responders (N=59) who completed protocol 371/372; sertraline 50-200 mg qd.
Protocol 237/248	DB, parallel group, 6 center, 8 week (plus 2 weeks down titration), flexible dose trial, sertraline v. placebo, outpatients, OCD (n=43 or 44 patients in each of two treatment groups); sertraline 50mg-200 mg qd.
Protocol 546	DB, parallel group, 10 center, 12 week, flexible dose trial, sertraline v. placebo, outpatients, OCD (n=approx. 80 in each of two treatment groups); sertraline 50mg-200 mg qd.
Protocol 495	DB, parallel group, 17 center, 16 week, flexible-dose trial, sertraline v. clomipramine (25mg-250mg) v placebo, outpatients, OCD (N=approx. 86 in each treatment group); sertraline 50mg-200mg qd.

Table 5.1.1 provides a summary enumeration of subject/patients participating in the completed trials in the development OCD program.

Table 5.1.1
Summary of All Completed OCD Studies in the Integrated Database (cut-off date: 6/30/94)

	ENUMERATION BY TREATMENT GROUP	
POOLS BY STUDY DESIGN	**SERTRALINE**	**PLACEBO**
PLACEBO CONTROLLED		
FIXED DOSE *	241	84
FLEXIBLE DOSE+	129	125
UNCONTROLLED**	6 (27)	
TOTAL	376	209

* Protocol 371/372
\+ Protocols 237/248 and 546
** Protocol 494 (twenty-seven of 33 patients previously treated with sertraline in Protocol 371/372).

Through June 30, 1994, the total exposure to sertraline in OCD trials (pooled data from protocols 237/248, 371/372 and 546) was 140 patient years; exposure to placebo was 54 patient years.

Appendix Table 5.1.1 lists all OCD studies reported by the sponsor with a brief description of each. Data from protocols 371/372, 237/248, 546 and 494 are included in this safety review. The remaining studies have either not been completed or data were not available at the time my review was implemented. Appendix Table 5.1.2 provides a list of the approximate numbers of sertraline OCD patients who have completed or discontinued treatment in ongoing or not-yet-submitted completed studies as of 10/10/94. Worldwide, approximately 577 sertraline-treated patients have been enrolled in OCD studies.

The yet to be submitted studies were also screened for serious events (cut-off date, October 7, 1994).

5.1.2 Demographics

Table 5.1.2 presents the demographic profile for patients participating in the OCD placebo-controlled studies.

TABLE 5.1.2
DEMOGRAPHIC PROFILE FOR OCD STUDIES*

	Sertraline N=370	Placebo N=209
AGE		
Mean (yrs)	38.6	37.5
Range (yrs)	18-77	18-88
Groups (%)		
<40 (yrs)	217 (59)	135 (65)
40-64 (yrs)	142 (38)	67 (32)
≥65 (yrs)	11 (3)	7 (3)
Not Reported	0 (0)	0 (0)
SEX (%)		
Female	146 (39)	76 (36)
Male	224 (61)	133 (64)
Not Reported	0 (0)	0 (0)
RACE (%)		
White	362 (98)	201(96)
Non-white	8 (2)	8 (4)
Not Reported	0 (0)	0 (0)

* Pooled data from Protocols 237/248, 371/372, and 546. Patients (N=6) enrolled in the uncontrolled extension study were not incorporated into this dataset. Therefore, the total sertraline exposure is 370 rather than 376.

As seen from Table 5.1.2, the OCD patients were more often males, primarily Caucasian and less often elderly.

5.1.3 Extent of Exposure (dose/duration)

Table 5.1.3 displays the mean daily dose and duration of sertraline treatment for patients in the OCD placebo-controlled clinical trials. In terms of the proposed daily dose range of 50-200mg, some 74% of the patients in the pooled data set received daily doses above 50mg/day. Slightly more than half of the patients received sertraline for at least one month, and approximately one quarter received the drug for more than 6 months.

Table 5.1.3
Number (Percent) of All Patients Receiving Sertraline According to Mean Daily Dose and Duration of Therapy (N=369)

	Dose Range (mg)					
Duration (days)	1-50	51-100	101-150	151-200	Total	(%)
1	1	--	--	--	1	(0.3)
2-10	5	7	--	--	12	(3.3)
11-31	11	9	6	1	27	(7.0)
32-90	17	27	56	55	155	(42.0)
91-180	28	32	2	23	85	(23.0)
181-364	14	14	--	18	46	(12.4)
>=365	16	9	--	18	43	(12.0)
Total	92	98	64	115	369	(100)
(%)	(26)	(26)	(17)	(31)	(100)	

Pooled data from Protocols 237/248, 371/372 and 546. Sertraline dose and duration of therapy for one patient, 91N0051, #111 (Protocol 546) unknown, hence, total number of patients is 369 rather than 370.

5.2 Secondary Sources

5.2.1 Non-IND Studies

Protocols 336, 601, 004 and 602 (studies conducted in New Zealand and Japan) were non-IND studies. These protocols are summarized in Appendix 5.1.1.

5.2.2 Post-Marketing Experience

Sertraline has been approved for the treatment of depression in the United States since December 30, 1991. The drug is marketed in 43 other countries for the treatment of depression. Sertraline has not been marketed for OCD, therefore, the post-marketing data experience has occurred in the treatment of depression.

From November 19, 1990 through June 31, 1994, the patient exposure for sertraline is estimated at patient days of therapy. This information can be broken down as follows:

United States	
Worldwide (excluding US)	
Total patient days of therapy	

During the time period from December 30, 1991 (the date of approval in the United States) to October 30, 1994, there were a total of 5,158 adverse events (all cases spontaneously reported to Pfizer, cases of serious adverse events reported from adverse event registries, and reports of serious adverse events published in the medical literature) entered into the Pfizer early alert database. Of these, 1,099 were considered serious.

Also during this time period there were a total of 145 cases where death was reported as the event outcome, or the event reported was "death", "sudden death" or "death by suicide" entered into the database. Of these, 92 involved non-clinical study cases, 52 involved cases reported from Pfizer sponsored clinical studies and one involved a case reported from a non-Pfizer sponsored clinical study. An itemized listing of causes of death is provided in Appendix Table 5.2.2.

5.2.3 Literature

The Medline electronic database provided a list of references under the key words "sertraline" (Zoloft) and "obsessive compulsive disorder" (OCD). The literature reviewed did not contain any new safety information that would affect the conclusion about the safety of sertraline.

The company availed itself of searches of the commercial databases, namely MedLine, Excerpta Medica and Biosis, to obtain worldwide literature relevant to the clinical use of sertraline. Clinical publications cited in the Zoloft database from January 1991 through June 1994 were retrieved and submitted (contained in 3 volumes). In a review of these publications for evidence of sertraline-associated safety issues, there was no obvious indication of any safety concerns which had not been addressed elsewhere.

6.0 Human Pharmacokinetics

Sertraline is rapidly absorbed after oral administration. The oral absorption of sertraline is not significantly affected by food (AUC was slightly increased when sertraline was given with food).

Mean peak plasma concentrations (Cmax) occurred between 5 to 8 hours after oral dosing. Sertraline is highly bound to human serum proteins. The parent drug undergoes N-demethylation to desmethylsertraline which is less active than the parent drug. Both compounds then undergo oxidative deamination and subsequent reduction, hydroxylation and glucuronide conjugation.

The elimination half-life of sertraline is 26 hours and for N-desmethylsertraline 62 to 104 hours. Patients with hepatic dysfunction have impaired clearance. Consequently, a lower or less frequent dose should be used.

Sertraline is a substrate for the cytochrome P450 isozyme 2D6. The biochemical activity of this drug metabolizing isozyme is inhibited to a certain extent by sertraline. Thus sertraline may increase the plasma concentrations of co-administered drugs that are metabolized by P450 2D6. Consequently, concomitant use of a drug metabolized by P450 2D6 with sertraline may require lower doses than usually prescribed for the other drug.

No additional biopharmaceutics studies were performed for this submission. However, therapeutic drug monitoring occurred and results supported a linear dose concentration relationship for sertraline and its metabolite but reveal no relationship between plasma drug or metabolite concentration to clinical improvement.

7.0 Efficacy Findings

Refer to Dr. R. Hamer's review.

8.0 Safety Findings

8.1 Methods

The sponsor has generated an integrated OCD database that compares data on 376 sertraline-treated patients and 209 placebo-treated patients. Safety findings from these database formed the primary source for the safety review. A search for serious events included evaluation of deaths, dropouts for adverse effects and an evaluation of other events identified as serious by the sponsor.

Sertraline is marketed domestically and internationally for the treatment of depression. Therefore, a considerable amount of safety data exists for sertraline

from both premarketing and post-marketing surveillance. Safety data from OCD clinical trials were compared to the safety profile for sertraline in the treatment of depression.

Additionally, Periodic Adverse Experience Reports and Annual Reports for sertraline (marketed for depression) were reviewed to ascertain any unusual trends or potential problem areas. Post-marketing surveillance data for sertraline (marketed for depression) from the United Kingdom and published literature were reviewed for increased frequency of reporting and potential problem areas with respect to safety issues.

8.2 Assessment of Deaths

There have been no reports of deaths in sertraline-treated OCD patients in either completed (N=376) or not-yet submitted studies (N=577) as of the cut-off date October 10, 1994.

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8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

Table 8.3.1 shows the percentage of premature dropouts by treatment groups and reasons in the OCD placebo-controlled studies.

Table 8.3.1
Dropout Rates and Reason by Treatment Group (for Pooled Studies)

	Percent Dropping Out	
Reason for Dropout	**Sertraline (N=370)***	**Placebo (N=209)**
Lack of Efficacy	9%	12%
Adverse Experience	13%	7%
Patient Improvement	0%	0%
Non-Treatment Related	12%	13%
Total Dropouts	34%	32%

Adverse experience includes intercurrent illnesses and abnormal lab results. Non-treatment related includes chose to discontinue, lost-to-follow-up, protocol violation and other reasons.
These data are for acute phases of the trials. The N=370 rather than 376 because 6 patients in the extension trial (protocol 494) are not included.

Premature dropouts were more frequent in the sertraline group for adverse experiences and more frequent in the placebo group for lack of efficacy.

In the fixed-dose study (protocol 371/372) more sertraline-treated patients exposed to the higher doses of 100 mg (13/81, 16%) and 200 mg (10/80, 13%) discontinued prematurely due to adverse experiences than those patients treated with the lowest dose of 50 mg (5/80, 8%). The lowest dose compared favorably with the placebo-treated patients (6/84, 7%) with respect to premature discontinuations from the study. Similarly, more sertraline-treated patients at the two higher doses of 100 mg (11/81, 14%) and 200 mg (10/80, 13%) discontinued due to insufficient clinical response than patients exposed to the 50 mg dose of sertraline (7/80, 9%). Of the placebo-treated patients, 17% (14/84) discontinued due to insufficient clinical response.

The fixed-dose 12 week study included an additional 40 weeks of double-blind treatment of responders. Four of 96 (4%) sertraline-treated responders and one of 22 (4%) placebo-treated patients entering this continuation phase discontinued because of adverse experience (as noted in sponsor's Table 2C, P. 60, Vol. 1, December 21, 1993 submission).

8.3.2 Adverse Events Associated with Dropouts

Adverse events associated with dropouts (in the pooled OCD trials protocols 237/248, 371/372, 546 and 494) in ≥ 1% of sertraline-treated patients are displayed below:

PERCENTAGE OF PATIENTS DROPPING OUT*

	SERTRALINE (N=376)	PLACEBO (N=209)
Psychiatric Disorders		
Somnolence	2%	0%
Anxiety	2%	1%
Insomnia	2%	1%
Libido Decreased	1%	0%
Nervousness	1%	0%
Gastro-Intestinal Disorders		
Nausea	2%	0%
Diarrhea	1%	1%
CNS and PNS Disorders		
Headache	1%	0%
Body as a Whole-General Disorders		
Fatigue	1%	0%
Pain	1%	0%

* Pooled data for the three placebo-controlled studies 237/248, 371/546 and one open-label study (protocol 494)

For comparison, in a larger pool of data in all U.S. premarketing trials of sertraline (N=3267), the most common (≥1%) adverse events leading to premature discontinuation were the following: nausea (4%), dizziness (2%), headache (2%), tremor (2%), diarrhea (2%), fatigue (2%), agitation (2%), insomnia (2%), somnolence (1%) and sexual dysfunction in the male (1%).

In both the OCD and non-OCD databases adverse experiences associated with discontinuation in sertraline-treated patients were most frequently associated with psychiatric, gastro-intestinal and CNS/PNS disorders.

8.4 Other Specific Search Strategies

8.4.1 Search for Emergence of Suicidality

It has been alleged that a small minority of patients treated with other members of the SSRI class have experienced the emergence of suicidal ideation. Therefore, the sertraline data base including the OCD database were searched for suicide attempts and emergence of suicidal ideation.

In OCD clinical trials (placebo-controlled and open-labelled), there were no reports of suicides in sertraline-treated patients (N=376).

There were 2 events classified as suicide attempts in sertraline-treated patients (2/376; 0.7%) and one event classified as a suicide attempt in the placebo-treated patients (1/209; 0.5%).

Two OCD patients, one treated with placebo and one treated with 200mg sertraline exhibited suicidal ideation.

The less than one percent incidence of suicidality in all sertraline-treated OCD patients is equivalent to the 0.4% incidence seen in the non-OCD sertraline-treated patients.

Since the submission of this supplemental NDA, there have been additional OCD studies either completed or ongoing (see Appendix Table 5.1.1) in which suicidal ideation (N=7), suicidal gestures (N=3) and suicidal tendencies have been reported in sertraline-treated patients. Additionally, there have been 2 reports of suicide attempts in studies which remain blinded as to treatment.

8.4.2 Search for Serious Adverse Events

Pfizer defined serious adverse experiences as events which: were fatal, were life-threatening, or potentially life-threatening, resulted in permanent disability, required hospitalization or prolongation of a hospital stay, involved cancer, a congenital anomaly, or the result of a drug overdose or which suggested significant hazard to the patient. The lists of serious adverse events were generated from the Pfizer early alert safety database and divided into serious events from those studies included in this supplement as well as additional studies that were not submitted as part of supplemental NDA. A total of 12 serious events were reported in the integrated safety database as of the cut-off date of June 30, 1994. Among the 12 patients, 2% (8/376) were in the sertraline group, while 2% (4/209) were in the placebo treatment group. Case reports from the sertraline-treated patients were reviewed.

In addition, there have been 24 reports of serious events in sertraline-treated patients enrolled in ongoing or completed studies, not included in this supplemental NDA for OCD (cut-off date, October 7, 1994), as well as 4 placebo-treated and 4 active-control-treated.

Certain of these events are discussed under specific sections of this safety review (i.e., suicide attempts-including overdose, emergence of suicidal ideation, seizure, changes in laboratory values). The remainder are presented under section 8.7 entitled "Summary of Other Serious Adverse Events Unlikely to be Drug Related". Narrative summaries of dropouts due to medical events in all sertraline-treated patients were reviewed for serious adverse events. No additional serious events were located.

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

The table which follows enumerates the adverse events that occurred at a frequency of 1% or more among sertraline-treated patients who participated in the placebo-controlled OCD studies comparing sertraline with placebo. The preferred adverse experience terms are used as listed in the Pfizer WHO Adverse Event Coding Glossary. For comparisons, Appendix 8.5.1 gives the analogous table as it appears in the current Zoloft® labeling, (September, 1993) for adverse events from placebo controlled-depression trials.

In both the OCD database and the depression trial database, the most frequently reported adverse events following sertraline administration were psychiatric, gastrointestinal and central/peripheral nervous system complaints. The majority of the reports of severe adverse experiences occurred within these 3 body systems.

Treatment Emergent Adverse Experience Incidences In Placebo-Controlled Trials*

Percentage of Patients Reporting Events

Adverse Experience	Sertraline (N=370)	Placebo (N=209)
Autonomic Nervous System Disorders		
Mouth Dry	13	8
Anorexia	11	1
Ejaculation Failure	10	1
Appetite Increased	4	1
Impotence	3	1
Hypertension	1	1
Body As A Whole		
Fatigue	15	10
Back Pain	4	1
Pain	4	1
Hot Flushes	4	1
Chest Pain	3	3
Fever	2	1
Malaise	2	1
Rigors	1	1
Asthenia	1	0
Central & Peripheral Nervous System Disorders		
Headache	36	24
Dizziness	21	11
Tremor	8	1
Paresthesia	5	1
Hypertonia	2	1
Hypoesthesia	2	1
Convulsions	2	0
Twitching	1	1
Hyperkinesia	1	0
Gastro-Intestinal Disorders		
Nausea	30	9
Diarrhea	27	10
Dyspepsia*	13	4
Abdominal Pain	6	6
Constipation	6	5
Flatulence	5	2
Vomiting	3	1
Tooth Caries Aggravated	1	1

Treatment Emergent Adverse Experience Incidences in Placebo-Controled Trials* (continued)

Adverse Experience	Percentage of Patients Reporting Events	
	Sertraline (N=370)	Placebo (N=209)
Hearing & Vestibular Disorders		
Earache	2	2
Tinnitus	2	2
Heart Rate & Rhythm Disorders		
Palpitations	4	1
Metabolic & Nutritional Disorders		
Weight Increase	6	1
Weight Decrease	2	1
Thirst	1	0
Musculo-Skeletal System Disorders		
Myalgia	2	3
Arthralgia	2	2
Arthrosis	1	1
Psychiatric Disorders		
Insomnia	33	14
Somnolence	16	10
Libido Decreased	14	1
Nervousness	9	8
Anxiety	8	7
Agitation	6	4
Depression	4	3
Depersonalization	3	1
Concentration Impaired	3	2
Amnesia	3	1
Paronia	2	1
Yawning	2	0
Teeth-Grinding	1	0
Apathy	1	0
Thinking Abnormal	1	0
Suicide Attempt	1	1
Reproductive Disorders, Female		
Menstrual Disorder	1	1

Treatment Emergent Adverse Experience Incidences In Placebo-Controlled Trials* (continued)

Adverse Experience	Percentage of Patients Reporting Events: Sertraline (N=370)	Placebo (N=209)
Respiratory System Disorders		
Respiratory Disorder	5	5
Pharyngitis	5	4
Dyspnea	2	1
Rhinitis	2	1
Coughing	1	2
Epistaxis	1	1
Skin & Appendages Disorders		
Sweating Increased	8	1
Rash	4	1
Urticaria	1	0
Acne	1	1
Pruritus	1	1
Special Senses Other, Disorders		
Taste Perversion	3	1
Urinary System Disorders		
Polyuria	2	1
Urinary Retention	2	0
Micturition Frequency	1	1
Vascular (Extracardiac) Disorders		
Purpura	1	0
Vision Disorders		
Vision Abnormal	4	1
Conjunctivitis	1	1

* Pooled from protocols 371/372, 237/248 and 546.
Each adverse experience was tabulated once per patient regardless of the number of times it was reported by that patient and the most severe occurrence is shown.

Common and Drug-Related Adverse Events

As an indication of which adverse events may be common and drug-related, those adverse events with an incidence among sertraline-treated patients of $\geq$5% and an incidence at least twice that among placebo were selected from the above table. The following were such adverse events.

ANS Disorders	GI Disorders	Metabolic and Nutritional Disorders
Sweating increased*	Nausea*	Weight Increase
	Diarrhea/Loose Stools*	
	Dyspepsia*	
	Anorexia	

CNS/PNS Disorders	Psychiatric Disorders
Tremor*	Sexual Dysfunction* (male and female)
Paresthesia	Insomnia*

Sexual dysfunction includes ejaculation failure and decreased libido. Terms followed by astericks appear in the current sertraline labeling (September, 1993) and meet the above criteria for common and drug-related adverse events in sertraline-treated OCD patients.

Evidence of Dose-Relatedness for Certain Adverse Events

The table that follows, Table 8.5.1.2, gives the incidence of treatment-emergent adverse events for those events reported by $\geq$5% of patients in any treatment group in protocol 371/372, the fixed-dose study. There was a statistically significant difference ($p<0.05$) in the incidence of side effects between placebo and pooled sertraline treatment groups for 6 groupings, specifically, psychiatric, gastrointestinal, CNS/PNS, ANS, skin and appendages and metabolic/nutritional disorders.

The study design of protocols 371/372 included a 12-week treatment phase followed by an additional 40 weeks of double-blind treatment for responders. During the continuation phase the 3 doses of sertraline were well tolerated.

The incidence, type and severity of adverse experiences were similar during the initial 12 weeks treatment period of protocol 371/372 as compared to the full 52 week study. Adverse experiences occurring in sertraline-treated patients with a statistically significantly higher incidence than in placebo-treated patients were similar in the two study periods with the exception of headache, which increased from 38% to 44% in the 200 mg treatment group. The incidence of adverse experiences first occurring after week 12 was consistently decreased relative to their occurrence during the initial 12 weeks of treatment. Only one type of adverse event (tooth disorder) was reported in more than one sertraline-treated patient exclusively after week 12 with no occurrences prior to week 12. Four of 96 sertraline-treated patients (4%) entering the discontinuation phase discontinued because of adverse experiences. There were no types of adverse experiences, the appearance or severity of which appeared to be related to the continuation of sertraline beyond 12 weeks.

Table 8.5.1.2

Summary of All Treatment-Emergent Adverse Events Occuring at ≥5% Incidence in Any Treatment Group Protocol 371/372

	Incidence in Safety Evaluable Patients			
	Sert. 50mg (N=80)	Sert. 100mg (N=81)	Sert. 200mg (N=80)	Placebo (N=84)
Adverse Experience	No. Pts. (%)	No. Pts. (%)	No. Pts. (%)	No. Pts. (%)
Autonomic Nervous System Disorders				
Mouth Dry	10 (13%)	9 (11%)	14 (18%)	9 (11%)
Anorexia	11 (14%)	10 (12%)	10 (13%)	3 (4%)
Ejaculation Failure	3 (4%)	6 (7%)	12 (15%)	1 (1%)
Appetite Increased	6 (8%)	2 (3%)	3 (4%)	1 (1%)
Body As A Whole - General Disorder				
Fatigue	18 (23%)	14 (17%)	17 (21%)	15 (18%)
Pain	8 (10%)	3 (4%)	2 (3%)	1 (1%)
Back Pain	5 (6%)	5 (6%)	2 (3%)	1 (1%)
Hot Flushes	3 (4%)	5 (6%)	4 (5%)	0 (0%)
Central & Peripheral Nervous System Disorders				
Headache	35 (44%)	30 (37%)	38 (48%)	23 (27%)
Dizziness	19 (24%)	17 (21%)	22 (28%)	15 (18%)
Tremor	2 (3%)	6 (7%)	13 (16%)	1 (1%)
Paresthesia	5 (6%)	8 (10%)	3 (4%)	1 (1%)
Hypertonia	2 (3%)	4 (5%)	2 (3%)	2 (2%)
Hypoesthesia	1 (1%)	1 (1%)	4 (5%)	1 (1%)
Twitching	1 (1%)	2 (3%)	1 (1%)	3 (4%)
Convulsions	0 (0%)	0 (0%)	4 (5%)	0 (0%)
Gastro-Intestinal Disorders				
Diarrhea	26 (33%)	27 (33%)	23 (30%)	9 (11%)
Nausea	20 (25%)	24 (30%)	28 (35%)	13 (16%)
Dyspepsia	8 (10%)	9 (11%)	15 (19%)	6 (7%)
Abdominal Pain	4 (5%)	8 (10%)	5 (6%)	8 (10%)
Flatulence	6 (8%)	6 (8%)	4 (5%)	2 (2%)
Constipation	3 (4%)	6 (7%)	6 (7%)	4 (5%)

	Incidence in Safety Evaluable Patients (CONTINUED)			
	Sert. 50mg (N=80)	Sert. 100mg (N=81)	Sert. 200mg (N=80)	Placebo (N=84)
Adverse Experience	No. Pts. (%)	No. Pts. (%)	No. Pts. (%)	No. Pts. (%)
Metabolic and Nutritional Disorders				
Weight Increase	4 (5%)	5 (6%)	10 (12%)	1 (1%)
Weight Decrease	2 (3%)	0 (0%)	6 (8%)	1 (1%)
Musculo-Skeletal System Disorders				
Myalgia	5 (6%)	2 (3%)	2 (3%)	3 (4%)
Arthralgia	4 (5%)	3 (4%)	0 (0%)	2 (2%)
Psychiatric Disorders				
Insomnia	27 (34%)	26 (32%)	36 (45%)	17 (20%)
Somnolence	14 (18%)	14 (17%)	14 (18%)	12 (14%)
Libido Decreased	11 (14%)	12 (15%)	17 (21%)	1 (1%)
Anxiety	2 (3%)	9 (12%)	11 (14%)	9 (11%)
Nervousness	7 (9%)	7 (9%)	8 (10%)	6 (7%)
Agitation	4 (5%)	4 (5%)	8 (10%)	3 (4%)
Depression	3 (4%)	4 (5%)	4 (5%)	4 (5%)
Amnesia	1 (1%)	1 (1%)	5 (6%)	2 (2%)
Depersonalization	1 (1%)	2 (3%)	4 (5%)	1 (1%)
Yawning	0 (0%)	0 (0%)	5 (6%)	0 (0%)
Respiratory System Disorders				
Pharyngitis	5 (6%)	6 (7%)	6 (8%)	7 (8%)
Respiratory Disorder	5 (6%)	3 (4%)	5 (6%)	7 (8%)
Rhinitis	0 (0%)	2 (3%)	4 (5%)	3 (4%)
Skin and Appendages Disorders				
Sweating Increased	2 (3%)	9 (11%)	10 (13%)	0 (0%)
Rash	4 (5%)	3 (4%)	3 (4%)	2 (2%)
Special Senses, Other Disorders				
Taste Perversion	2 (3%)	1 (1%)	4 (5%)	1 (1%)

	Incidence in Safety Evaluable Patients (CONTINUED)			
	Sert. 50mg (N=80)	Sert. 100mg (N=81)	Sert. 200mg (N=80)	Placebo (N=84)
Adverse Experience	No. Pts. (%)	No. Pts. (%)	No. Pts. (%)	No. Pts. (%)
Urinary System Disorder				
Polyuria	1 (1%)	4 (5%)	1 (1%)	0 (0%)
Vision Disorders				
Vision Abnormal	2 (3%)	2 (3%)	7 (9%)	2 (2%)

Adapted from Sponsor's Table 22, P. 164, in Vol. 21.1.

Adverse experiences that occurred with a statistically greater frequency in one or more of the sertraline groups, compared with placebo are marked with an asterick in the table which follows.

Incidence of Adverse Experiences
(Baseline to Week 12)
Fixed Dose OCD Study (Protocol 371/372)

	Number (%) of Patients			
Adverse Experience	Sertraline 50 mg (N=80)	Sertraline 100 mg (N=81)	Sertraline 200 mg (N=80)	Placebo (N=84)
Headache	35 (44)*	30 (37)	38 (48)*	23 (27)
Insomnia	27 (34)	26 (32)	36 (45)*	17 (20)
Diarrhea	26 (33)*	27 (33)*	23 (30)*	9 (11)
Nausea	20 (25)	24 (30)*	28 (35)*	13 (16)
Libido Decreased	11 (14)*	12 (15)*	17 (21)*	1 (1)
Dyspepsia	8 (10)	9 (11)	15 (19)*	6 (7)
Anorexia	11 (14)*	10 (12)*	10 (13)*	3 (4)
Ejaculation Failure	3 (4)	6 (7)	12 (15)*	1 (1)
Tremor	2 (3)	6 (7)	13 (16)*	1 (1)
Sweating Increased	2 (3)	9 (11)*	10 (13)*	0 (0)
Weight Increase	4 (5)	5 (6)	10 (13)*	1 (1)
Paresthesia	5 (6)	8 (10)*	3 (4)	1 (1)
Pain	8 (10)*	3 (4)	2 (3)	1 (1)
Yawning	0 (0)	0 (0)	5 (6)*	0 (0)

* $p \leq 0.05$ compared with placebo, Fishers Exact Test, 2-tailed.

Adapted from Sponsor's Table on P. 79, in Vol. 21.1.

From the examination of this table, the incidence of adverse experiences appears to be dose-related. The 50mg/d sertraline treatment group experienced a statistically significant greater incidence of 5 adverse events compared to the placebo treatment group: headache, diarrhea, libido decreased, anorexia and pain. The 100mg sertraline treatment group experienced a statistically significant greater incidence of 6 adverse events compared to placebo: nausea, libido decreased, diarrhea, anorexia, sweating increased and paresthesia. Twelve of the 14 adverse events listed in the above table occurred in a significantly greater percentage of sertraline-treated patients receiving the 200mg/d dose compared with placebo.

Three of the adverse experiences showed a statistically significant dose-related increase in incidence from 50 to 200 mg. These 3 events were: ejaculation failure, tremor and increased sweating.

The majority of all adverse experiences were characterized as either mild or moderate without significant difference in severity between groups.

8.5.2 Laboratory Findings

Clinical laboratory data were obtained at screen or baseline and post-dose visits. The following discussion will focus on the 3 placebo-controlled OCD studies (237/248, 371372 and 546). The Appendix tables provides proportions of patients in these pooled placebo-controlled studies who met arbitrarily defined criteria for changes in laboratory analytes of possible clinical significance. The criteria for determining the clinically significant laboratory abnormalities were identical to the those used in the non-OCD patient database analyses.
The methods used to evaluate laboratory data were to examine:

1) clinically significant laboratory test abnormalities as defined previously;
2) statistical comparisons of the change from baseline in each laboratory analyte;
3) premature discontinuations due to laboratory abnormalities.

8.5.2.1 Blood Chemistry

Appendix 8.5.2.1.1 lists the abnormal chemistry values considered to be of potential clincial significance.

Appendix 8.5.2.1.2 provides a table which displays the proportion of patients in the 3 placebo-controlled OCD studies with normal baseline blood chemistry values and that exceeded the criteria values at some time on assigned treatment. The incidences of laboratory abnormalities were similar in the sertraline and placebo groups with the exception of reports of abnormalities in the blood analytes albumin, SGOT, total bilirubin and uric acid, in which the incidence rate was

somewhat higher in the placebo than sertraline group. Elevations in the blood analytes cholesterol, glucose and SGPT were reported more frequently in the sertraline-treatment group.

Sertraline-treated patients did not show a statistically significantly greater incidence (using Fishers Exact Test) of clinically significant abnormalities compared with placebo-treated patients for any laboratory analyte.

Serum electrolytes were measured but data were not submitted. Communication with sponsor revealed that there were no clinically or statistically significant changes in blood electrolyte measurements. No patients discontinued due to clinically significant abnormalities in serum electrolytes.

Changes from baseline for each laboratory analytes were examined. Of the 3 placebo-controlled OCD studies, protocol 546 was completed recently. Therefore, separate analyses were submitted for protocol 546 after the submission of the other placebo-controlled OCD studies (237/248 and 371/372). A comparison of the mean change from baseline for laboratory analytes between sertraline and placebo treatment groups using the Wilcoxon Rank Sum Test revealed a statistically significant between group difference in the change from baseline to final visit for the following analytes: total cholesterol, uric acid, SGOT and SGPT in the pooled OCD studies (237/248, 371/372) and study 546. Data for these studies for mean change from baseline are presented below.

Mean Change From Baseline				
Protocols 237/248 and 371/372			Protocol 546	
DRUGS				
Analyte	Sertraline (N=273)	Placebo (N=125)	Sertraline (N=86)	Placebo (N=76)
Cholesterol (mg/dl)	+7	-4	+13	-1.3
Uric Acid (mg/dl)	-0.2	+0.1	-0.5	+0.2
SGOT (u/L)	+2	+3	+2	-0.2
SGPT (u/L)	+3	-0.2	+4	-0.7

Data assimilated from sponsor's Tables 32 (p. 213, vol. 21) and Table 16 (p. 54, vol. 32).

In the entire placebo-controlled OCD database (protocols 237/248, 371/372 and 546) one patient (1/370, 0.3%) prematurely discontinued study drug due to elevated serum transaminases. The case report was reviewed. Patient #7 (study 88N0178), protocol 371/372, a 27 YOM had asymptomatic elevation of serum transaminases (SGOT 246 units and SGPT 172 units (NR; 11-36 u/L and 6-43 u/l, respectively) after 196 days of sertraline 100 mg/day at which time therapy was discontinued; transaminases returned to normal 30 days after discontinuing therapy. No placebo-treated patients discontinued because of chemistry analyte abnormalities.

8.5.2.2 Hematology

Appendix 8.5.2.2.1 lists the abnormal hematology values considered to be of potential clinical significance.

Appendix 8.5.2.2.2 provides a table which displays the proportion of patients with normal baseline values and that exceeded the criteria values at some time on assigned treatment in the 3 placebo-controlled OCD studies. With the exception of the hematology analyte eosinophils in which the proportion of placebo-treated patients having potentially clinically significant elevations was 3 fold higher than in the sertraline-treated patients, the incidence of hematology abnormalities was similar in the sertraline and placebo-treated patients.

There were no statistically significant differences between the sertraline and placebo groups in the mean change from baseline in hematological analytes.

One sertraline-treated patient (1/370; 0.3%) discontinued from an OCD study because of a decreased WBC. Patient #14 (study 88N0178), protocol 371/372, a 22YOM had asymptomatic transient leukopenia; WBC count dropped from 4.2 x 10^3/uL at baseline [NR: 4-11 x 10^3/uL] to 3 x 10^3/uL after 27 days of sertraline (100mg/d) exposure at which time sertraline treatment was discontinued because of the patient's request. WBC count returned to the normal range (5 x 10^3/uL) 17 days later. There were no reports of premature discontinuations due to hematological analytes in the placebo-treated groups.

8.5.2.3 Urinalyses

The criteria for identifying patients with changes from baseline of potential clinical significance on the urinalysis variables of interest are as follows: protein, a value of 2 or above; glucose, a value of 2 or above; casts, a value of 2 or above.

Appendix 8.5.2.3.1 provides a table which displays the proportion of patients with normal baseline urinalysis values and than exceeded the criteria values at some time on the assigned treatment in the 3 placebo-controlled OCD studies. There were no meaningful differences between the sertraline and placebo-treated groups.

There were no statistically significant differences between the sertraline and placebo groups in the mean change form baseline in urinalysis analytes.

There were no reports of discontinuations in either the sertraline or placebo-treated patient because of urinalysis analytes.

8.5.3 Vital Signs and Weight

The 3 placebo-controlled OCD studies provided the main data source for review of vital signs findings. The criteria for determination of clinically significant vital signs abnormalities were identical to those used in the non-OCD patient database analyses and are included in Appendix 8.5.3.1.

Appendix Table 8.5.3.2 displays the proportion of patients in the 3 placebo-controlled studies having potentially clinically significant changes in vital signs variables. There were no statistically significant differences in the incidence of clinically significant abnormalities of vital signs between the sertraline and placebo treatment groups. These findings are consistent with the results from the placebo-controlled non-OCD studies.

Additionally, vital sign data were analyzed in terms of mean changes from baseline to last visit for the 3 placebo-controlled studies, (protocol 546 was completed most recently and as such analyses of these data were submitted separately from the other 2 protocols). From the examination of the sponsor's Table 37 (Vol. 21, P. 231) in the 2 pooled placebo-controlled OCD studies (protocols 237/248 and 371/372), using the Wilcoxon Rank Sum Test, there were no statistically significant differences between sertraline and placebo-treatment groups, regarding the change from baseline to final visit in any of the following measurements: supine or standing pulse rate, supine or standing systolic and supine or standing diastolic blood pressures. From the examination of the sponsor's Table 19 (Vol. 32, P. 58) for protocol 546, mean change scores in the sertraline group differed significantly from the mean change scores in the placebo group for the following measurements:

Standing Diastolic Blood Pressure

-0.62 mm/Hg (-1%) in the sertraline vs 1.75 mm/Hg (2%) in the placebo group.

Supine Heart Rate

-3.0 bpm (-4%) in the sertraline group vs 0.5 bpm (1%) in the placebo group.

From a survey of Table 18A and B (Vol. 21.7, P. 401) there was no evidence of any dose response relationship to vital sign variability in the fixed dose protocol 371/372.

There were no reports of premature discontinuations in any of the 3 protocols.

The above findings are consistent with results for the placebo-controlled non-OCD studies.

Weight

The proportion of patients having potentially clinically significant changes in weight in the 3 placebo-controlled OCD studies is provided in Appendix Table 7.5.3.1. In the sertraline-treated group, approximately 10% (35/365) versus 1% (2/207) in the placebo-treated group experienced a clinically significant weight gain. (Increase of ≥ 7%, relative to baseline). Clinically significant weight loss (≤7%, relative to baseline) was reported by 6% (21/365) of the sertraline-treated patients and 2% (5/207) of the placebo-treated patients.

The mean change in weight from baseline to final visit in the 2 pooled placebo-controlled OCD studies was 0.9 pounds among the sertraline-treated patients and -0.2 pounds in the placebo-treated patients. In protocol 546, the mean change in weight from baseline to final visit was -0.3 pounds in the sertraline-treated patients and +0.08 pounds among the placebo-treated patients. The changes were not statistically or clinically significant.

There was one report of a premature discontinuation due to increase in body weight. The 28 YOF (88N0177-5, protocol 371/372) sustained moderate hunger for 2½ months leading to a weight gain of 56 pounds. Increased appetite resolved during downward titration of drug from a maximum dose of 200mg/d.

There was one report of a premature discontinuation due to a report of weight loss (CRF did not reveal the magnitude of weight loss), nausea, diarrhea and sedation in a 33YOM (88N0171-22, protocol 371/372). Patient was treated with sertraline 200mg/d for 16 days. Patient had a history of G.I. upset.

In premarketing depression studies, statistically significant ($p<0.001$) weight change in association with sertraline was demonstrated in a 6-week multicenter trial comparing sertraline, amitriptyline and placebo. There was a -2.0 pound loss for sertraline, and a mean weight gain for both amitriptyline (2.0 pounds) and placebo (1.0 pounds). Weight loss is listed under PRECAUTIONS in the current Zoloft® (sertraline) labeling (indication for depression).

8.5.4 Electrocardiograms

ECGs from the 3 placebo-controlled studies which were reported as showing an ECG abnormality were examined by a Pfizer physician, who was unaware of the patient's treatment group.

A summary of the findings from the pooled data of protocols 371/372 and 237/248 is presented below. Protocol 546 was completed after the submission of data from the above 2 protocols. Therefore, data are presented separately.

	ECG FINDINGS: Placebo-Controlled Studies Protocols 371/372 and 237/236	
	SERTRALINE	PLACEBO
# Patients with ≥1 ECG on double-blind therapy	284	127
Clinically significant deterioration compared with baseline ECG	0 (0%)	0 (0%)
Normal baseline with abnormality on double-blind (investigator's evaluation)	40 (14%)	17 (13%)
Abnormal baseline with new abnormal finding on double-blind (investigator's evaluation)	34 12%	12 (9%)

Adapted from sponsor's Table 44 (Vol. 21.1, P. 243)

There were no differences between the treatment groups. No patient was considered to have had clinically significant deterioration of the ECG.

Similar findings were reported in protocol 546 with one exception. There was one clinically significant treatment emergent ECG abnormality recorded during the study in a placebo-treated patient.

The table which follows summarizes the incidence of ECG abnormalities in the 3 sertraline groups and placebo. The incidence of subsequent ECG abnormalities relative to baseline was somewhat higher in the 3 sertraline gorups compared to placebo (15-18% vs 10% for the 3 treatment groups vs placebo, respectively). There was no association between the dose of sertraline and the incidence of these events. By investigator evaluation, the most frequently observed abnormalities during double-blind therapy that were either not present at baseline or became more pronounced during double-blind treatment were: sinus bradycardia, and nonspecific ST/T segment abnormalities. Ten percent (25/241) sertraline-treated patients compared with 4% (3/83) placebo-treated patients were reported to have sinus bradycardia. There were no differences between the 3 doses of sertraline.

Nonspecific ST/T wave segment abnormalities were reported by 6% (14/241) of the sertraline-treated patients and 2% (2/83) of the placebo-treated patients. The incidence was similar among the 3 doses of sertraline. All the abnormalities were found not clinically significant.

Incidence of ECG Abnormalities in Protocol 546 Week (0-52)

	Sertraline 50 mg	Sertraline 100 mg	Sertraline 200 mg	Placebo
* Patients with ≥1 ECG during double-blind treatment	80	81	80	83[1]
Clin. significant treatment-emergent abnormalities	0	0	0	0
Normal baseline; ≥1 subsequent ECG abnormal	13 (16%)	12 (15%)	14 (18%)	8 (10%)
Abnormal baseline; ≥1 subsequent ECG abnormal	16 (20%)	20 (25%)	20 (25%)	21 (25%)

[1] patient no.18, 88N0172 did not have ECG recordings

From Sponsor's Table 24A, (Vol. 1, P. 214, submitted December 21, 1993).

There were no reports of premature discontinuations because of ECG abnormalities in the 3 placebo-controlled trials.

From the data submitted there was no evidence of clinically significant adverse effects of sertraline on the ECG in OCD patients. A similar conclusion was made in the non-OCD database.

8.5.5 Special Studies

There were no special studies submitted with this NDA, supplement.

8.5.6 Withdrawal Phenomena/Abuse Potential

8.5.6.1 Possible Withdrawal Phenomenon

Discontinuation-emergent adverse events were not systematically evaluated in this NDA. However, a recent report (Louis, AK etal. Arn J Psychiatry 1994) documents a withdrawal reaction following abrupt sertraline discontinuation in one patient.

Recently, it has been reported J Clin Psychopharmacol 14: 206,1994) that unexpected and sometimes disabling withdrawal symptoms of lightheadedness and dizziness have occurred in paroxetine-treated OCD patients (5/13; 39%) within 1 to 3 days of withdrawal. Paroxetine is an SSRI with a half-life similar to sertraline.

Sertraline has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependance.

8.5.7 Human Reproduction Data

One pregnancy occurred during protocol 371/372 in a 23 YOF. (Study 88N0179-36). No follow-up is available on the outcome of the pregnancy.

There have been no adequate and well controlled trials involving sertraline in pregnant women.

8.5.8 Overdose Experience

There has been one report of an overdose in an OCD patient (patient L-14-90-N-0171) enrolled in the open-label protocol 494. This 20 YOM with a history of suicidal gestures took 500 to 1000 mg of sertraline after 415 days of treatment and experienced symptoms of drowsiness and dizziness. He recovered.

In the non-OCD database, there have been 79 reports of non-fatal overdoses as of November, 1992, of which 28 were overdoses with sertraline alone and the remainder involved a combination of other drugs and/or alcohol in addition to sertraline.

8.6 Summary of Potentially Important Adverse Events Considered Possibly or Probably Drug-Related

The safety profile of sertraline in OCD patients is consistent with that in sertraline-treated non-OCD patients with one exception. Seizures were reported in sertraline-treated OCD patients. There were no reports of seizures in patients diagnosed with depression and treated with sertraline.

8.6.1 Seizures

There was one report of a seizure in the 3 placebo-controlled OCD trials (1/370; 0.3%). This 33 YOM (protocol #372, pt. #33) with a family history of seizure disorder had a witnessed seizure with associated enuresis after receiving sertraline (200mg/day) for 146 days. The patient was not hospitalized. Sertraline was discontinued and an anticonvulsant was started. There were no reports of seizure in the placebo-treated patients.

Incidentally, there were 5 patients (5/370; 1.3%) in the 3 OCD placebo-controlled studies which, according to the WHO dictionary preferred coding requirements, were recorded as convulsions but represented mild to moderate myoclonus twitching and did not represent seizure activity. There were no reports in placebo-treated patients (N=209).

In addition to the one seizure reported in the 3 placebo-controlled OCD trials, there were 3 reports of seizures (as of 10/10/94) in ongoing or not-yet completed OCD studies (not submitted as part of the supplemental NDA). Available information on the 3 additional sertraline-treated patients in which reports of seizures occurred are summarized below.

Patient No. (protocol)	Gender/ Age (yrs)	Daily Dose (mg)	Event Onset (day)	Comment
823 (536)	M/15	50	4	1.Sertraline implicated by investigator. 2. outcome. resolved
222B (498)	F/14	200	74	1.Family h/o seizure; 2.Pt. had abnormal EEG 3.Sertraline could not be excluded as contributing factor. 4. Outcome: resolved
223B (536)	F/15	100	16	1.Sertraline implicated by investigator. 2.Pt had abnormal EEG. 3. Outcome: resolved

The only other report of seizure in this dataset was from a patient treated with the active control drug desipramine.

In summary, the frequency of seizures in completed and ongoing OCD studies is 0.3% (4/1289) as of October 10, 1994. The 1289 patients consisted of 577 patients completed or discontinued in ongoing or not yet submitted studies, 457 patients submitted as part of the original OCD NDA. (370 patients from the 3 placebo-controlled studies - 371/372, 237/248, 546 and 87 from protocol 495 entitled, "The Double-Blind Comparison of Sertraline, Clomipramine and Placebo in Outpatients with OCD) and 255 patients derived as a best estimate of ongoing patients in OCD studies worldwide. There were no reports of seizures in the clinical trials for depression in which more than 2,900 patients were exposed to sertraline.

8.6.2 Suicidality

The incidence of suicidality among patients in OCD trials is discussed in section 8.4.1.

8.6.3 Activation of Mania/Hypomania

During Premarketing testing, hypomania or mania was reported to occur in 0.4% (10/2710) of sertraline-treated patients necessitating dose reduction or discontinuation. There were no reports of mania/hypomania in sertraline-treated patients in OCD trials.

8.6.4 Weight Loss/Anorexia

The findings regarding weight loss have been discussed previously in the review in the section entitled "Vital Signs" (8.5.3).

In premarketing placebo-controlled trials for depression, anorexia was reported to occur in 3% of 861 sertraline-treated patients compared with 2% of 853 placebo-treated patients. In the 3 placebo-controlled trials for OCD, 11% of 370 patients treated with sertraline and 1% of 209 patients treated with placebo reported anorexia. There was no dose response in the fixed dose study 371/372 with respect to the occurrence of anorexia.

One sertraline-treated patient in the OCD trials (protocol 371/372) discontinued treatment prematurely because of anorexia, as well as complaints of facial rash, anorgasmia, insomnia, thirst, somnolence, twitching and depression. This 44 YOF (88N0179-30) with a post-medical history of endometriosis, fibrocystic disease and mitral valve stenosis, had been treated with 100mg of sertraline. She had been treated with sertraline for 72 days before discontinuing. Follow-up revealed no further complaints after 1 week of discontinuation.

8.6.5 Increased Serum Transaminase Levels

In premarketing clinical trials, 21 of 2710 (0.8%) of sertraline-treated patients discontinued due to increases in transaminases, compared with 3/541 (0.6%) of the active control. No placebo patients (N=1303) discontinued prematurely from the trials.

In the section entitled "Blood Chemistry" (8.5.2.1), it was pointed out that in the entire OCD database, 1 of 370 (0.3%) patients discontinued study drug due to elevated serum transaminases. This one patient was asymptomatic. No placebo-treated patients discontinued prematurely.

8.6.6 Increased Serum Cholesterol

No patients discontinued because of elevated serum cholesterol levels in any clinical trial.

In premarketing clinical trials, 5.0% (113/2083) of sertraline-treated patients and 3% (37/1228) placebo-treated patients met criteria for clinically significant cholesterol abnormality (>=330mg/dl for cholesterol).

In the 3 placebo-controlled OCD studies, 3% (11/361) of sertraline-treated and 1% (3/203) of placebo-treated patients had clinically significant cholesterol abnormalities. These differences were not statistically significant (comparison of incidence values using Fisher's Exact Test).

However, a comparison of the mean change from baseline to final visit for serum cholesterol, between sertraline and placebo in the 3 placebo-controlled OCD studies using the Wilcoxon Rank Test showed a statistically significant ($p<0.001$) between group difference. (A range of change from baseline means between +7 and +13mg/dl for sertraline-treated patients vs between -4 to -1mg/dl for placebo-treated patients). A similar change occurred in the non-OCD placebo-controlled trials (baseline to final visit). The mean change from baseline to final visit for serum cholesterol in sertraline-treated patients enrolled in these non-OCD placebo-controlled trials was +9mg/dl. and for placebo-treated, -1.0mg/dl.

The change in cholesterol level during sertraline treatment may be attributed to induction of the liver microsomal enzyme systems or to alteration (decrease) in the serum concentration of free thyroxine which is known to be associated with an increase in serum lipid levels.

The clinical significance of these changes in serum cholesterol are unknown. However, it has long been appreciated that cardiovascular risk is a continuous function of cholesterol concentration.

8.6.7 Decrease in Serum Uric Acid Levels

In premarketing clinical trials, sertraline was associated with a mean decrease in serum uric acid levels of approximately 7%.

The mean reduction from baseline in uric and seen in the OCD studies was comparable to that seen in the premarketing non-OCD studies.

The mechanism of action whereby sertraline lowers serum uric acid levels is unknown.

The clinical significance of such an effect is unknown, but it should be pointed out that other drugs with such an effect have been occasionally associated with renal dysfunction in vulnerable patients.

8.6.8 Search For Other Significant Events Alleged To Occur In Other Members Of This Drug Class

The following events have been reported in association with other members of the general class of antidepressant medications known as selective serotonin reuptake inhibitors and were examined in the OCD database to determine the extent of potential risk associated with sertraline.

8.6.8.1 Insomnia

In premarketing placebo-controlled trials, insomnia was reported at a rate of 16% of 861 sertraline-treated patients, and 9% of 853 placebo-treated patients. Of the sertraline-treated patients, two (1%) discontinued compared to one (0.3%) of the placebo-treated patients.

In the 3 placebo-controlled clinical trials for OCD, insomnia was reported in 33% of 370 patients treated with sertraline and 14% of 209 patients treated with placebo. Insomnia was one of the principal experiences associated with discontinuation of sertraline therapy in OCD trials. Insomnia was indicated as a reason or one of the reasons for premature discontinuation in 2% of 370 sertraline-treated patients compared with 1% of 209 placebo-treated patients.

8.6.8.2 Anxiety

In premarketing placebo-controlled clinical trials, anxiety was reported at a rate of 2% of 861 sertraline-treated patients and 1% of placebo-treated patients.

In the 3 placebo-controlled OCD studies, the overall incidence of anxiety was comparable in the sertraline (8% of 370) and the placebo (7% of 209) treatment groups. The rate of discontinuation for anxiety was low for sertraline (2% of 370) and not different from placebo-treated patients (1% of 209).

8.6.8.3 Rash and Possible Allergic Events

Skin rash may be associated with events suggestive of allergic phenomena and is mentioned in the WARNING section of the fluoxetine labelling. Since fluoxetine and sertraline are both members of the SSRI group of antidepressants, the adverse event rash was explored for sertraline in premarketing clinical trials for the indication depression as well as for the indication OCD.

The incidence rates of skin rash in controlled clinical trials was 2% (N=861) in sertraline-treated and 1% (N=853) in the placebo-treated group. The rate of discontinuation was low for sertraline (0.4%) and not significantly different from the placebo (0.2%) treatment group. The rate of reports of skin rash was 4% (N=370) and 2% (N=209) in the OCD placebo-controlled trials. In these trials, one patient (88N0170-2) a 32 YOF treated with 100mg of sertraline for 17 days discontinued prematurely because of reports of contact dermatitis on armpits, chest, abdomen and inguinal area. The CRF was examined and there were no events found suggestive of an allergic phenomenon. No placebo-treated patients discontinued.

Other adverse event terms searched for in this assessment of allergic reactions were: eosinophilia and urticaria. The incidence rates for these events were similar for sertraline and placebo.

8.6.8.4 Zimelidine Syndrome

A hypersensitivity reaction resembling influenza has been associated with the antidepressant zimelidine, serotonin reuptake blocker. The zimelidine syndrome has been characterized by a complex of symptoms that include fever, pain or stiffness in muscles or joints, headache, exanthema, and hepatic effects. The onset of symptoms occurs within 3 weeks of starting zimelidine treatment, and the occurrence was seen in at least 0.3% of treated patients.

There were no reports of clustering of these events in the OCD database.

8.6.8.5 Platelet Function

SSRIs are know to block serotonin reuptake in platelets as well as central neurons. As serotonin is involved in platelet aggregation, its depletion by these SSRIs may be associated with bleeding diatheses.

Treatment-emergent events that may have indicated a potential bleeding diathesis were examined in the placebo-controlled OCD studies. There were 5 cases of purpura out of 370 (1.3%) in sertraline-treated patients, 4 of which were reported as mild in severity and 1 moderate in severity. There were no reports of discontinuation due to purpura. There was no obvious dose response. No reports of purpura appeared in placebo-treated patients. The incidence of purpura in premarketing placebo-controlled studies in depression was 0.7% of 861 sertraline-treated compared to 0.4% placebo-treated patients.

Recently, Ottervanger etal (Am J Psychiatry 151:781,1994, letter) have reported on 2 cases of ecchymoses attributed to the intake of paroxetine. Additionally, there have been rare reports of altered platelet function in patients taking fluoxetine, and are described in the current package insert.

8.6.8.6 Extrapyramidal Side-Effects

There were no reports of extrapyramidal symptoms and akathisia either in the premarketing clinical trials or in the OCD clinical trials. However, as of November 6, 1993, a search of the FDA SRS revealed 23 reports in which the COSTART term akathisia was used, (sertraline was approved December 30, 1991). There were 10 reports of extrapyramidal syndrome during this reporting period including 4 reports of cogwheel rigidity. Published reports exist associating sertraline with akathisia (LaPorta, J Clin Psychopharmacol 13:219, 1993 and Settle, J Clin Psychiatry 54:321, 1993) and extrapyramidal symptoms (Shihabuddin and Rapport, Am J Psych 151:2881 1994). Sertraline may share with the other SSRIs the possibility of extrapyramidal symptoms. Enhanced serotonergic neurotransmission may have the net effect of altering dopaminergic neurotransmission, and as such, paralleling the dopaminergic blockade of neuroleptics and the development of akathisia. The serotonergic system has been called a modulator of motor activity (Jacobs, etal. Trends in Neuroscience

16:346,1993). Serotonin neurons in the brain stem not only coordinate autonomic and neuroendocrine output, but also influence motor-neuron activity.

Parkinsonian symptoms (tremor, rigidity and akathisia) have been reported in association with the use of paroxetine and fluoxetine, two marketed SSRIs. In fact, the cumulative number of spontaneous reports of these disorders in the U.K. in association with paroxetine has been reported to be higher than the number received from other SSRIs including reports of Parkinsonian-like symptoms in patients treated with sertraline.

8.6.8.7 "Serotonin Syndrome"

Symptoms involving the central nervous system, the gastrointestinal system, and the body as a whole have been reported primarily in some patients who have taken two or more drugs that impact upon the serotonergic system. Symptoms seen have included tremor, diarrhea, shivering, muscular rigidity, incoordination, tachycardia, agitation, diaphoresis, confusion, hyperflexia, hyperthermia, or, in extreme cases, death due to cardiovascular collapse (Sternbach, Am J Psychiatry 148:705, 1991). However, whether or not this entity can be separated from NMS or incorporated into it and catatonic disorders awaits judgement.

There have been reports that paroxetine (an SSRI) administration in close proximity to either fluoxetine, fluvoxamine or tryptophan has resulted in adverse events suggestive of the "serotonin syndrome". There have been reports of the serotonin syndrome associated with fluoxetine use. The "serotonin syndrome" has been reported in post-marketing reports in patients treated with sertraline, one involving an interaction of serotonin and phenelzine, a second involving a possible intersection between sertraline and haloperidol. The third case occurred in a 9 YOM following an accidental overdose of sertraline. This patient (MRF control no. R-65892) accidentally ingested one 50 mg tablet. There were no concomitant medications reported (patient was reported to have received his last dose of methylphenidate HCl, 9 days previously. One hour after ingestion of sertraline, patient developed chills and vomiting. In the ER, patient was described as agitated, tachycardic (pulse greater than 200 bpm) uncooperative and hyperthermic (42.2°C). In the PICU, he was shaking and had intense tonic shaking in all extremities. Laboratory values showed increased leukocytes, BUN, serum creatinine, LDG, CPK values (21, 285 u/L on day 2). The patient was treated with 4 doses of physostigmine. On day 4 of treatment, patient was reported as improved. Although this case was designated as the serotonin syndrome, the case, more closely, displays characteristics of the hypodopaminergic, hyperexia syndrome (the neuroleptic malignant syndrome). Other reports of NMS in association with sertraline and SSRIs have been received.

8.7 Summary of Other Serious Adverse Events Considered Unlikely to be Drug Related

In clinical trials, serious events may occur incidentally. Appendix 8.7.1 lists such events with the exclusion of those discussed previously and which, in my judgement, are both serious and unlikely to be related to sertraline-treatment.

Appendix 8.7.2 provides a similar listing for serious adverse events considered unlikely to be treatment-related in patients receiving placebo.

8.8 Summary of Drug Interactions

8.8.1 Drug-Demographics Interactions

The sertraline geriatric (≥65YOA) OCD database included fewer than 20 patients and does not provide sufficient data to draw conclusions in the elderly without reference to the much larger non-OCD patient database of sertraline-treated patients.

In the premarketing clinical trials for depression the sertraline adverse event profile appeared to be comparable for the elderly and normal age adults.

8.8.2 Drug-Disease Interactions

Drug-disease interactions were not specifically addressed in this NDA. Caution is advisable in using sertraline in patients with diseases or conditions that could effect metabolism.

8.8.3 Drug-Drug Interactions

Drug-drug interactions were not specifically addressed in this NDA.

Sertraline and its metabolite, desmethylsertraline, are inhibitors of the isoenzyme CYP4502D6 albeit to a lesser extent than fluoxetine and its metabolite norfluoxetine (Preskorn etal J Clin Psychopharmacol 14:90,1994). Therefore, sertraline, like the SSRIs, has the potential for causing pharmacokinetic interactions with other drugs metabolized by the same enzyme, such as TCAs. Despite an in vitro action of sertraline against CYP4502D6, Preskorn and colleagues (J Clin Psychopharmacol 14:90, 1994) found limited clinical effects of sertraline on circulating levels of the TCA desipramine in human subjects. However, recently published case reports describe potentially clinically significant interactions between the two drugs. (Lyniard et al., Am J Psychiatry 150: 1125,1993 and Barros and Asnis, Am J Psychiatry 150:1751,1993).

9.0 Labeling Review

Some revisions to the sponsor's draft labeling for OCD, which was submitted on February 14, 1995 may be desirable.

In an effort to maintain consistency of labeling among the SSRIs, the package insert for Prozac® (fluoxetine) was examined. Of the marketed SSRIs in the United States, fluoxetine was selected because it has been approved for the treatment of depression and OCD, and this is reflected in the labeling for fluoxetine (March 14, 1994).

Under the **DESCRIPTION** of the proposed package insert for sertraline, the second sentence reads as follows, "It is also an orally administered treatment for Obsessive Compulsive Disorder (OCD)". Although the placement of this statement here under the DESCRIPTION section appears to be appropriate, a similar sentence is not found in the fluoxetine labeling in the **DESCRIPTION** section.

In the **CONTRAINDICATIONS** section of the labeling, presently the wording is "unknown". Pfizer was requested in a letter stamped December 5, 1994 to insert the following sentence, "Concomitant use in patients taking monoamine oxidase inhibitors (MAOIS) is contraindicated (see **WARNINGS**)."

Pfizer was requested in a letter to them stamped December 5, 1994 to revise the paragraph under **WARNINGS** to include that deaths have been reported with concomitant use of Zoloft® and monoamine oxidase inhibitors.

Under the **PRECAUTIONS** section of the present labeling, under the subsection seizure, presently reads as follows, "Zoloft® has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical trials during the product's pre-marketed testing. Accordingly, like other antidepressants, Zoloft® should be introduced with care in epileptic patients". This section should be changed to reflect the fact that seizures have now been reported in sertraline-treated patients. It may read as follows " In the course of pre-marketing development of sertraline, there were no reports of seizures among more than 3000 evaluated patients. In completed and ongoing or not yet submitted clinical trials for OCD, seizures were reported in 0.3% (4/1287) of sertraline-treated patients.

In the same precautions section, the subsection, **Suicide** , I note that in the Prozac® labeling, a second paragraph is added to the suicide section which reads as follows, "Because of well-established comorbidity between OCD and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD." This sentence is not incorporated in the Zoloft® proposed labeling, and for consistency in labeling probably should be.

Under **PRECAUTIONS**, Drug Interactions section: it was requested of Pfizer (12/5/94) to add a monoamine oxidase inhibitors subsection which should read as follows: "**Monoamine Oxidase Inhibitors**". See "**Contraindications**" and "**Warnings**".

Under the **Adverse Reactions** section of the sertraline labeling, a section has to be added which enumerates the adverse events that occurred in the OCD studies. It would seem, at this point, that combining the treatment-emergent adverse experience incidence in the placebo-controlled depression studies with the placebo-controlled clinical trials for OCD in one table would be appropriate.

Under **DOSE AND ADMINISTRATION** Pfizer was requested (December 5, 1994) to add the following subsection: "Switching patients to or from a monoamine oxidase inhibitor at least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Zoloft®. In addition, at least 14 days should be allowed after stopping Zoloft® before starting an MAOI (see "**CONTRAINDICATIONS**" and "**WARNINGS**").

10.0 Conclusions

The sponsor has provided data demonstrating that sertraline (Zoloft®) is reasonably safe when used as recommended for the treatment of OCD.

11.0 Recommendations

My review revealed no safety concerns that would prohibit approval of sertraline for the indication OCD.

James T. Knudsen 5/6/95

James F. Knudsen, M.D., Ph.D.
Psychiatric Clinical Reviewer,
Division of Neuropharmacological Drug Products
Office of Drug Evaluation and Research
Center for Drug Evaluation and Research

6-14-95
I agree that there are no safety concerns that would preclude the approval of sertraline for OCD. See my review & the file for a more detailed discussion of the safety & efficacy issues.
Thomas P. Laughren, MD
TL, FDA

cc: Original NDA 19-839
Div. File HFD-120/
/CSO/PDavid/
/JFKnudsen/
/TLaughren/

Appendicies

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Appendix 5.1 Table of Sertraline OCD Studies
Includes all studies completed or with active patients as of 6/30/94

Placebo-Controlled Studies

Protocol 371/372	DB, parallel group, 11 center, 12 week fixed-dose trial, sertraline v. placebo, outpatients, OCD (n=approx. 80 in each of four treatment groups); Sertraline 50, 100, 200 mg qd and placebo responders could continue double-blind therapy for an additional 40 weeks.
Protocol 237/248	DB, parallel group, 6 center, 8 week (plus 2 weeks down titration), flexible dose trial, sertraline v. placebo, outpatients, OCD (n = 43 or 44 patients in each of two treatment groups); sertraline 50-200 mg qd.
Protocol 546	DB, parallel group, 10 center, 12 week, flexible dose trial, sertraline v. placebo, outpatients, OCD (n = approx. 80 in each of two treatment groups); sertraline 50-200 mg qd.
Protocol 495	DB, parallel group, 17 center, 16 week (plus 2 weeks down titration), flexible dose trial, sertraline v. clomipramine v. placebo, outpatients, OCD (n = approx. 80 in each of three treatment groups); sertraline 50-200 mg qd, clomipramine 25-250 mg bid.
Protocol 498	DB, parallel group, 12 center, 12 week, flexible dose trial, sertraline v. placebo, outpatients 6-17 years of age, OCD (n = approx. 80 in each of two treatment groups); sertraline 25-200 mg qd for age 6-12 years, sertraline 50-200 mg qd for age 13-17 years.
Protocol 336	DB, parallel group, 27 center, 12 week, flexible dose trial, sertraline v. placebo, outpatients, OCD (n = approx. 80 in each of two treatment groups); sertraline 50-200 mg qd; conducted in UK, Ireland, Australia, New Zealand.
Protocol 615	SB to DB, parallel group, 21 center, 80 week, flexible dose trial, outpatients, OCD (n = approx. 600); 52 weeks SB sertraline; responders randomized to 28 weeks DB sertraline v. placebo; sertraline 50-200 mg qd.
Protocol 601	DB, parallel group, 42 center, 8 week, flexible dose trial, sertraline 25-100 mg v. sertraline 50-200 mg v. placebo, outpatient and inpatient, OCD (n = approx. 40 in each of three treatment groups); sertraline 25-100 mg qd, sertraline 50-200 mg qd; conducted in Japan.

Table 5.1 (cont.)
Uncontrolled Studies

Protocol 494	Open, 11 center, 52 week, flexible dose trial, outpatients, OCD (n=59); responders who completed 52 weeks of Protocol 371/372; sertraline 50-200 mg qd.
Protocol 525	Open, parallel group, 6 center, 5 week, fixed dose trial, sertraline 25-200 mg v. sertraline 50-200 mg, outpatient and inpatient, 6-17 years of age, OCD or major depression (n = approx. 14 patients in each of four treatment groups); single initial 50 mg sertraline dose for all patients; four treatment groups: age 6-12 and sertraline 25-200 mg qd, age 6-12 and sertraline 50-200 mg qd, age 13-17 and sertraline 25-200 mg qd, age 13-17 and sertraline 50-200 mg qd.
Protocol 550	Open, 6 center, 24 week, flexible dose trial, outpatients 6-17 years of age, OCD or major depression (n = 43); patients who completed Protocol 525; sertraline 50-200 mg qd.
Protocol 536	Open, 12 center, 52 week, flexible dose trial, outpatients 6-17 years of age, OCD (n = 132); patients who completed Protocol 498; sertraline 25-200 mg qd for age 6-12 years, sertraline 50-200 mg qd for age 13-17 years.
Protocol 533	SB, 1 center, 12 week, flexible dose trial, outpatients, OCD (n = 6); positron emission tomography study; sertraline 50-200 mg qd.
Protocol 004	Open, 24 center, 8 week, flexible dose trial, outpatient and inpatient, OCD (n = 36); sertraline 25-200 mg qd; conducted in Japan.
Protocol 602	Open, 20 center, 26 week, flexible dose trial, outpatient and inpatient, OCD (n = approx. 20); sertraline 25-200 mg qd; conducted in Japan.

Table 5.1 (cont.)
Active-Controlled Studies

Protocol 007	DB, parallel group, 19 center, 16 week (plus 2 weeks down titration), flexible dose trial, sertraline v. clomipramine, outpatients, OCD (n = approx. 80 in each of two treatment groups); sertraline 50-200 mg qd, clomipramine 50-200 mg qd; conducted in France.
Protocol 234	DB, parallel group, 16 center, 12 week (plus 1 week down titration), flexible dose trial, sertraline v. desipramine, outpatients, OCD with major depression (n = approx. 80 in each of two treatment groups); sertraline 50-200 mg qd, desipramine 50-300 mg qd.
Protocol 241	DB, parallel group, 16 center, 20 week (plus 1 week down titration), flexible dose trial, sertraline v. desipramine, outpatients, OCD with major depression (n = up to approx. 80 in each of two treatment groups); DB continuation for responders from Protocol 234; sertraline 50-200 mg qd, desipramine 50-300 mg qd.
Protocol 643	DB, parallel group, 21 center, 12 week, fixed and flexible dose trial, sertraline 200 mg v. sertraline 250-400 mg, outpatients, OCD (n = approx. 80 patients in each of two treatment groups); nonresponders from Protocol 615 who tolerate 200 mg; sertraline 200 mg qd, sertraline 250-400 mg qd.

Appendix 5.1.2

Sertraline OCD Patients Who Have Completed or Discontinued Treatment in Ongoing or Not-Yet-Submitted Completed Studies As of 10/10/94

Numbers Are Approximate
Sertraline-Treated Patients Counted One Time Only

	Total	Unblinded	Blinded
In Completed U.S. Studies	172	77	95
In Ongoing U.S. Studies	214	144	70
In All U.S. Studies	386	221	165
In International Studies	191	36	155
In All Studies*	577	257	320

*Status of 100 planned patients in 2 Japanese protocols not included.

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Appendix Table 5.2.2

Adverse Events Resulting in Death in Sertraline Non-Clinical Study Cases Entered Into Early Alert Safety Database, December 30, 1991 to October 30, 1994.

Adverse Event(s)	# of Cases	Case Number(s)
Accidental Multiple Drug Overdose	2	9306529 9401798
Acute Myocardial Infarction	1	9202801
Agitation, Confusion, Paranoia	1	R-26C1192
Aggressive Reaction, Hypomania	1	9390142[1]
Asphyxiation Following Industrial Accident	1	9400119
Aspiration of Vomitus	1	9401121
Cardiac Arrest	3	R-6G892 9385015 9400907
Cardiac Failure/Congestive Heart Failure	3	9404140 9405188 9405189
Cerebrovascular Accident, Coma, Convulsions	1	9400927
Convulsions, Lethargy, Twitching, Visual Disturbance, Voice Alteration	1	9400978[2]
Disseminated Intravascular Coagulation	1	R-2D992
Drug Interaction with Phenelzine ("Serotonin Syndrome")	1	9402481
Possible Drug Interaction with Digoxin	1	9304833
Possible Drug Interaction with Pre-ECT Anesthesia	1	R-20C692
Erythema Multiforme, Perforated Duodenal Ulcer	1	9401559
Esophageal Ulceration, Gastrointestinal Hemorrhage, SIADH	1	9406907
Hepatic Adenocarcinoma	1	R-30992

Appendix Table 5.2.2

Adverse Events Resulting in Death in Sertraline Non-Clinical Study Cases Entered Into Early Alert Safety Database, December 30, 1991 to October 30, 1994. (Continued).

Adverse Event(s)	# of Cases	Case Number(s)
Hepatic Failure	1	9305666
Hepatic Necrosis	1	9404623
Hepatitis, Pleural Effusion	1	9300254
Hyperglycemia, Renal Failure	1	9200056
Hyperkalemia Followed by Aspiration Pneumonia	1	9402126
Hypovolemic Shock Following Possible Interaction with Warfarin	1	9401631
Ischemic Heart Disease	1	9408684
Multiple Sclerosis, Increased Liver Function Tests	1	9385120
Neuroleptic Malignant Syndrome	2	R-7E1192 9385118
Pancytopenia, Sepsis	1	9300916
Pneumonia	3	R-23B1092 9403146 9408326
Pulmonary Fibrosis	1	R-43B892
Renal Necrosis, Intra-abdominal Hemorrhage, Acute Pancreatitis, Systemic Atherosclerosis, Hypertension	1	9402567[3]
Shock, Gastrointestinal Disorder	1	9306585
Sudden Cardiac Death	4	9390574 9403852 9404859 9405187[3]
Suicide by Carbon Monoxide Poisoning	2	R-5S892 9305738

Appendix Table 5.2.2

Adverse Events Resulting in Death in Sertraline Non-Clinical Study Cases Entered Into Early Alert Safety Database, December 30, 1991 to October 30, 1994. (Continued).

Adverse Event(s)	# of Cases	Case Number(s)
Suicide by Drowning	2	R-1L1092 R-14K692
Suicide by Gunshot Wound	9	9400846* R-16D1192 R-5G792 R-7C592 9300152 9300595 9303110 9303714 9305809
Suicide by Hanging	5	R-12P492 R-2L1092A R-30S1092 9201388 9302235
Suicide by Intentional Benztropine Overdose	1	R-8R792
Suicide by Intentional Multiple Drug Overdose (Other Than Sertraline)	3	9201438 9401300 9405018
Suicide by Intentional Multiple Drug Overdose (Including Sertraline)	6	9408517 9401797 9390627 R-9L992 R-6T692 R-12L1192
Suicide by Intentional Drug Overdose (Sertraline Only)	3	R-2D592 9305306 9405026
Suicide by Suffocation	1	R-2L1092B

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Appendix Table 5.2.2

Adverse Events Resulting in Death in Sertraline Non-Clinical Study Cases Entered Into Early Alert Safety Database, December 30, 1991 to October 30, 1994. (Continued).

Adverse Event(s)	# of Cases	Case Number(s)
Suicide, Method Unknown	5	9401233 R-11T792 9391072 9402584 9407840
Death	12	R-1F392 R-8K992 R-8P1292 9201997 9300681 9300766 9301672 9306238 9306549 9306772 9407402 9408239

*1 - The patient murdered an uncle, and was killed by another uncle in self defense.
*2 - Death due to advanced HIV-related disease.
*3 - The patient's death was attributed to these causes five days after ingesting intentional overdose of 20 x 50 mg of sertraline. The death was reported as not related to the overdose.
*4 - The patient also ingested an intentional overdose of sertraline, lorazepam, and clonazepam.

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Appendix Table 5.2.2
Itemized Causes of Death in Sertraline Clinical Study Cases Entered Into Early Alert Safety Database, December 30, 1991 to October 30, 1994.

Cause of Death	# of Cases	Case Number(s)
Acute Myocardial Infarction	6	9200378 9304430 9405452 9200727 9201046 9404954
Acute Myocardial Infarction, Cardiac Arrhythmia, Hypoglycemic Shock	1	9306539
Bronchial Asthma, Chronic Obstructive Pulmonary Disease, Heart Failure, Renal Failure	1	9407361
Bronchial Pneumonia, Emphysema, Pulmonary Fibrosis	1	9385004
Bronchopneumonia/Pneumonia	6	9403196 9304039 9200482 9202503 9385134 9391061
Bronchopneumonia, Congestive Heart Failure	1	9406947
Bronchopneumonia, Renal Failure	1	9385071
Cardiac Arrest	1	RUS6211
Cardiac Failure/Congestive Heart Failure	5	9390461 9200487 9385005 9404068 9402972
Cerebrovascular Accident (Including Brainstem Hemorrhage)	3	9406748 9391065 9402940
Coronary Atheroma/Acute Myocardial Ischemia	2	9303776* 9304153
Coronary Atheroma, Acute Myocardial Ischemia, Hypothyroidism	1	9385152

Appendix Table 5.2.2

Itemized Causes of Death in Sertraline Clinical Study Cases Entered Early Alert Safety Database, December 30, 1991 to October 30, 1994. (Continued).

Cause of Death	# of Cases	Case Number(s)
Crohn's Disease	1	9200997
Deep Venous Thrombosis/Pulmonary Embolus	2	9200442 9300804
Fibrosing Alveolitis	1	9400494
Glioblastoma	1	RUS6275
Lung Carcinoma	1	9306562
Renal Failure	2	9407875 9201792
Respiratory Failure, Septic Embolus	1	RUS6884
Shock, Penetrating Gastric Ulcer, Metastatic Bronchial Carcinoma	1	9300358
Starvation	1	9403738
Suicide by Carbon Monoxide Poisoning/Gas/Automobile Exhaust	3	R-1B392 9303669 9402208
Suicide by Gunshot Wound	2	9200244 9303943
Suicide by Hanging	3	RF263B RD245B 9303304
Suicide by Intentional Dextroproxyphene and Acetaminophen Overdose	1	9201126
Suicide by Throwing Self Under Train	1	9200138
Suicide, Method Unknown	1	9202298
Cause of Death Unknown	2	9201572 9406672

* - Non-Pfizer sponsored study case.

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Appendix Table 8.5.1.1

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials*

Adverse Experience	(Percent of Patients Reporting) ZOLOFT (N=861)	Placebo (N=853)
Autonomic Nervous System Disorders		
Mouth Dry	18.3	9.3
Sweating Increased	6.4	2.9
Cardiovascular		
Palpitations	3.5	1.6
Chest Pain	1.0	1.6
Centr. & Periph. Nerv. System Disorders		
Headache	20.5	19.0
Dizziness	11.7	6.7
Tremor	10.7	2.7
Paresthesia	2.0	1.8
Hypoesthesia	1.7	0.6
Twitching	1.4	0.1
Hypertonia	1.3	0.4
Disorders of Skin and Appendages		
Rash	2.1	1.5
Gastrointestinal Disorders		
Nausea	26.1	11.8
Diarrhea/Loose Stools	17.7	9.3
Constipation	8.4	6.3
Dyspepsia	6.0	2.8
Vomiting	3.8	1.8
Flatulence	3.3	2.5
Anorexia	2.8	1.6
Abdominal Pain	2.4	2.2
Appetite Increased	1.3	0.9
General		
Fatigue	10.6	8.1
Hot Flushes	2.2	0.5
Fever	1.6	0.6
Back Pain	1.5	0.9
Metabolic and Nutritional Disorders		
Thirst	1.4	0.9
Musculoskeletal System Disorders		
Myalgia	1.7	1.5
Psychiatric Disorders		
Insomnia	16.4	8.8
Sexual Dysfunction – Male (1)	15.5	2.2
Somnolence	13.4	5.9
Agitation	5.6	4.0
Nervousness	3.4	1.9
Anxiety	2.6	1.3
Yawning	1.9	0.2
Sexual Dysfunction – Female (2)	1.7	0.2
Concentration Impaired	1.3	0.5
Reproductive		
Menstrual Disorder (2)	1.0	0.5
Respiratory System Disorders		
Rhinitis	2.0	1.5
Pharyngitis	1.2	0.9
Special Senses		
Vision Abnormal	4.2	2.1
Tinnitus	1.4	1.1
Taste Perversion	1.2	0.7
Urinary System Disorders		
Micturition Frequency	2.0	1.2
Micturition Disorder	1.4	0.5

*Events reported by at least 1% of patients treated with ZOLOFT are included.

(1) – Primarily ejaculatory delay; % based on male patients only: 271 ZOLOFT and 271 placebo patients.

(2) – % based on female patients only: 590 ZOLOFT and 582 placebo patients.

Appendix 8.5.2.1.1

Criteria for Identifying Patients as Having Potentially Clinically Significant Changes in Blood Chemistry Analytes		
Analytes	**Criterion Values**	
	High	**Low**
BUN	>=30 mg/dl	—
Creatinine	>=2 mg/dl	—
Total Bilirubin	>=2 mg/dl	—
Alkaline Phosphatase	3 X ULN (U/L)	—
SGOT and SGPT	3 X ULN (U/L)	—
Total Protein	—	<=4.5 g/dl
Albumin	—	<=3.5 g/dl
Cholesterol	>=330	—
Triglycerides	>=340	—
Glucose (Fasting)	>=140 mg/dl	45 mg/dl
Uric Acid (Males)	>=10.5 mg/dl	—
Uric Acid (Females)	>=8.5 mg/dl	—

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Appendix 8.5.2.1.3
Proportion of Sertraline-Treated Patients Having Potentially Clinically Significant Changes in Serum Chemistry Analytes Placebo-Controlled OCD Studies*

	Sertraline			Placebo		
Blood Chemistry Analytes	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Albumin	361	13	3.6	203	10	4.9
Alk. P'tase	361	0	0.0	203	0	0.0
BUN	361	1	0.3	203	1	0.5
Cholesterol	361	11	3.1	203	2	1.0
Creatinine-High	361	0	0.0	203	0	0.0
Globulin	--	--	--	--	--	--
Glucose-Low	--	--	--	--	--	--
Glucose-High	361	14	3.9	203	5	2.5
LDH	275	0	0.0	127	0	0.0
SGOT High	361	2	0.6	203	2	1.0
SGPT-High	361	4	1.1	203	0	0.0
Total Bilirubin-High	361	1	0.3	203	3	1.5
Total Protein	361	0	0.0	203	0	0.0
Triglycerides	--	--	--	--	--	--
Uric Acid	361	1	0.3	203	2	1.0

Patients were required to have at least one on-treatment value.
* Pooled data from Protocols 237/248, 371/372, and 546. Table supplied by sponsor.

Appendix 8.5.2.2.1

Potentially Clinically Significant Changes in Hematology analytes		
Hematology Analytes	**High**	**Low**
Hemoglobin (Males)	18.5 g/dl	=<11.5 g/dl
Hemoglobin (Females)	16.5 g/dl	=<9.5 g/dl
Hematocrit (Males)	55%	37%
Hematocrit (Females)	50%	32%
White Blood Cells	>=16 X 10^3/mm^3	<=2.8 X 10^3/mm^3
Neutrophils	---	<=15%
Eosinophils	>=10%	---
Platelets	700 X 10^3/mm^3	75 X 10^3/mm^3

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Appendix 8.5.2.2.2
Proportion of Sertraline-Treated Patients
Having Potentially Clinically Significant Changes
in Hematology Analytes
Placebo-Controlled OCD Studies*

	Sertraline			Placebo		
Hematology Analytes	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Hemoglobin-Low	359	0	0.0	203	1	0.5
Hematocrit-Low	359	11	3.1	203	5	2.5
WBC-Low	359	2	0.6	203	1	0.5
WBC-High	359	0	0.0	203	0	0.0
Eosinophils-High	359	3	0.8	203	5	2.5
Platelet Ct-Low	359	1	0.3	203	1	0.5
Platelet Ct-High	359	0	0.0	203	0	0.0

Patients were required to have at least one on-treatment value.
* Pooled data from Protocols 237/248, 371/372, and 546. Table supplied by sponsor.

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Appendix 8.5.2.3.1
Proportion of Sertraline-Treated Patients Having Potentially Clinically Significant Changes in Urinalysis Analytes Placebo-Controlled OCD Studies*

	Sertraline			Placebo		
Urinalysis Analytes	Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Protein-High	357	6	1.7	203	3	1.5
Glucose-High	358	0	0.0	203	1	0.5

Patients were required to have at least one on-treatment value.
* Pooled data from Protocols 237/248, 371/372, and 546. Table supplied by sponsor.

Appendix 8.5.3.1

Criteria for Identifying Patterns as Having Potentially Clinically Significant Changes in Vital Signs Variables

Vital Signs

	Criterion Values	
Variables	**High**	**Low**
Systolic Blood Pressure	180 mmHg	90 mmHg
Diastolic Blood Pressure	105 mmHg	50 mmHg
Pulse Rate	120 bts/min	50 bts/min
Temperature	101 °F	96 °F

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Appendix 8.5.3.3
Proportion of Sertraline-Treated Patients Having Potentially Clinically Significant Changes in Vital Signs Variables Placebo-Controlled OCD Studies*

Vital Signs Variables		Sertraline			Placebo		
		Total Patients	Abnormal #	%	Total Patients	Abnormal #	%
Weight	Decr. of ≥ 7%	365	21	(5.8)	207	5	(2.4)
	Incr. of ≥ 7%	365	35	(9.6)	207	2	(1.0)
Supine Systolic BP (mmHg)	Decr. of ≥ 20 & ≤ 90	365	10	(2.7)	207	6	(2.9)
	Incr. of ≥ 20 & ≥ 180	365	1	(0.3)	207	1	(0.5)
Supine Diastolic BP (mmHg)	Decr. of ≥ 15 & ≤ 50	365	5	(1.4)	207	5	(2.4)
	Incr. of ≥ 15 & ≥ 105	365	4	(1.1)	207	1	(0.5)
Supine Pulse (bpm)	Decr. of ≥ 15 & ≤ 50	365	6	(1.6)	207	2	(1.0)
	Incr. of ≥ 15 & ≥ 120	365	2	(0.6)	207	1	(0.5)

Patients were required to have a baseline and at least one on treatment value.
* Pooled data from Protocols 237/248, 371/372, and 546. Table supplied by sponsor.

Appendix 8.7.1
Summary of Serious Adverse Events Occurring in Sertraline-Treated Patients and Considered Unlikely to be Sertraline-Related

Study/Patient Number	Age (yrs)	Sex	Mean Dose (mg/d)	Duration (days)	Adverse Event
BODY AS A WHOLE					
88-N-0177/13	65	F	100	68	Surgical procedure/closed reduction of a fractured ankle
88-N-0171/28	21	M	100	31	Hospitalized for workup of calf pain, h/o thrombosis, patient discontinued.
GASTROINTESTINAL DISORDERS					
88-N-0171/12	71	F	50	92	Lower GI bleeding. No active site found. She recovered. She discontinued.
PSYCHIATRIC DISORDERS					
88-N-0173	21	F	200	61	Homicidal threat to boyfriend. Patient hospitalized for short-term crisis intervention. Patient discontinued.

Appendix 8.7.2
Summary of Serious Adverse Events Occurring in Placebo-Treated Patients and Considered Unlikely to be Placebo-Related

Study/Patient Number	Age (yrs)	Sex	Experience/Outcome
BODY AS A WHOLE			
91-N-0055/190	53	F	Surgical procedure done. Lumpectomy upon completion of study.
88-N-0172/8	[illegible]	M	Hernio[illegible]phy, continued in the study.
88-N-0176/24	20	M	Hospitalized after 13 days because of worsening OCD. He discontinued from study.
Gastrointestinal			
88-N-0179/41	36	M	Abdominal pain, ↓ HCT. Recovered , continued study.

STATISTICAL REVIEW OF NDA 19-839
ROBERT M. HAMER, PH.D.

INTRODUCTION

Sertraline Hydrochloride (*Zoloft, Pfizer*) is an established, approved antidepressant, unrelated to tricyclic, tetracyclic, or most other approved antidepressant agents. It is a potent selective serotonin reuptake inhibitor (SSRI), and that is presumed to be related to its method of action.

The sponsor has submitted a supplement to NDA (19-839) to gain approval for sertraline for an indication for Obsessive-Compulsive Disorder. This NDA supplement contains the results of two clinical trials, run from two protocols, a third trial run from a third protocol, and an extension of one of the original trials. It also contained several small clinical trials which will not be discussed.

Although studies 371 and 372 were designed as two trials to be run under a common protocol, difficulty in obtaining a sufficient number of subjects for two trials led the sponsor to combine the two studies into one, to be referred to here as "Protocol 371/372." Similarly, although studies 237 and 248 were designed as two trials to be run under a common protocol, difficulty in obtaining a sufficient number of subjects for two trials led the sponsor to combine the two studies into one, to be referred to here as "Protocol 237/248." Thus, the studies reviewed here include:

1. Protocol 237/248 – randomized, double blind, multicenter, parallel groups, flexible dose, placebo controlled
2. Protocol 371/372 (acute phase) – randomized, double blind, multicenter, parallel groups, three fixed doses, placebo controlled, 12 weeks
3. Protocol 546 – randomized, double blind, multicenter, parallel groups, flexible dose, placebo controlled
4. Protocol 371/372 (responder followup phase) – randomized, double blind, multicenter, parallel groups, three fixed doses, placebo controlled, 40 weeks responder followup

Protocol 237/248

STUDY DESCRIPTION

Protocol 237/248 was originally designed as two three center trials to operate under the same protocol. When the sponsor had difficulty obtaining sufficient subjects for the two trials, the sponsor decided to combine them into one trial with six centers. This was thus a randomized, double blind, multicenter, parallel groups, flexible dose, placebo controlled trial. The two parallel groups comprised a placebo group and a flexible dose sertraline group, with titration up to 200 mg per day. Forty-three subjects received sertraline and 44 received placebo. Table 1 contains the number of subjects at entry to washout, at randomization, and the number of evaluable subjects in each group.

SAMPLE SIZE AND POWER

I could find nothing about power calculations in the protocol. According to the protocol, the study was designed as two 60 patient trials, with 20 patients per each of three centers per trial. This would have led to two 60-subject trials. As stated earlier, due to difficulty obtaining subjects, the two trials were combined into one trial with six centers, for a total of 87 subjects.

STUDY PLAN

This trial consisted of a one-week single-blind lead-in phase followed by a ten-week active medication phase. Evaluations were done at day one of the lead-in phase (also called "screen"), at the end of the one-week lead-in (also called "baseline," or "week 0"), and at the end of weeks 1, 2, 4, 6, 8, and 10 on active medication or placebo. Since medication was downtitrated between weeks 8 and 10, the evaluation done at the end of week 8 was the final measure. During the final two weeks the subjects were titrated downward and then off the medication.

There were parallel two groups – placebo and a flexible sertraline group which could be titrated up to 200 mg active medication during the first two weeks. Random assignment to either placebo or sertraline took place at the end of the lead-in period. Sparing use of triazolam was allowed for sleep, and the use was recorded.

There was no mention in the protocol nor in the NDA of whether sufficient improvement during the washout lead-in period would exclude a subject from the trial. The protocol stated that subjects were required to have a Hamilton Depression Scale (24 item) score below 15, and a score of less than 2 on item 1 of the 24 item scale.

ASSESSMENT PLAN

Rating scale evaluations were done at day 1 of the lead-in, baseline (after one week on single-blind placebo) and the end of weeks 1, 2, 4, 6, 8 and 10 on active medication or placebo. Vital signs were gathered on the same schedule. Lab work and ECGs were gathered at day 1 of the lead-in, and at the end of weeks 2 and 10. Plasma samples were collected at day 1 of the lead-in, and the end of weeks 2, 6, and 8. A physical and opthalmologic examination were done at day 1 of the lead-in, and the end of week 10.

INSTRUMENTS

Efficacy instruments used included: the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total score, the NIMH Global Obsessive Compulsive Scale (NIMH-OC), the Clinical Global Impressions Severity score (CGI-S), the Clinical Global Impressions Improvement (CGI-I) score, the Maudsley Obsessive Compulsive Inventory (MOC), and the Hamilton Depression Rating Scale (HRS).

The Y-BOCS is a 14-item questionnaire, with 10 scorable items each scored on a 0-4 scale, giving a total score in the 0-40 range. This total score was the primary dependent variable used. Additionally, these 10 scorable items can be divided into two subgroups of 5 items each, each producing an Obsession subscore (0-20) and a Compulsion subscore (0-20). These two subscores will not be regarded as primary efficacy measures.

The NIMH-OC was a scale rated from 1-to-15, with scores of 1-to-3 indicating minimal pathology to scores of 13-to-15 indicating very severe obsessive and compulsive behavior.

The CGI-S scale is scored from 1 to 7, with 1 indicating no illness to 7 indicating extremely ill. The CGI-I scale is scored from 1 to 7, with 1 indicating very much improved and 7 indicating very much worse.

The MOC is a self-rating scale of 30 items, each of which the patient scores as true or false. Thus the score on the MOC ranges from 0 to 30, with 0 indicating no self-rated obsessive or compulsive behavior, and 30 indicating a maximal amount of such behavior.

The HRS is a 24-item rating scale, scored from 0 to 73, with scores of 16 or below generally indicating no or mild depression and scores at the high end indicating a high amount of depression.

INCLUSION AND EXCLUSION CRITERIA

Inclusion and exclusion criteria were unremarkable.

Inclusion criteria as per the protocol were outpatients of both sexes aged 18 or older with a DSM-III diagnosis of Obsessive-Compulsive Disorder without depression. Hamilton Depression Rating Scale (HRS) score below 15 was required and a score of less than 2 on item 1 of the HRS. (This level of depression is below that which would usually be required for entry into an an idepressant trial, but nonetheless might indicate significantly more depression than would nonpatients.) Item 1 is the depressed mood item, and a criterion of "below 2" corresponds to either absent (0) or elicited only on questioning (1). Other inclusion criterion were a complete medical and psychiatric history, a physical examination, normal or clinically insignificant laboratory values, and discontinuation of all other psychotropic medication before entry.

Exclusion criteria as per the protocol excluded pregnant or nursing women, women of childbearing potential not using appropriate birth control, Organic Mental Disorders or Organic Brain Syndrome. Also excluded were subjects with a primary DSM-III diagnosis of Bipolar Disorder, depressed, Atypical Bipolar Depression, depressed, or Major Depression, Schizophrenic Disorders, Paranoid Disorders, other psychotic disorders, various anxiety states including Panic Disorder, Phobic Disorders, Severe Generalized Anxiety States, or personality disorders severe enough to interfere with the patient's ability to participate. Further, subjects with a history of various schizophrenic and other psychotic disorders (including paranoid) were excluded, as were persons abusing drugs currently or within six months. Further exclusion criteria were a current or historic contraindications to antidepressants, SSRIs, benzodiazepines, as well as patients taking MAO inhibitors within two weeks or depot neuroleptics within 6 weeks, etc. The exclusion criteria were unremarkable.

The protocol did not state although the NDA did that sparing use of chloral hydrate and triazolam would be allowed during the study.

METHODOLOGIC CONSIDERATIONS

There were several methodologic choices made. First, they chose to use improvement or gain scores over baseline as the dependent variable. That is, for any dependent variable (except CGI-I), each subject's baseline score was subtracted from the scores at successive

intervals, and it was these difference scores which were analyzed when examining changes within groups or when comparing groups. This is but one of several choices the sponsor might have made. ANCOVA using the baseline as a covariate with the dependent variable being the scores at each point would have been a reasonable alternative, as would a repeated measures analysis using the baseline as the first level of the repeated factor and examining differences between it and later time points using appropriate contrasts.

I note that an ANCOVA model using gain scores as the dependent variable and baseline as the covariate produces exactly the same hypothesis test results on all effects except the covariate as would the same ANCOVA using the endpoint rather than gain score as the dependent variable.

The protocol section of the NDA results section stated that the endpoint was the week 8 visit. In the statistical methods portion, this section stated that for all variables except CGI-I (which has no meaningful baseline) they would use an ANOVA model with the dependent variable being change from baseline, and the independent variables being fixed effects for site, treatment, and the site-by-treatment interaction. For CGI-S since there was a significant baseline-response correlation, they chose to add baseline as a covariate to the analyses. They also stated that since there was no significant correlation between baseline and endpoint for the Y-BOCS, NIMH-OC, or MOC, they did not use baseline as a covariate. However, in volume 6, page 8 50, they showed these correlations as .43, .60, and .77, respectively, which were not insubstantial.

Another methodological choice they made was to treat center as a fixed effect. I have seen center treated as random, and as fixed, and I think there are reasonable arguments one might make in either case.

DEMOGRAPHIC COMPARABILITY

Table 2 contains demographic statistics for the two groups. The mean age of the 44 subjects who received placebo was 38.0, and of the 43 subjects who received sertraline was 36.5, with a comparable distribution in both groups. Most subjects in both groups were between 20 and 50 years of age. Both groups were largely male, with 88 percent males in the placebo group and 81 percent males in the sertraline group. Social class index distributions were comparable. Both groups were largely white, with the placebo group being 97 percent white, and the sertraline group being 100 percent white.

I do not consider it appropriate to do hypothesis tests on baseline distributions as there is usually a multiple comparison problem.

RESULTS

In the discussion of efficacy, I will concentrate on the Y-BOCS and the NIMH-OC, and mention the other variables. Results were largely consistent.

Baseline Comparability on Efficacy Variables

Table 3 contains baseline measurements for both groups on the major efficacy variables. I did not do any hypothesis tests on group differences as I believe they are inappropriate here. The groups appeared comparable.

Y-BOCS: LOCF and OC Analyses

Table 4 contains dropouts, broken down by week, for each of the two treatment groups. There were fewer dropouts over the course of the study in the sertraline group than the placebo group (6 vs 10). Table 5 contains the reasons for termination through week 8 (beginning of down-titration), and as is often the case, there were more dropouts (5 vs 1) in the placebo group for lack of effect.

Table 6 contains means and standard deviations for the Y-BOCS at baseline and for each of the time points to 10 weeks. We see a decline over time in the sertraline group, with a less steep decline in the placebo group.

Note that there was still substantial decline in the sertraline group after week 8, when the protocol said the taper was to begin. In the placebo group, however, after week 8 the scores increased slightly. (The sponsor said in the NDA that it appeared that most investigators didn't taper their subjects much until just before the week 10 measurements, meaning that there were substantial amounts of sertraline in the sertraline-group subjects through most of the week-8-to-week-10 period.)

Table 9 contains plots of the relations between baseline and endpoint measures for the Y-BOCS, and there appears to be a substantial linear relation between the two, indicating that baseline might be a reasonable covariate in analyses using the endpoint as the dependent variable.

The sponsor calculated a correlation for this relationship and allowed to influence whether to use baselines as a covariate in later analyses, but this correlation was calculated without respect to group membership. A better measure of linear relationship between baseline and endpoint uncontaminated by the design structure would have been a pooled within-groups-center correlation, which produces the same hypothesis test as the test on baseline when used as a covariate in the model.

Table 12 shows sample sizes by week. By week 8, 40 of 43 subjects (93 percent) remained in the sertraline group, while 37 of 44 (84 percent) remained in the placebo group. Recalling that 4 more subjects dropped out out of the placebo group for lack of effect than dropped of the sertraline group, these numbers were comparable and unremarkable. Few subjects dropped out for adverse effects.

The sponsor did not appear to do any weekly OC analyses. The sponser allowed the correlations or lack thereof between baseline and endpoint, uncorrected for group membership, to influence the model cited in the NDA. In general, the sponsor's models predicted the gain score from treatment (TG), investigator (GRANT), the treatment-by-investigator interaction, and depending on the above-mentioned correlation, baseline. (Since there is no baseline for CGI-Improvement) it was never used as a covariate.

Using such endpoint analyses, the sponsor found significant group differences at endpoint (LOCF) between placebo and sertraline. Table 13 contains a plot of group means over time for the Y-BOCS, and the results of an endpoint analysis, as well as the results of my data analysis.

I analyzed these data fitting a model predicting weekly OC scores from treatment (TG), investigator (GRANT), and using baseline as the covariate. I did not include a treatment-by-investigator interaction in the model.

Note that they sponsor fitted models with gain scores as the dependent variables,

but for the variables of interest (e.g., treatment effect), in an analysis of covariance with baseline as the covariate, the use of gain scores is really a disguised endpoint and does not influence hypothesis tests on these effects.

Using these weekly analyses, I found no differences between the treatments except at week 4 and week 10, and a significant ($p < 0.05$) difference between treatments at week 10. An endpoint analysis in the context of this model found a borderline p-value ($p < 0.056$) at endpoint (LOCF). These data are consistent with a drug with a rather long period of onset, especially at the doses used. Note that with respect to group means at each time point, after randomization the treatment group beat the placebo group for all weeks. For weeks 2 and beyond, sertraline beat placebo every week although only the week 4 and week 10 differences reached statistical significance. The small sample size used in this trial may have contributed to this result.

Y-BOCS means (Table 6) show that the sertraline group began at baseline with a mean of 23.4, declining to 17.5 by week 10, the placebo group began with a comparable mean of 22.6, declining only to 21.2 by week 10. In the sertraline group the decline continued past week 8, while in the placebo group the mean actually went up from week 8 to week 10.

NIMH-OC: LOCF and OC Analyses

Table 7 contains similar means and standard deviations on the NIMH-OC variable, for both groups, over time. We see a decline over time in the sertraline group and a less steep decline in the placebo group. Note that there was still stubstantial decline in the sertraline group after week 8, when the protocol said the taper was to begin. In the placebo group, however, after week 8 the scores increased slightly. (The sponsor said in the NDA that it appeared that most investigators didn't taper their subjects much until just before the week 10 measurements, meaning that there were substantial amounts of sertraline in the sertraline-group subjects through most of the week-8-to-week-10 period.

Table 10 contains a plot of the baseline vs endpoint for the NIMH-OC variable. Although we see what appears to be an attenuation in this relationship due to a probable floor effect at baseline (subjects did not enter the study unless scores were above a minimum amount), there appears to be a relationship, indicating that baseline might be a useful covariate.

As with the Y-BOCS, the sponsor calculated a correlation between baseline and endpoint and allowed this correlation to determine whether to include baseline as a covariate. However, the correlation was calculated without respect to group membership, and hence was contaminated by group differences. A better measure of linear relationship between baseline and endpoint uncontaminated by this design structure would have been a pooled within-groups-center correlation, which would produce the same hypothesis test as the test on the covariate in the model I used.

For the NIMH-OC, as with the Y-BOCS, the sponsor appeared to do only an endpoint analysis, and no weekly OC analyses. Table 14 contains a plot of both groups, over time, with weekly OC hypothesis tests and an endpoint LOCF analysis. I did the weekly analyses.

Fitting the same model for the NIMH-OC produced a similar picture (Table 14). After randomization, sertraline beat placebo for all weeks, with significance appearing at week 6 and week 10, and an endpoint (LOCF) analysis showing a significant treatment effect

($p < 0.036$).

Table 7 contains the weekly means and standard deviations for the NIMH-OC. While the sertraline group declined from a baseline of 9.8 to a week 10 score of 7.7, the placebo group declined only from a baseline of 9.3 to a week 10 score of 8.6. As with the Y-BOCS, the placebo group actually showed a slight increase from week 8 to week 10, while the sertraline group continued declining during that period. It may be that the small sample size contributed to the lack of significance.

CGI-Severity: LOCF and OC Analyses

The CGI-Severity was administered on the same schedule as were the Y-BOCS and NIMH-OC. Table 8 contains means and standard deviations for both groups, over time, and a pattern similar to that seen with the previously examined variables emerges. There is a decline in both groups, with more of a decline in the sertraline group. In fact, although the decline in CGI-S continued between weeks 8 and 10 in the sertraline group, the score in the placebo group increased during the same period.

Table 11 contains a plot of baseline vs endpoint for CGI-Severity. There appears to be a substantial linear relationship indicating that baseline CGI-Severity might be a reasonable covariate when examining endpoint.

As with the previous variables, the sponsor calculated the correlation between baseline and endpoint, and allowed it to influence the decision as to whether to include baseline as a covariate. As before, a better measure of the linear relationship uncontaminated by the design structure would have been a pooled within-groups-center correlation.

As before, the sponsor did only a endpoint analysis, and I did both LOCF endpoint analyses and weekly OC analyses (table 15). The only weekly analysis to show significant differences between the groups was at week 10, and the endpoint (LOCF) analysis showed a marginal sertraline effect ($p < 0.055$). Sertraline beat placebo, although not statistically significantly different, for all weeks past week 1, with the actual magnitude of the differences between the group means increasing over time.

Table 8 presents means and standard deviations for the CGI-Severity. The pattern here was similar to that shown for the Y-BOCS and NIMH-OC. Both groups showed a decline over time; the sertraline group declined more, and the sertraline group continued the decline from week 8 to week 10 while the placebo group did not. The sponsor did not present a table for the MOC, but weekly analyses showed no significant group differences at any week.

Remarks

I also tested the treatment-by-investigator interaction in the context of a model with endpoint as the dependent variable, covarying baseline for the Y-BOCS, NIMH-OC, and CGI-Severity. There was no significant investigator-by-treatment interaction. Table 19 contains a series of box plots of scores on the Y-BOCS for the six investigators in this study, broken down by treatment. Table 20 contains the same series of box plots for scores on the NIMH-OC, and Table 21 contains the same series of boxplots for the CGI-Severity. These tables reflects the lack of investigator-by-treatment interaction.

Results for the CGI-Improvement were similar to those for the other dependent variables.

I examined residuals from the above analyses, and from the distributions of the resid-

uals, there does not appear to be evidence of violation of the normality assumptions on the error terms in the models.

Although the plots of group means over time appear to show that sertraline beats placebo, differences between group means were inconsistent among the various time points, with significance appearing somewhat early in the study and frequently disappearing towards week 8. It would be difficult to characterize these results as positive, and at best we might call them supportive. Calling it a failed study may be more accurate.

I performed a post-hoc power analysis on their data, and using their variance estimates and other estimates as if they were the appropriate population parameters, I found the the actual power to detect a difference between the least squares means (in the endpoint) analysis as great or greater than the difference they observed, with the sample size they used, was less than 0.5.

Protocol 371/372 (acute phase)

STUDY DESCRIPTION

Protocol 371/372 was originally designed as two five-center trials to be run under identical protocols, but difficulty in obtaining sufficient numbers of subjects led the sponsor to obtain an additional center, and combine the 11 centers into one trial. This was a randomized, double blind, multicenter, parallel groups, fixed-dose, placebo-controlled trial. There were four parallel groups, consisting of one placebo group, and three sertraline groups, at three fixed doses: 50 mg, 100 mg, and 200 mg sertraline per day. Study medication was administered once per day, and titrated to the assigned dose during the first two weeks of the trial. At screen, 342 subjects entered placebo washout, 325 were randomized to one of the 4 arms, with 84 randomized to placebo, 80 to sertraline 50 mg, 81 to sertraline 100 mg, and 80 to sertraline 200 mg. There were evaluable for efficacy 84 placebo subjects, 79 sertraline 50 mg subjects, 81 sertraline 100 mg subjects, and 80 sertraline 200 mg subjects. Table 22 gives sample sizes at the various points in the study.

SAMPLE SIZE AND POWER

I could find no power and sample size calculations in the protocol. However, since the study was largely positive, it may be of less concern as to whether the study was designed with sufficient power to detect a meaningful treatment difference. According to the protocol, this was originally designed as two five-center trials, with 32 subjects per center. Due to difficulty obtaining subjects, the two trials were were combined into one, and an eleventh center was added, for a total of 325 subjects randomized, and 324 subjects evaluable for efficacy.

STUDY PLAN

This trial consisted of a 1-week single-blind placebo lead-in, followed by randomization and a baseline evaluation, and a 12-week double-blind clinical trial, with evaluations at the end of the washout ("Baseline;" "Week 0"), and the end of weeks 1,2,4,6, 8,10, and 12. There was a 40-week treatment-responder extension, which will not be discussed here.

There were 4 treatment groups – placebo and three fixed dose sertraline groups, with fixed doses at 50, 100, and 200 mg of sertraline. Random assignment to treatment took place at the end of the placebo lead-in. After the week 12 visit, nonresponders were titrated

down to 0 mg and discontinued; responders were given the opportunity to continue double-blind for 40 more weeks. Initial dose titration took place during the first 2 weeks.

There was no mention in the protocol of whether sufficient improvement during the one-week placebo lead-in would exclude the subject from the trial.

ASSESSMENT PLAN

Rating scale evaluations were done at screen (beginning of the lead-in week), baseline (week 0; end of the lead-in week), and the end of weeks 1, 2, 4, 6, 8, 10, and 12. A 24-item Hamilton scale was administered at baseline, and subjects who scored greater than 17 were excluded. Plasma samples were also taken at the end of week 10.

Instruments

Efficacy instruments used included: the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total score, the NIMH Global Obsessive Compulsive Scale (NIMH-OC), the Clinical Global Impressions Severity score (CGI-S), the Clinical Global Impressions Improvement (CGI-I) score, the Maudsley Obsessive Compulsive Inventory (MOC), and the Hamilton Depression Rating Scale (HRD).

As stated earlier, the Hamilton Depression Scale was administered at screen, while the MOC was administered only at baseline and during the final week of the 40-week extension, for those subjects who entered the extension. Thus the MOC was not available for use as an efficacy measure for the 12-week study that this review covers.

The Y-BOCS is a 14-item questionnaire, with 10 scorable items each scored on a 0-4 scale, giving a total score in the 0-40 range. This total score was the primary dependent variable used. Additionally, these 10 scorable items can be divided into two subgroups of 5 items each, each producing an Obsession subscore (0-20) and a Compulsion subscore (0-20). These two subscores will not be regarded as primary efficacy measures.

The NIMH-OC was a scale rated from 1-to-15, with scores of 1-to-3 indicating minimal pathology to scores of 13-to-15 indicating very severe obsessive and compulsive behavior.

The CGI-S scale is scored from 1 to 7, with 1 indicating no illness to 7 indicating extremely ill. The CGI-I scale is scored from 1 to 7, with 1 indicating very much improved and 7 indicating very much worse.

The MOC is a self-rating scale of 30 items, each of which the patient scores as true or false. Thus the score on the MOC ranges from 0 to 30, with 0 indicating no self-rated obsessive or compulsive behavior, and 30 indicating a maximal amount of such behavior.

The HRS is a 24-item rating scale, scored from 0 to 73, with scores of 16 or below generally indicating no or mild depression and scores at the high end indicating a high amount of depression.

INCLUSION AND EXCLUSION CRITERIA

Inclusion and exclusion criteria were unremarkable. Outpatient patients of both sexes, 18 and older, who met DSM-III-R criteria for obsessive compulsive disorder without depression were eligible. The original protocol stated women had to be without childbearing potential but the protocol was amended to permit women using adequate contraception. HRS had to be 17 or less, with a score of 7 or less for item 1. The NIMH Global Obsessive Compulsive Scale had to have a score of 7 or more. Exclusion criteria included abnormal and clinically significant ECG or lab values. Patients with organic mental disorders, organic brain syndrome, major axis I disorders, anxiety states or disorders were excluded.

Drug or alcohol abuse within 6 months were exclusion criteria. Allergy or hypersensitivity to antidepressants, contraindications to antidepressants, clinically significant hepatic, hematologic, endocrine, cardiovascular, renal, gastrointestinal, or neurological functions were exclusion criteria. Use of other investigational drugs within one month prior to study entry, except chloral hydrate, and behavior therapy while in the study were exclusion criteria. Use of an MAO inhibitor within 2 weeks of baseline, any depot neuroleptic within 6 weeks, regular use of anxiolytics, neuroleptics, or antidepressants within 2 weeks prior to baseline were exclusion criteria. Investigators excluded illiterates or subjects judged unlikely to be able to follow the protocol.

Subjects were allowed sparing use of chloral hydrate during the study.

METHODOLOGIC CONSIDERATIONS

For the primary efficacy measures (Y-BOCS and NIMH-OC), as well as for the CGI-Severity, the sponsor chose to fit linear models with change-from-baseline as the dependent variable, investigator as a blocking variable, baseline as a covariate, and treatment as the factor of greatest interest. This is but one of several choices the investigator might have made. They tested the investigator-by-treatment interactions, and finding only no significant interactions, chose to fit models without these interactions. For CGI-Improvement, there was no baseline, and hence the dependent variable was the weekly score (or endpoint) and there was no covariate.

I note that an ANCOVA model using gain scores as the dependent variable and baseline as the covariate produces exactly the same hypothesis test results on all effects except the covariate as would the same ANCOVA using the endpoint rather than gain score as the dependent variable.

They used the baseline (week 0) measures as the covariate, and the week 12 as the desired endpoint in the LOCF analyses. They did several analyses for each dependent variable, first lumping all sertraline groups together and testing treatment vs placebo, and then testing least squares (adjusted) means of each sertraline group vs placebo using LSD (uncorrected t) tests.

DEMOGRAPHIC COMPARABILITY

Table 23 contains demographic statistics for the four treatment groups. All four groups were roughly 55 to 60 percent male, and roughly 40 to 45 percent female. All four groups were largely white, with percentage white above 96 percent. All four groups were comparable on age, with age ranges in the roughly 18-to-80 range.

I don't consider it appropriate to perform hypothesis tests on baseline distributions in randomized clinical trials.

RESULTS

In the discussion of efficacy, I will concentrate largely on the Y-BOCS, and the NIMH-OC scales, although I will mention the other results. Results were largely consistent.

Baseline Comparability on Efficacy Variables

Table 24 contains baseline comparisons of the efficacy variables, as well as the Hamilton Depression Scale. The groups were all nondepressed, with Hamilton Depression Scale mean scores ranging from 10.0 (Placebo and Sertraline 50 mg) to 10.6 and 1.7 (Sertraline 200 mg and 100 mg, respectively). Scores on all the efficacy variables were comparable.

I did not do hypothesis testing of baseline comparability as I believe it inappropriate

in a randomized trial.

Y-BOCS: LOCF and OC Analyses

Table 25 contains dropouts by treatment groups for baseline and weeks 1, 2, 4, 6, 8, 10, and 12. Seventeen subjects were not randomized at baseline, and of the subjects randomized, the pattern of dropouts was unremarkable. Table 26 contains the reasons for termination, and unsurprisingly, more subjects dropped out in the placebo group for lack of effect than for adverse effects, while the reverse held in in the 50 mg and 100 mg sertraline groups. For the 200 mg group, 6 subjects dropped out for adverse effects, and 7 for lack of effect.

Completion rates were 71 percent in the placebo group, 79 percent in the sertraline 50 mg group, 66 percent in the sertraline 100 mg group, and 73 percent in the sertraline 200 mg group. (The sertraline 100 mg group had nearly twice the number of dropouts for adverse effects as any of the other groups.)

Table 27 contains weekly Y-BOCS means and standard deviations for all four treatment groups. The placebo group declined from 23.4 to 18.6 over the 12 week period, while the 50 mg and 100 mg sertraline groups declined from roughly 23.5 to 16 over the same period. The 100 mg sertraline group produced little more decline than did the placebo group.

Table 31 contains a [illegible] of the baseline and weekly scores for all four groups for the Y-BOCS, as well as hypothesis tests (uncorrected LSD tests for each sertraline group against placebo in an ANCOVA model on the OC scores, covarying baseline, and with investigator as a blocking factor) comparing each of the sertraline groups to placebo. Significant placebo-sertraline differences began to appear in week 4 for the 50 and 200 mg groups, with all three sertraline groups different from placebo at week 6, and the 200 mg sertraline group remained significantly different from placebo for the remainder of the visits up to week 12. Additionally, at week 10, the 50 mg sertraline group differed significantly from placebo. The 100 mg group differed significantly from placebo only at week 6.

While the sponsor did an analysis in which the three sertraline groups were simply lumped together before the joint sertraline means were tested to see if they differed significantly from placebo, I did an analysis in which I did a 1-df contrast of placebo from the average of the sertraline weekly means, and found significant differences between this average of the three sertraline group means and the placebo mean for weeks 2 through 10, and a marginally nonsignificant p-value ($p < 0.0765$) at week 12.

An LOCF endpoint analysis shows all three groups differing significantly from placebo.

It appears that for this variable, sertraline beats placebo in this study. There does not appear to be any dose-response effect.

NIMH-OC: LOCF and OC Analyses

With respect to the NIMH-OC, weekly means and standard deviations for each group are given in table 29, and a plot of these means is given in table 32. For this variable, sertraline 50 mg and sertraline 100 differed significantly form placebo at week 4 (uncorrected LSD tests for each sertraline group against placebo in an ANCOVA model on the OC scores, covarying baseline, and with investigator as a blocking factor), all three groups differed significantly from placebo at week 6, the 50 and 200 mg sertraline groups differed from placebo at week 8, and the 200 mg sertraline group continued to differ significantly

from placebo for the remainder of the study.

While the sponsor did an analysis in which the three sertraline groups were simply lumped together before the joint sertraline means were tested to see if they differed significantly from placebo, I did an analysis in which I did a 1-df contrast of placebo from the average of the sertraline weekly means. The mean of the sertraline group means differed significantly from placebo starting at week 4 ($p < 0.0027$) and the mean of the sertraline group means differed significantly from placebo through the rest of the study.

An LOCF endpoint analysis showed all three groups differed significantly from placebo on this variable.

It appears that for this variable, sertraline beat placebo, in this study.

CGI-Severity: LOCF and OC Analyses

Although CGI-Severity was not one of the primary variables, I analyzed that, too. Table 28 contains means and standard deviations for all four treatment groups for baseline and weeks 1, 2, 4, 6, 8, 10, and 12. The four groups were comparable at baseline, and as with the Y-BOCS, the sertraline 50 mg and sertraline 200 mg groups declined more during the 12 weeks than did the placebo or sertraline 100 mg groups.

Table 33 shows a plot of group means for the four groups over time, with hypothesis tests between each of the sertraline groups and the placebo group at each time point. (These were uncorrected LSD tests for each sertraline group against placebo in an ANCOVA model on the OC scores, covarying baseline, and with investigator as a blocking factor.) This table also contains an LOCF (endpoint) analysis. The pattern shown here is strikingly similar to the pattern for the Y-BOCS, with significant differences between sertraline and placebo emerging at week 4, and except for the sertraline 100 mg group, continuing the rest of the way through the study, except for week 12.

As before, while the sponsor did an analysis in which the three sertraline groups were simply lumped together before the joint sertraline means were tested to see if they differed significantly from placebo, I did an analysis in which I did a 1-df contrast of placebo from the average of the sertraline weekly means. In this analysis, the mean of the three sertraline means differed significantly from placebo for weeks 4 through 10, but did not differ significantly from placebo at week 12.

The LOCF endpoint analysis showed the sertraline 50 mg and sertraline 200 mg groups different from placebo, but not the sertraline 100 mg group.

Although the inconsistent efficacy on the part of the sertraline 100 mg group is troubling, as is the occasional return to nonsignificance at week 12, it appears that for this variable, sertraline beats placebo, in this study.

Remarks

There appears to be a clear and consistent sertraline – placebo difference in this study for the 50 mg and 200 mg doses. The results for the 100 mg dose are troubling. There does not appear to be a dose-response, although it may well be that if the 100 mg sertraline group had differed significantly from placebo, it would have appeared.

Nonetheless, in this study, considering all the dependent variables, and over time, including the contrast I did, sertraline appears to beat placebo. I would characterize this study as positive.

With respect to CGI-Improvement, a similar pattern held. I would characterize this

study as demonstrating efficacy.

Protocol 546

STUDY DESCRIPTION

Protocol 546 was a multicenter, double-blind, parallel groups, randomized, clinical trial designed to evaluate safety and efficacy of sertraline versus placebo

This was a 12-week, flexible dose, following a one-week single-blind placebo lead-in, with two parallel groups: placebo of flexible dose sertraline up to 200 mg. It was designed as an 10 center study, with 16 subjects per center (8 placebo and 8 sertraline), for a total of 160 subjects. Table 40 indicates that 193 subjects made it through screening and entered the placebo lead-in, with 168 making it through the placebo lead-in and randomized. Of the 168 randomized, 82 were randomized to placebo, and 86 randomized to sertraline. Of the 82 randomized to placebo, 79 were evaluable for efficacy, and of the 86 randomized to sertraline, 85 were evaluable for efficacy.

This trial consisted of a one-week single-blind lead-in phase followed by a 12-week active medication phase. Evaluations were done at day one of the lead-in phase (also called "screen"), at the end of the one-week lead-in (also called "baseline," or "week 0"), and at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12 on active medication or placebo.

There were parallel two groups – placebo and a flexible sertraline group which could be titrated up to 200 mg active medication. Random assignment to either placebo or sertraline took place at the end of the lead-in period. Intermittent use of chloral hydrate was allowed for sleep, and the use was recorded.

Subjects had to have a DSM-III-R diagnosis of Obsessive Compulsive Disorder, without depression, as determined by a total score of 20 or higher at the beginning and end of lead-in on the Y-BOCS, and a score of 7 or higher on the NIMH-OC at the same time points, and a score of 15 or less (excluding item 21) on the 24-item HRS, and a score of 1 or less on the HRS item 1, and a CGI-Severity score of 3 or greater on the same occasions.

SAMPLE SIZE AND POWER

I could find nothing about sample size and power calculations in the NDA or the protocol. Since the study was largely positive, it may be of less importance then it would have been had the study failed to detect sertraline – placebo differences. There were 167 subjects randomized to the two treatment groups, with 86 to sertraline and 81 to placebo. The 12-week completion rate was 69 percent in the placebo group, and 71 percent in the sertraline group.

STUDY PLAN

This trial consisted of a one-week single-blind lead-in phase followed by a 12-week active medication phase. Evaluations were done at day one of the lead-in phase (also called "screen"), at the end of the one-week lead-in (also called "baseline," or "week 0"), and at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12 on active medication or placebo.

There were parallel two groups – placebo and a flexible sertraline group which could be titrated up to 200 mg. Random assignment to either placebo or sertraline took place

at the end of the lead-in period. Sparing use of chloral hydrate was allowed for sleep, and the use was recorded. The titration schedule (volume 1, 8 78) specified that all subjects began at 50 mg sertraline daily, for the first three weeks, and titration upward was done in 50 mg increments only after satisfactory responses had not been observed for at least one week on doses above 50 mg daily. Subjects could be down-titrated if need be after the end of week 6 as long as the dose remained between 50 and 200 mg sertraline. Note that upward titration above 50 mg did not even begin until after the third week.

ASSESSMENT PLAN

Rating scale evaluations and vital signs were done on all occasions: day 1 of the lead-in, after the washout (end of week 0), and the end of weeks 1, 2, 3, 4, 6, 8, 10, 12. Lab work and ECG were were done on day 1 of the lead-in, the end of week 2, end of week 6, and end of week 12. A physical exam was done on day 1 of the washout and the end of week 12. Week 12 measurements were done at termination if the subject terminated early.

Instruments

Efficacy instruments used included: the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total score, the NIMH Global Obsessive Compulsive Scale (NIMH-OC), the Clinical Global Impressions Severity score (CGI-S), the Clinical Global Impressions Improvement (CGI-I) score, and the Hamilton Depression Rating Scale (HRS). (The HRS was administered only at day 1 of the lead-in and was not really an efficacy instrument but rather used as an entry criterion.)

The Y-BOCS is a 14-item questionnaire, with 10 scorable items each scored on a 0-4 scale, giving a total score in the 0-40 range. This total score was the primary dependent variable used. Additionally, these 10 scorable items can be divided into two subgroups of 5 items each, each producing an Obsession subscore (0-20) and a Compulsion subscore (0-20). These two subscores will not be regarded as primary efficacy measures.

The NIMH-OC was a scale rated from 1-to-15, with scores of 1-to-3 indicating minimal pathology to scores of 13-to-15 indicating very severe obsessive and compulsive behavior.

The CGI-S scale is scored from 1 to 7, with 1 indicating no illness to 7 indicating extremely ill. The CGI-I scale is scored from 1 to 7, with 1 indicating very much improved and 7 indicating very much worse.

The CGI-I scale is scored from 1 to 7, with 1 indicating very much improvement, and 7 indicating no improvement.

The HRS is a 24-item rating scale, scored from 0 to 73, with scores of 16 or below generally indicating no or mild depression and scores at the high end indicating a high amount of depression.

INCLUSION AND EXCLUSION CRITERIA

Inclusion and exclusion criteria were unremarkable.

Inclusion:

Male and female outpatients 18 years of age and older, DSM-III-R diagnosis of Obsessive Compulsive Disorder without depression (Y-BOCS score of 20 or higher, NIMH-OC score of 7 or higher, HRS score of 15 or lower (excluding item 1), HRS item 1 score of 1 or less, GCI-Severity score of 3 or greater, all on both day 1 of the lead-in and at base-

line), normal or clinically insignificant lab values on day 1 of lead-in, nonpregnant, and discontinuation of any other psychotropic medication except chloral hydrate for sleep.
Exclusion:

Pregnant or nursing women, women of child-bearing potential not practicing effective birth control, subjects with organic mental disorders or organic brain syndromes, subjects meeting DSM-III-R criteria for: bipolar disorders of various types, depressions of various types, schizophrenia and other psychotic disorders of various types, anxiety states of various types, and severe personality disorders (complete criteria given on volume 1, page 8 75), history of schizophrenia or psychotic disorders, a 6-month history of substance or alcohol abuse or dependence, contraindications to antidepressants, subjects with evidence or history of various significant diseases, allergy or hypersensitivity to sertraline or other antidepressants, subjects intending to donate blood during the study, patients on concomitant therapy with other investigational drugs or a 28-day previous history thereof, and subjects requiring psychotropics, hypnotics, or anxiolytics (except intermittent chloral hydrate), patients with current or a 14-day history of MAO inhibitors, or current or a 6-month history of depot neuroleptics, current or 4 week history of fluoxetine, current anticoagulant therapy, liver dysfunction twice the normal range, or subjects who are illiterate of judged unable to follow the protocol.

METHODOLOGIC CONSIDERATIONS

There were several methodologic choices made. First, they chose to use improvement or gain scores over baseline as the dependent variable. That is, for any dependent variable (except CGI-I), each subject's baseline score was subtracted from the scores at successive intervals, and it was these difference scores which were analyzed when examining changes within groups or when comparing groups. This is but one of several choices the sponsor might have made. ANCOVA using the baseline as a covariate with the dependent variable being the scores at each point would have been a reasonable alternative, as would a repeated measures analysis using the baseline as the first level of the repeated factor and examining differences between it and later time points using appropriate contrasts.

I note that an ANCOVA model using gain scores as the dependent variable and baseline as the covariate produces exactly the same hypothesis test results on all effects except the covariate as would the same ANCOVA using the endpoint rather than gain score as the dependent variable.

For the endpoint analyses, the endpoint was the score at the end of week 12 score, or the last score observed, if the subject dropped out prior to week 12.

The statistical analysis section (volume 1, 8 10) stated that for the Y-BOCS, NIMH-OC, and CGI-Severity scales, the model fitted used the change score for the dependent variable, and the treatment, site, treatment-by-site interaction, and baseline as independent variables. For CGI-Improvement, there was no baseline, and thus for that dependent variable, the dependent variable was just the CGI-Improvement score observed at the time point, and there was no baseline covariate in the model.

Another methodological choice they made was to treat center as a fixed effect. I have seen center treated as random, and as fixed, and I think there are reasonable arguments

one might make in either case.

DEMOGRAPHIC COMPARABILITY

Table 41 contains baseline measurements on demographic variables. Both groups were approximately half male and half female. Both groups were between 3/4 and 4/5 white, and both groups had median ages of about 35, with age ranges of about 18-70. The groups seem comparable, and I would consider it inappropriate to perform hypothesis tests on these baseline measures.

RESULTS

In the discussion of efficacy, I will mention all the efficacy measures: Y-BOCS, NIMH-OC, CGI-Severity, and CGI-Improvement. Results were largely consistent.

Baseline Comparability on Efficacy Variables

Table 42 contains baseline measures for the 3 efficacy measures that had baselines, as well as for the HRS. The groups appeared comparable. I consider it inappropriate to test the significance of differences on baseline measurements of groups to which there was random assignment.

Y-BOCS: LOCF and OC Analyses

Table 43 contains weekly dropouts, by group. There were 25 dropouts in each group. Table 44 contains the reasons for termination in each group. In both groups, roughly 70 percent (69 percent in the placebo group; 71 percent in the sertraline group) completed the study, with more dropouts in the placebo group than the sertraline group for lack of effect (11 percent vs 7 percent) and more dropouts in the sertraline group than the placebo group for adverse effects (10 percent vs 5 percent). This is entirely unremarkable.

Table 45 contains the means and standard deviations on the Y-BOCS, weekly for both groups, and shows a decline in both groups, with more of a decline in the sertraline group. Table 51 contains a plot of these means, with error bars, and with significance tests at each week and for the endpoints. Table 47 contains a plot of the endpoint Y-BOCS scores with the baseline Y-BOCS scores, and we see an indication of a positive correlation with an attenuation at the left edge of the data point cloud due to the floor effect of the inclusion criteria.

Although the sponsor did an analysis with the change score as the dependent variable, and the treatment, site, treatement-by-site interaction, and baseline Y-BOCS as a covariate, I did a slightly different analysis. I used the weekly OC scores as the dependent variables, treatment, site and baseline scores as covariates. A covariance analysis with change scores as the dependent variable produces the same hypothesis test on all factors except the covariate as the analysis on the weekly score, and thus the covariance analysis they did was in fact simply a disguised version of the analysis using the weekly scores as the dependent variables. Further, there were no significant treatment-by-site interactions, and it is in general not a good idea to include such interactions unless one has very strong evidence that it would be wrong not to include them.

Table 51 contains weekly plots of the means and significance tests between the least squares means in the analysis I did at each time point, and at endpoint.

Note that in general (table 51) that the distance between the groups in general increases over time, with statistical significance of the difference between the means first appearing at week 3, disappearing at week 4, and then reappearing for good from weeks 6

through 12. An endpoint analysis shows that the groups differed at endpoint($p < 0.01$).

These data are consistent with a drug with a non-brief period of onset, and at the doses used, with a drug that affects the dependent variable. (Because of the dosing schedule, subjects did not begin receiving doses above 50 mg until several weeks into the study. That is one plausible explanation for the fact that the drug did not seem to take effect strongly until week 5.)

For this variable, sertraline beat placebo.

NIMH-OC: LOCF and OC Analyses

Table 46 contains weekly means and standard deviations for both groups and table 53 contains a plot of these means with error bars. Table 48 contains a plot of endpoint NIMH-OC scores against baseline NIMH-OC scores.

Both groups began at baseline with similar scores on the NIMH-OC, and both groups declined over time, with more of a decline in the sertraline group than in the placebo group.

The plot (Table 48) of endpoint against baseline NIMH-OC scores indicates a positive relationship, with an attenuation in the baseline score due to the floor effect of the inclusion criteria.

As with the Y-BOCS, the analysis I fit had the weekly OC NIMH-OC score (or endpoint) as the dependent variable, and the treatment, site, and baseline NIMH-OC score as the covariate. The plot (table 53) shows a decline in both groups, with the sertraline scores lower than the placebo scores beginning at week 2, and the difference between the groups becoming statistically significant at week 8 and continuing for the rest of the study. (At week 4, the difference between the groups just missed statistical significance, with $p < 0.055$.)

The endpoint analysis missed statistical significance ($p < 0.074$). This analysis seems to indicate a treatment with a long onset. (Because of the dosing schedule, subjects did not begin receiving doses above 50 mg until several weeks into the study. That is one plausible explanation for the fact that the drug did not seem to differ strongly from placebo until late in the study.) For this measure, it appears that sertraline beat placebo.

CGI-Severity: LOCF and OC Analyses

The CGI-Severity scale was administered on the same schedule as were the Y-BOCS and NIMH-OC. Table 47 contains means and standard deviations weekly, by treatment groups. Table 49 contains a plot of baseline by endpoint for CGI-Severity, and table 52 contains a plot of the weekly means for both groups, with error bars, and weekly OC between-groups significance tests, and an endpoint LOCF analysis. I will explain the weekly OC significance tests later.

The CGI-Severity scores were comparable at baseline (4.7 for the placebo group and 4.6 for the sertraline group) and both groups showed declines in the scores over the course of the trial. The sertraline group had uniformly lower scores over the 12 weeks of the trial, and over time, the difference between the two groups increased fivefold.

The weekly OC analyses showed the groups differing at weeks 8, 10, and 12, but the endpoint analysis did not show a difference. This ambiguity makes it unclear as to whether sertraline could be considered to have beaten placebo.

CGI-Improvement: LOCF and Weekly OC Analyses

Since there was no baseline measure for this variable, the analysis I used was a blocked ANOVA with TG and GRANT as predictor variables. The significance tests are on the adjusted treatment means, or least squares means.

The dependent variable was CGI-Improvement at each week.

The sertraline group had numerically lower means for all weeks after the first, and the difference between the adjusted means was significant at week 3, 6, and all weeks beyond 6. The week 4 difference just barely missed significance.

An LOCF endpoint analysis also showed the group least squares means to differ ($p < 0.007$)

For this variable, sertraline beat placebo.

Remarks

Although results were not completely consistent, it appears that sertraline beats placebo.

Protocol 371/372 40 week responder extension

Protocol 371/372 down-titrated nonresponders from their assigned doses to zero between the 12th and 14th weeks. Responders were offered the opportunity to continue on their assigned medication for 40 more weeks, for a total of 52 weeks. For those subjects who continued, down-titration began at week 48, and hence week 48 was considered the endpoint for the responder extension.

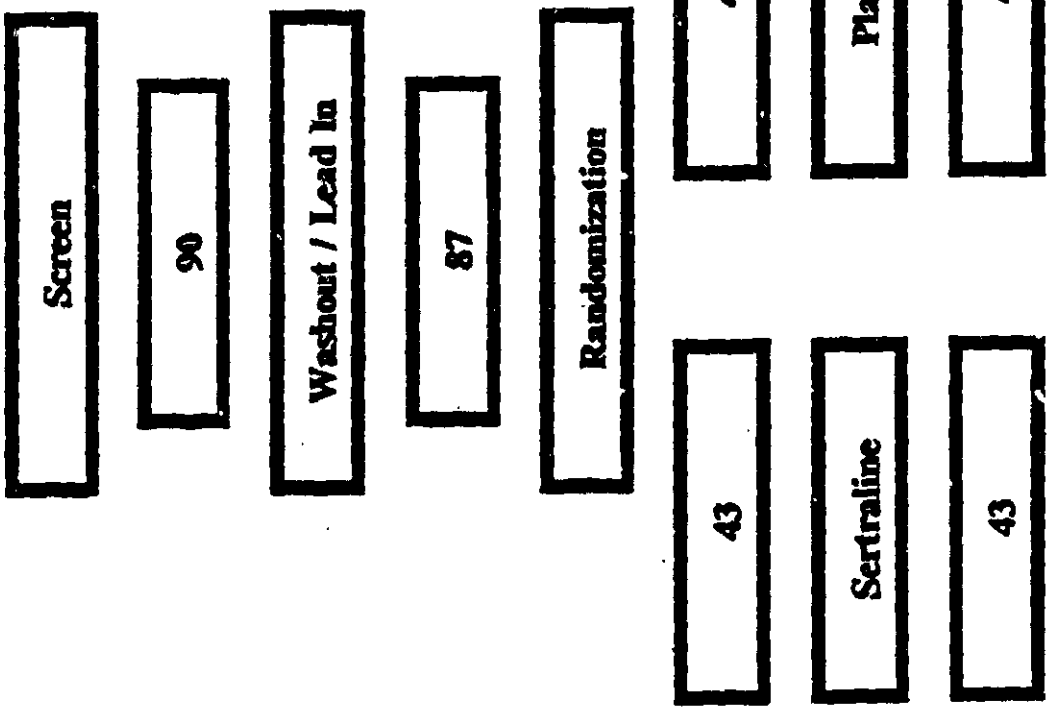
Of the 325 subjects randomized and who received at least one post-leadin dose, 118 completed the initial 12-week acute phase showing "marked" or "moderate" improvement and entered the 40-week continuation. Significantly more (40 percent) of the sertraline subjects entered this continuation than did the placebo subjects (22 percent).

It is difficult to learn much about efficacy by comparing treatment to control subjects in a responder extension. However, in general, analysis of the data shows that at the end of the extension, there appeared to be little difference between the groups, and the improvement maintained itself over the extension period.

Summary

Of the three randomized, multicenter, short-term studies covered here, one failed to show efficacy (237/248) but due to small sample size and a lack of post-hoc power, it would be easy to argue that it was a failed study. Study 371/372 unambiguously showed efficacy, while 546 took longer to show group differences. The slowness of efficacy to appear with 546 might have been due to the slow titration schedule and the fact that subjects took somewhat long to titrate up to an effective dose. Nonetheless, it appears to me that the sponsor has showed efficacy with two well controlled clinical trials.

NDA 19-839: Sertraline (Zoloft) in OCD
Protocol 237/248 Number of Subjects



NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 237/248 Demographic Characteristics

N (Percent)

	Sertraline (N = 43)	Placebo (N = 44)
Sex		
Male	35 (81.4%)	39 (88.6%)
Female	8 (18.6%)	5 (11.4%)
Race		
Caucasian	43 (100%)	43 (97.8%)
Other	0 (0%)	1 (2.2%)
Mean Age (yrs)	36.5	38.0
Median Age	35	36.5
Age Range	19-63	19-68

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 237/248 Baseline Comparisons

	Sertraline			Placebo		
	n	Mean	S.D.	n	Mean	S.D.
Y-BOCS	43	23.4	4.9	44	22.6	6.1
NIMH-OC	43	9.8	1.5	44	9.3	1.6
CGI-S	42	4.9	0.7	43	4.7	0.8
CGI-I						
MOC	43	14.8	5.5	43	15.3	5.7
HDRS	43	8.1	4.2	44	7.8	3.9

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 237/248 Dropouts

Week

	Baseline	1	2	4	6	8	10
Sertraline		1	1	0	1	0	3
Placebo		0	3	2	2	0	3
Non-randomized	3						

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 237/248 Reasons for Termination Through Week 8

n (percent)

	Sertraline	Placebo
Completers	40 (93.0%)	(84.1%)
Adverse Effects	1 (2.3%)	0 (0.0%)
Lack of Effect	1 (2.3%)	5 (11.4%)
Other	1 (2.3%)	2 (4.5%)

Three patients on sertraline refused to continue between weeks 8 and 10.
Two patients on placebo refused to continue between weeks 8 and 10.
One patient on placebo discontinued for lack of effect between weeks 8 and 10.

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 237/248 Y-BOCS

Mean (S.D.)

Week

	Baseline	1	2	4	6	8	10
Sertraline	23.4 (4.9)	22.5 (5.2)	21.3 (5.6)	20.3 (6.2)	19.9 (7.2)	19.4 (6.7)	17.5 (7.3)
Placebo	22.6 (6.1)	21.8 (6.2)	22.4 (6.2)	22.3 (6.3)	21.3 (7.4)	20.0 (7.8)	21.2 (7.8)

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 237/248 NIMH-OC

Mean (S.D.)

Week

	Baseline	1	2	4	6	8	10
Sertraline	9.8 (1.5)	9.5 (1.7)	9.1 (1.9)	8.7 (2.2)	8.4 (2.7)	8.2 (2.5)	7.7 (2.6)
Placebo	9.3 (1.6)	9.2 (1.8)	9.1 (1.8)	8.9 (1.8)	8.7 (2.2)	8.4 (2.0)	8.6 (2.0)

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 237/248 CGI-S

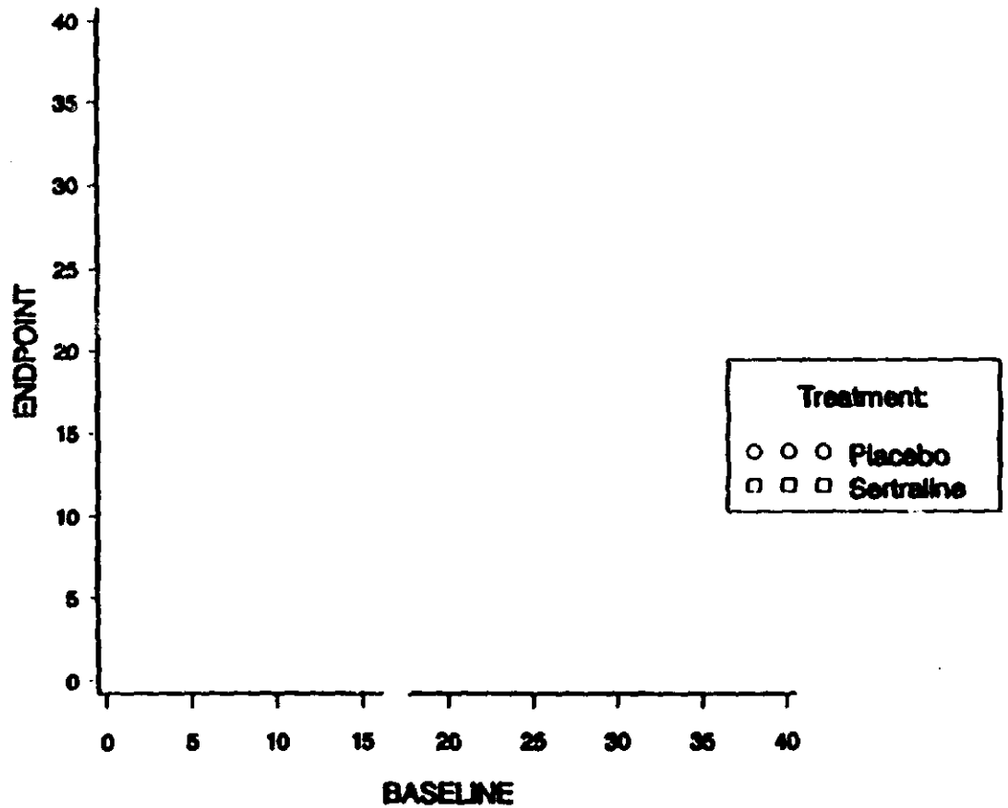
Mean (S.D.)

Week

	Baseline	1	2	4	6	8	10
Sertraline	4.9 (0.7)	4.8 (0.8)	4.8 (0.9)	4.5 (1.1)	4.4 (1.1)	4.2 (1.1)	4.0 (1.2)
Placebo	4.7 (0.8)	4.7 (0.8)	4.6 (0.8)	4.6 (0.8)	4.4 (1.0)	4.3 (0.8)	4.3 (0.8)

NDA 19-839: Sertraline (Zoloft)
Protocol: 237/248

Y-BOCS AT BASELINE
BY Y-BOCS AT ENDPOINT



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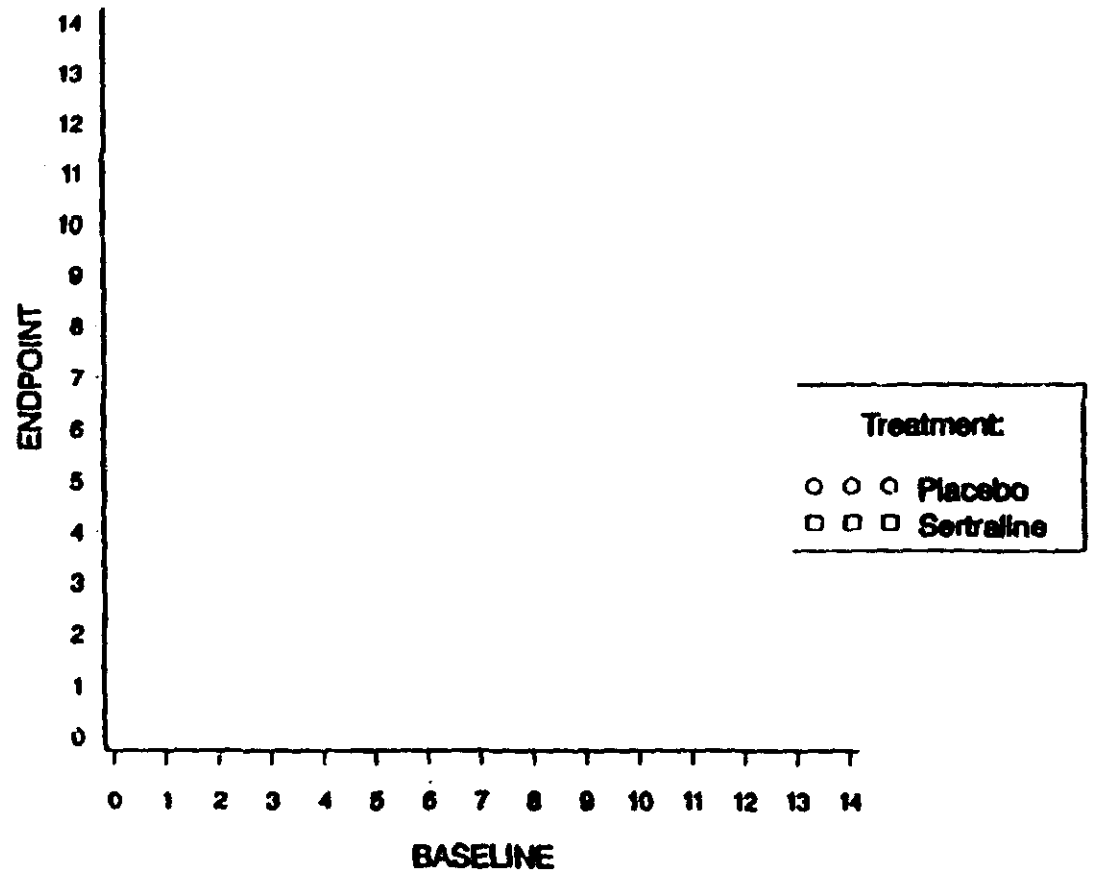
NDA 19-839: Sertraline (Zoloft)
Protocol: 237/248

NIMH SCORE AT BASELINE
BY NIMH SCORE AT ENDPOINT



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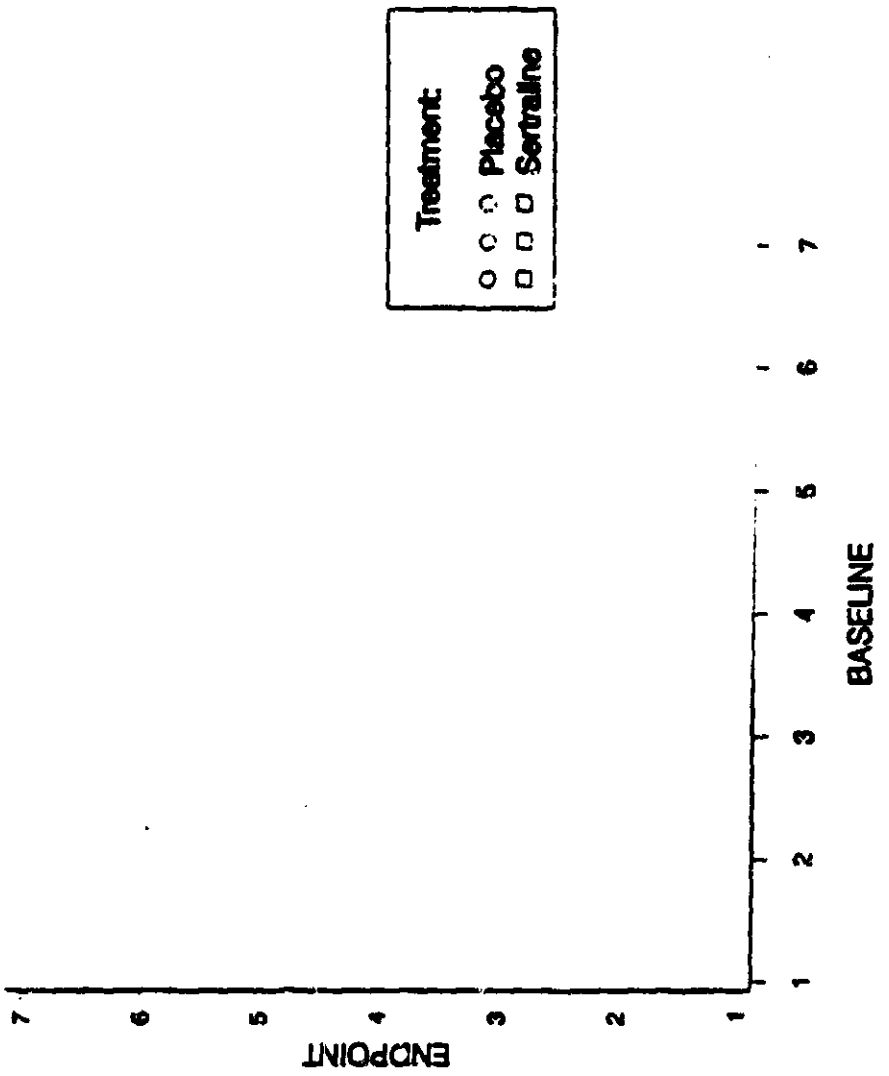
NDA 19-839: Sertraline (Zoloft)
Protocol: 237/248

CGI SEVERITY AT BASELINE
BY CGI SEVERITY AT ENDPOINT

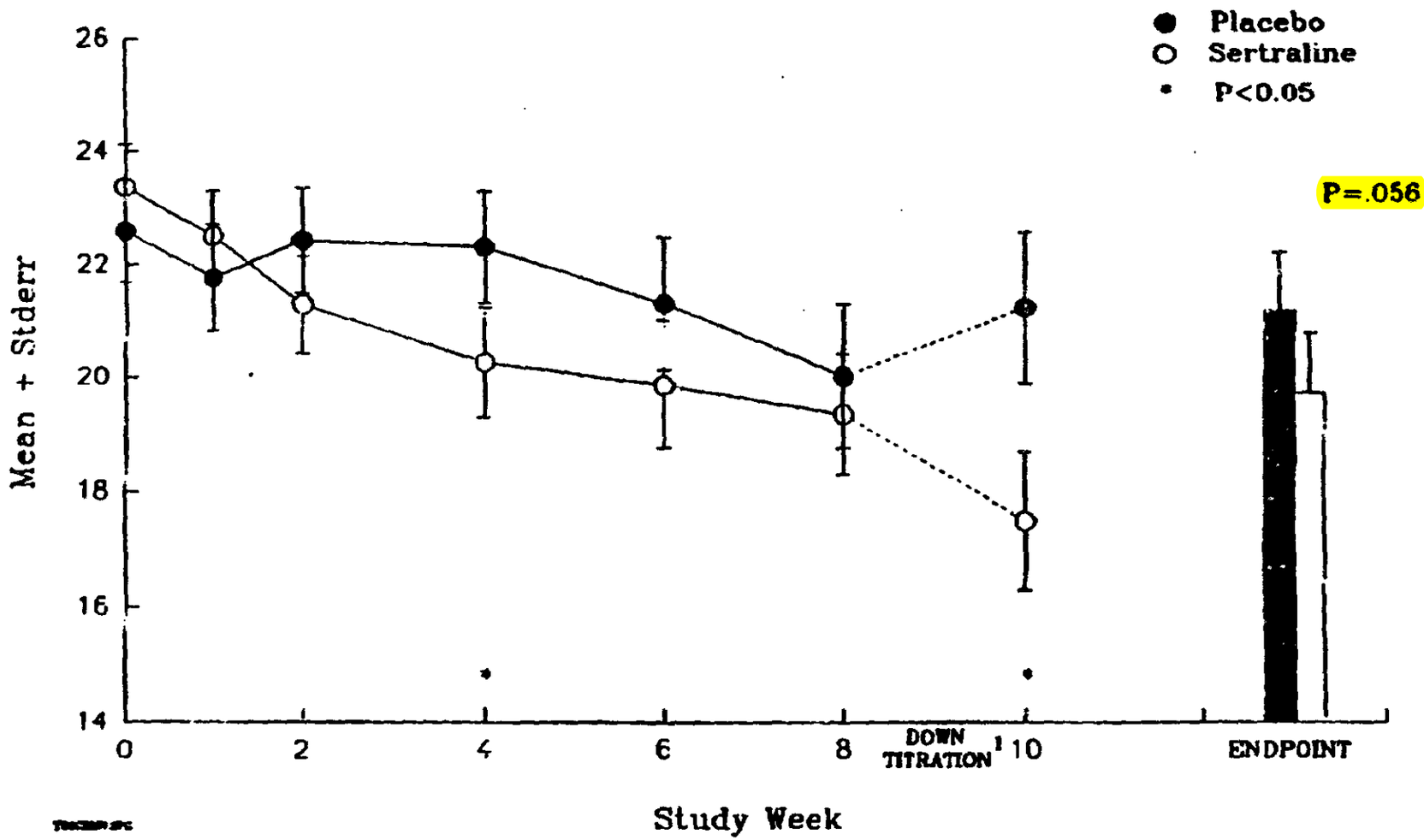


(Sample size chart for weekly graph for protocol 237/248.)

Sample Size		
Week	Sert.	Plac.
0	43	44
1	43	44
2	42	44
4	41	41
6	41	39
8	40	37
10	37	34
Endpoint	43	44

NDA 19-839: Sertraline (Zoloft) Protocol 237/248

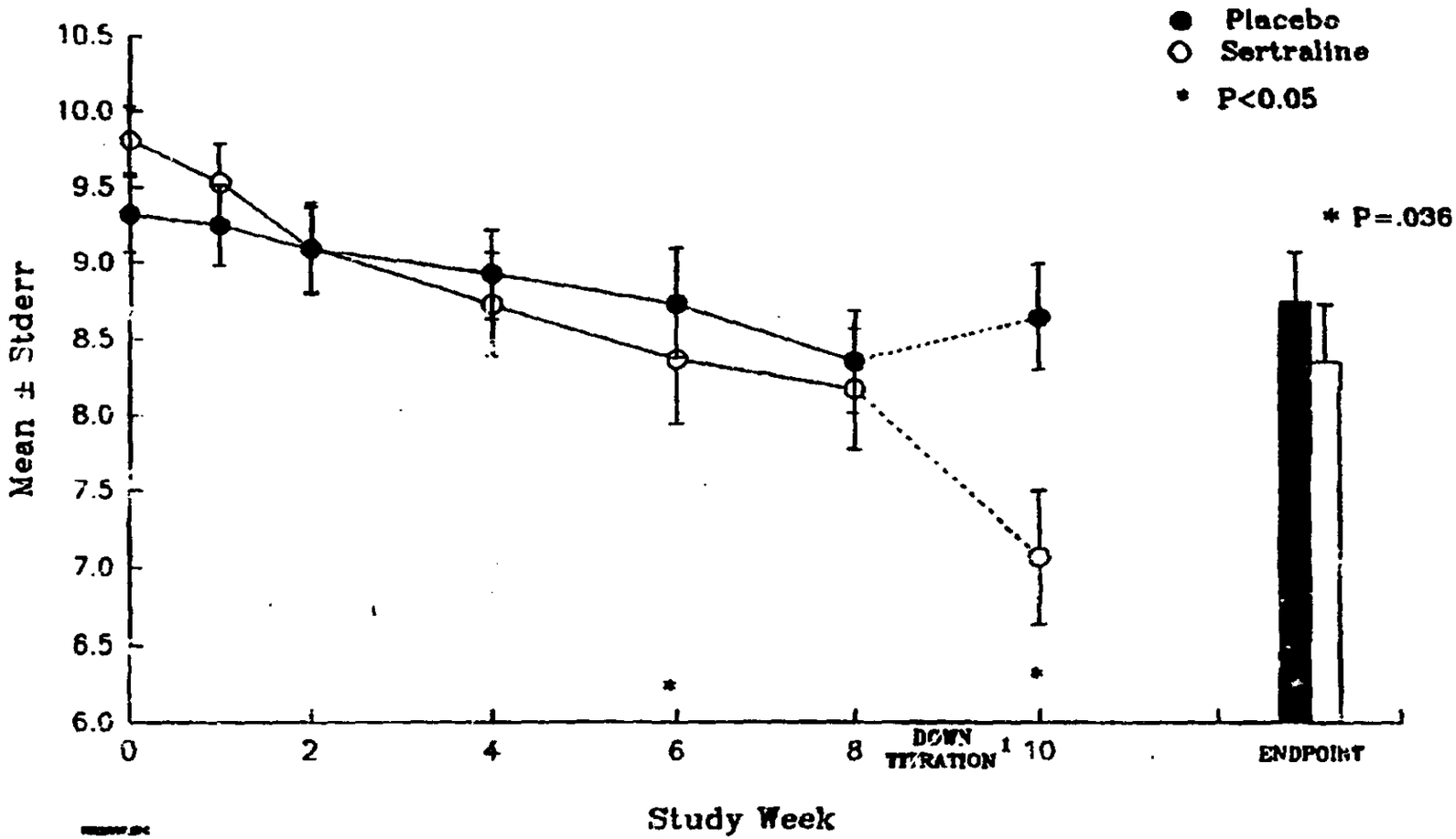
Y-BOCS



1. Most patients remained on medication through the end of week 10.

13

NDA 19--839: Sertraline (Zoloft) Protocol 237/248
NIMH

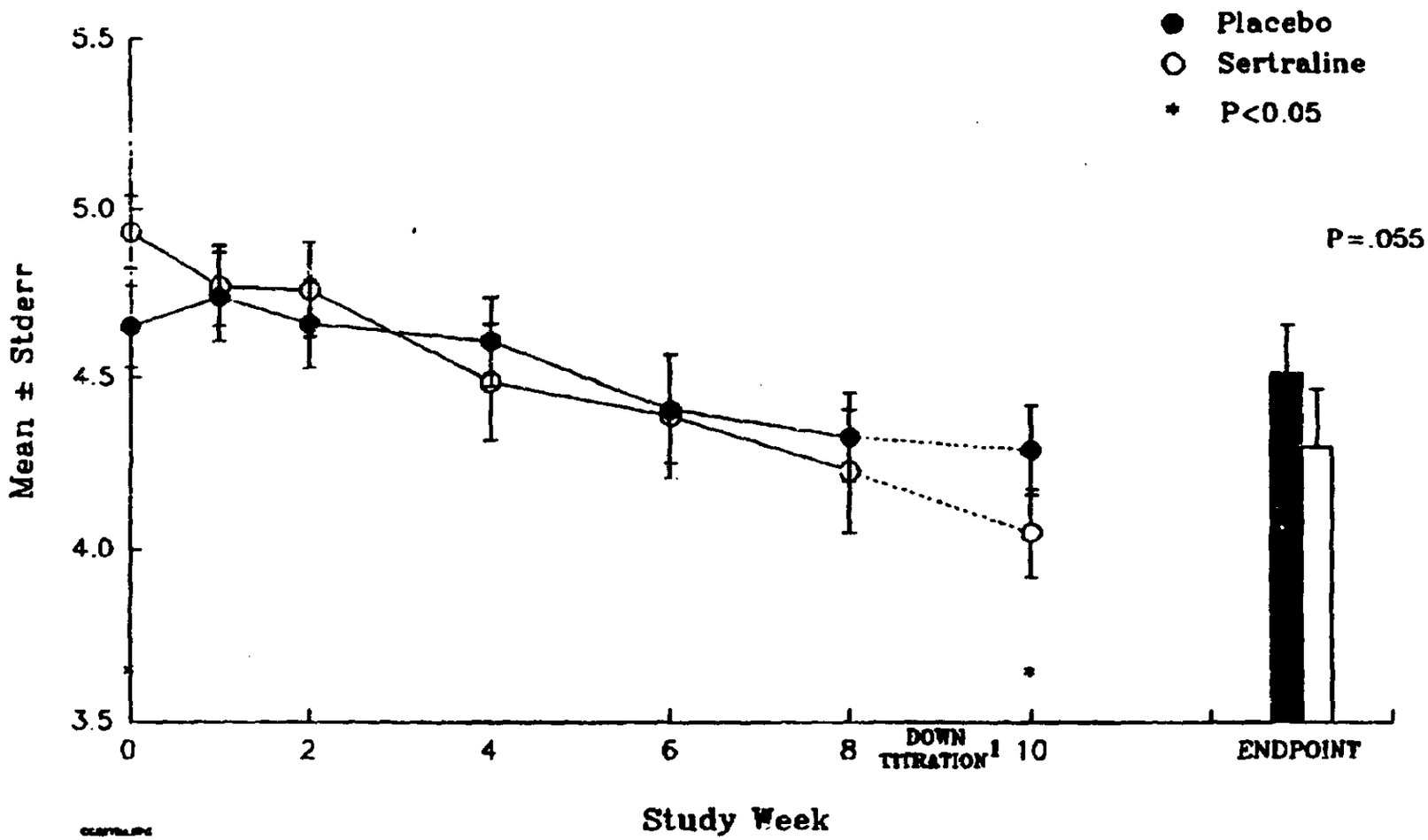


1. Most patients remained on medication through the end of Week 10.

h1

NDA 19-839: Sertraline (Zoloft) Protocol 237/248

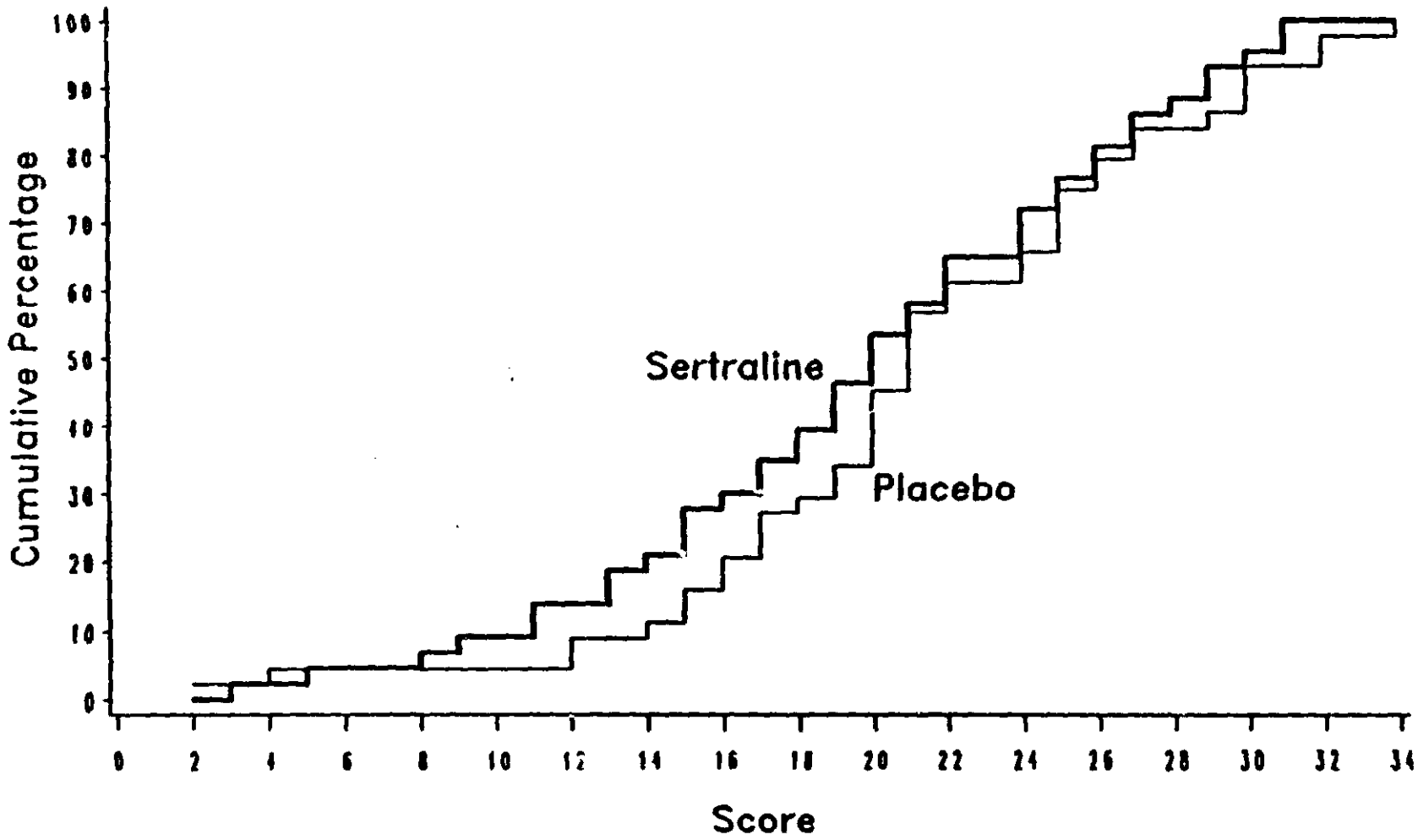
CGI Severity



1. Most patients remained on medication through the end of Week 10.

NDA 19-839: Sertraline (Zoloft)
Protocol: 237/248

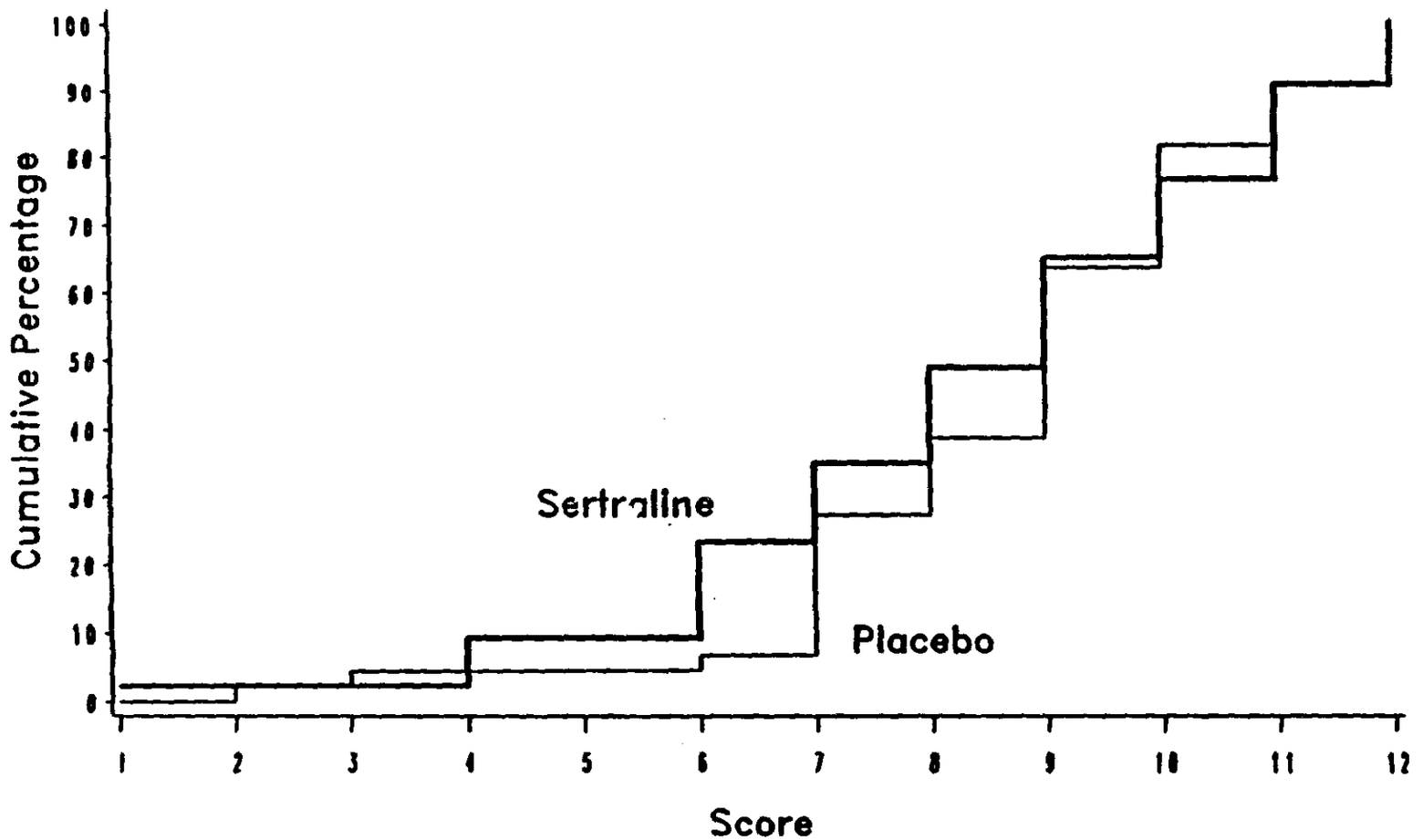
CUMULATIVE DISTRIBUTION FUNCTION OF Y-BOCS SCORES AT ENDPOINT



C: SASLIZ S237 CUMDEP.SAS,LAL 08MAR94

NDA 19-839: Sertraline (Zoloft)
Protocol: 237/248

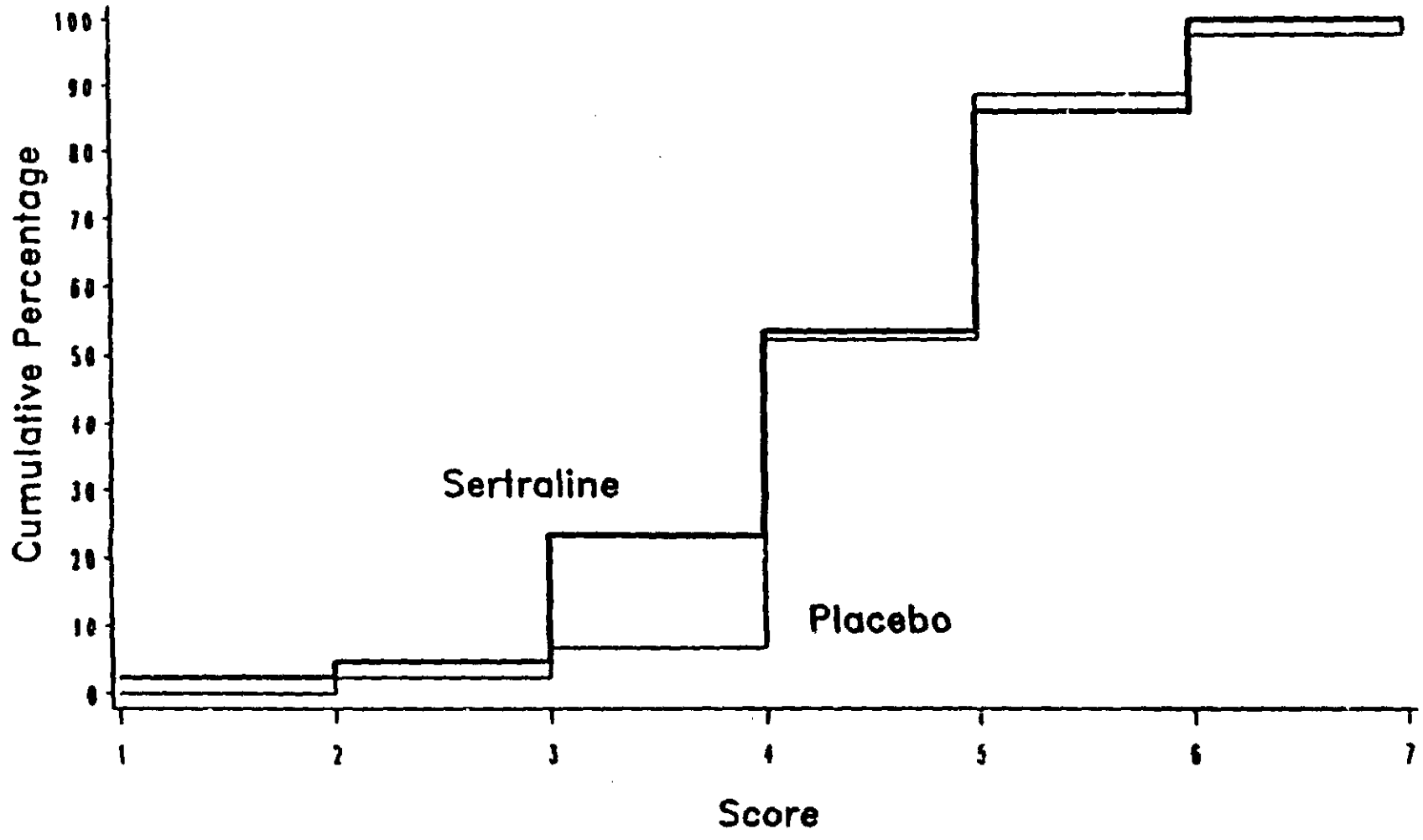
CUMULATIVE DISTRIBUTION FUNCTION OF NIMH SCORES AT ENDPOINT



C: SASUZ S237 CUMDEP.SAS,LAL 01MAR94

NDA 19-839: Sertraline (Zoloft)
Protocol: 237/248

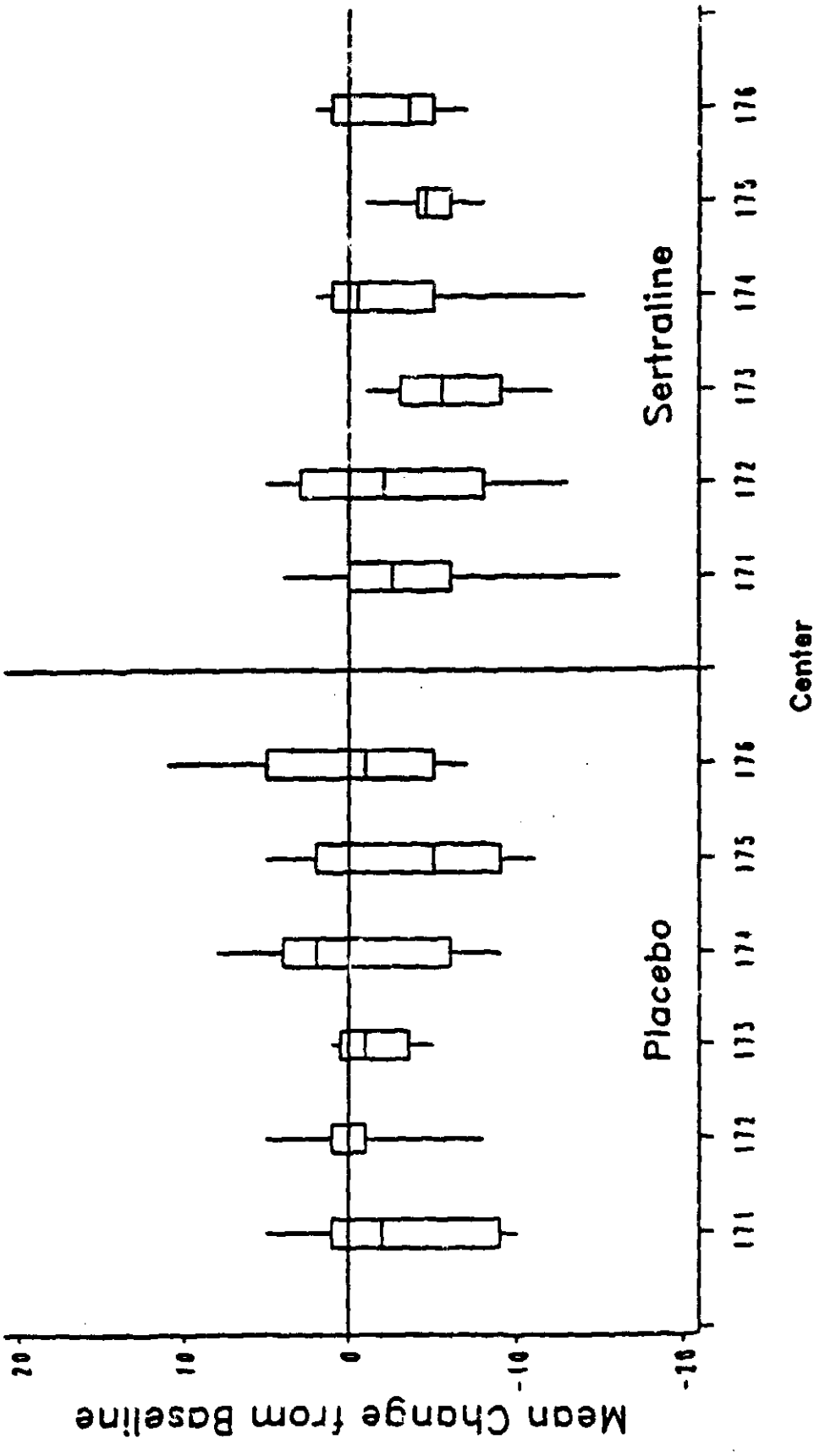
CUMULATIVE DISTRIBUTION FUNCTION OF CGI SEVERITY AT ENDPOINT



C: SASUZ S237 CUMDEP.SAS,LAL 01MAR94

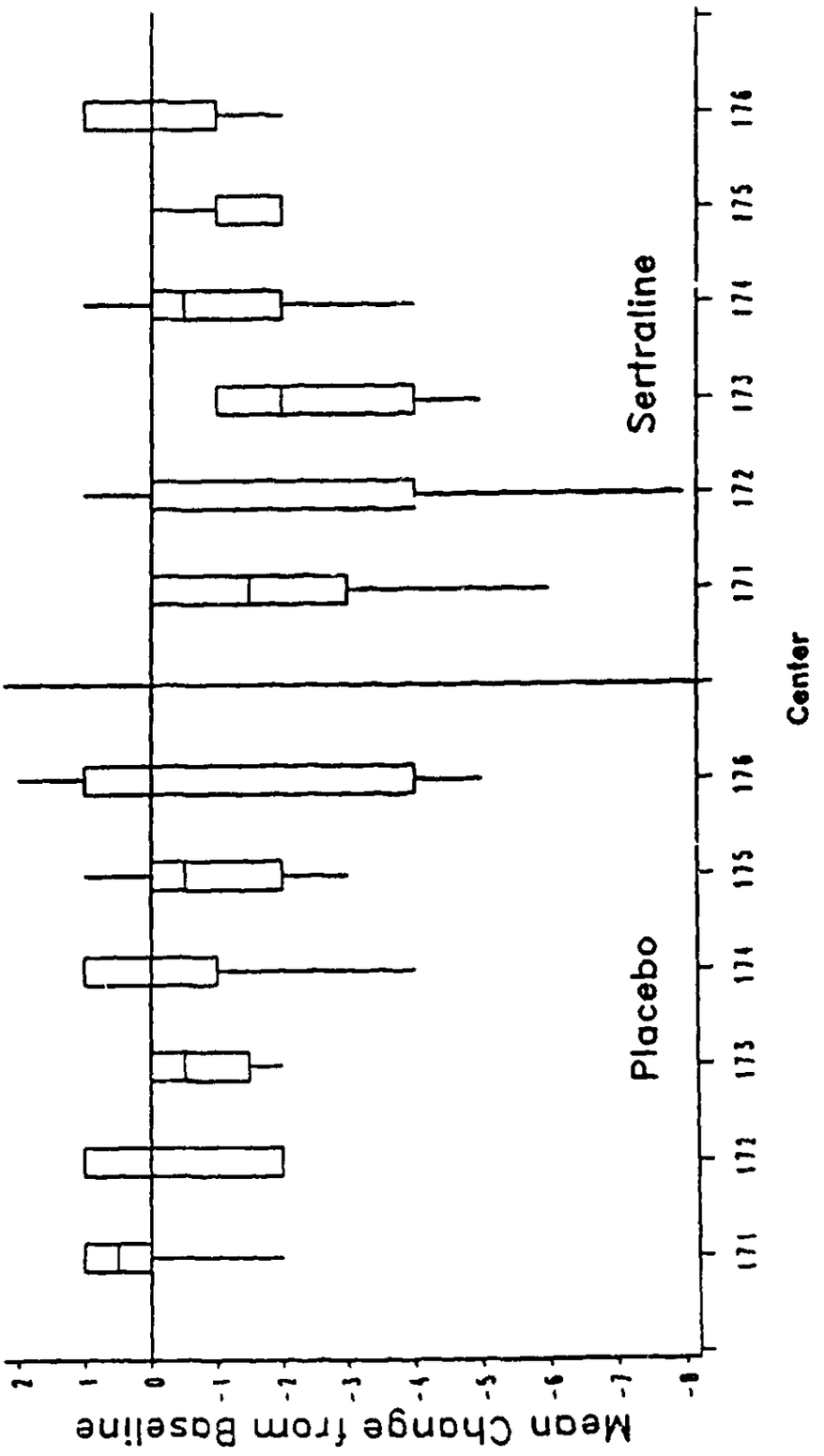
NDA 19-839: Sertraline (Zoloft)
Protocol 237/248

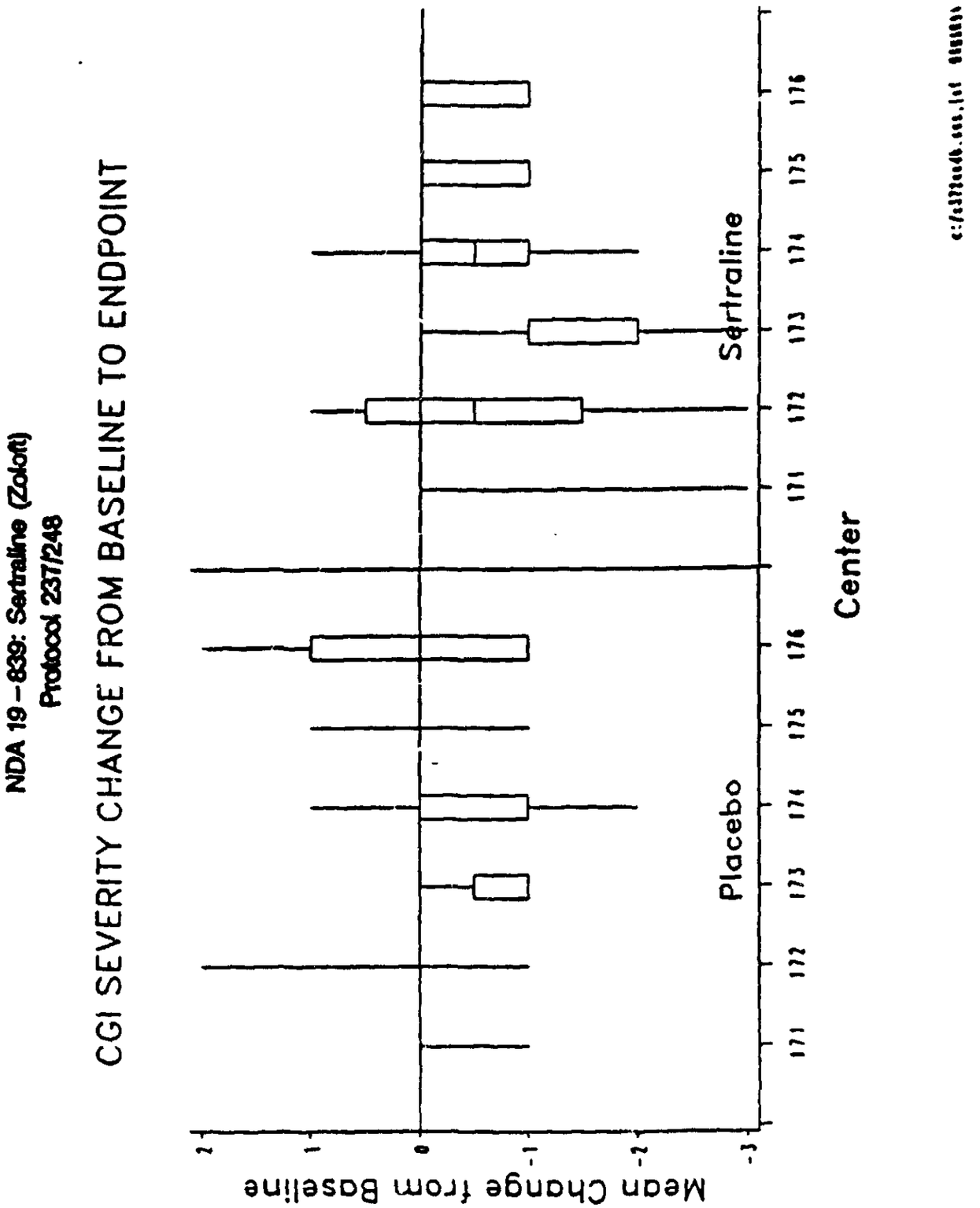
Y-BOCS CHANGE FROM BASELINE TO ENDPOINT



NDA 19-839: Sertraline (Zoloft)
Protocol 237/248

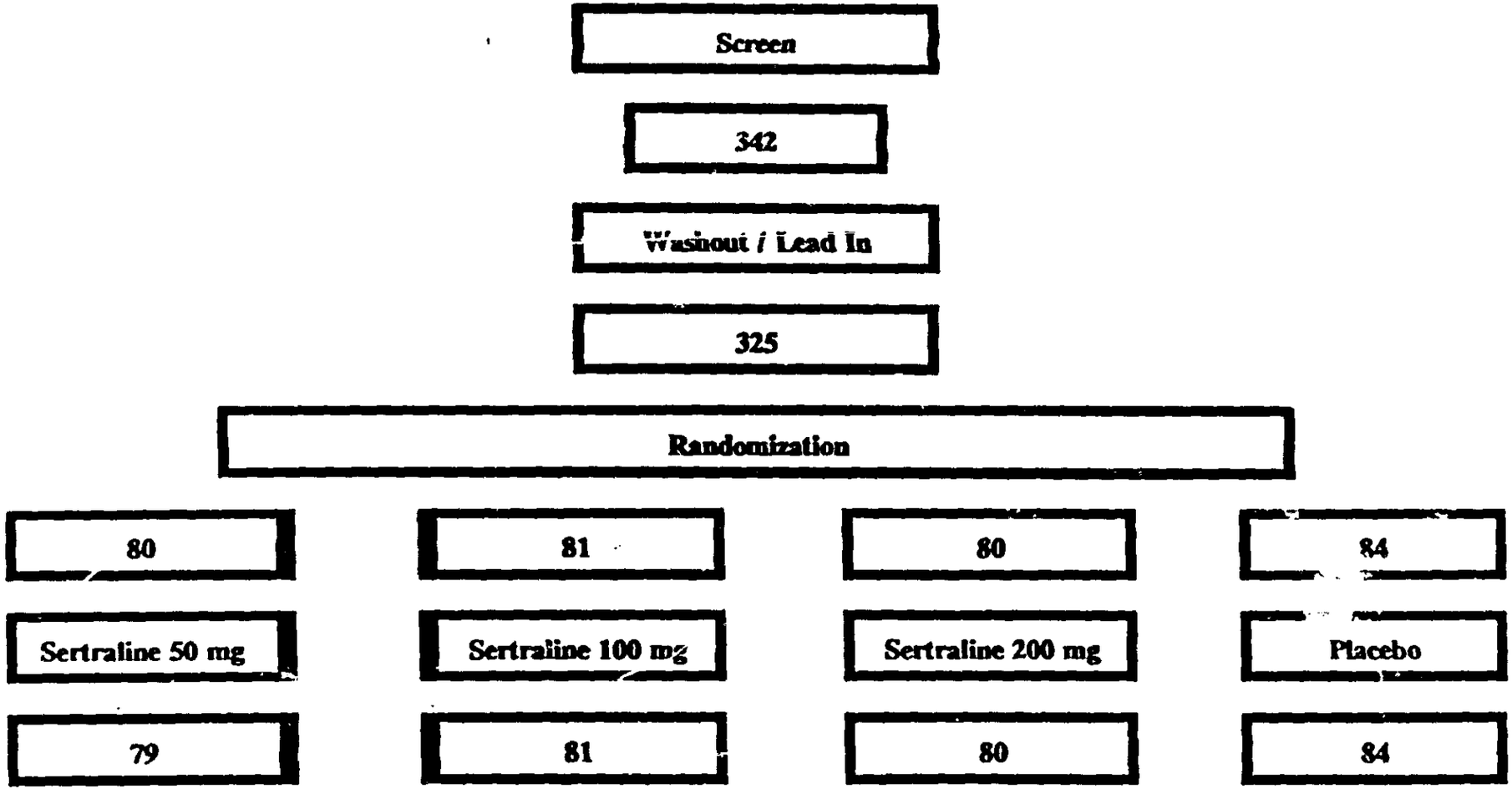
NIMH CHANGE FROM BASELINE TO ENDPOINT




NDA 19-839: Sertraline (Zoloft)
Protocol 237/248
CGI SEVERITY CHANGE FROM BASELINE TO ENDPOINT
Mean Change from Baseline
2
1
0
-1
-2
-3
Placebo
Sertraline
171 172 173 174 175 176 171 172 173 174 175 176
Center

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 371/372 Number of Subjects



NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 371/372 Demographic Characteristics

N (Percent)

	Sertraline 50 mg (N = 80)	Sertraline 100 mg (N = 81)	Sertraline 200 mg (N = 80)	Placebo (N = 84)
Sex				
Male	45 (56.2%)	45 (55.6%)	50 (62.5%)	51 (60.7%)
Female	35 (43.8%)	36 (44.4%)	30 (37.5%)	33 (39.3%)
Race				
Caucasian	79 (98.8%)	79 (97.5%)	78 (97.5%)	81 (96.4%)
Other	1 (1.2%)	2 (2.5%)	2 (2.5%)	3 (3.6%)
Mean Age (yrs)	39.6	40.1	39.1	35.9
Median Age	37	40	37.5	33
Age Range	19-72	18-67	19-77	18-88

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 371/372 Baseline Comparisons

	Sertraline 50 mg			Sertraline 100 mg			Sertraline 200 mg			Placebo		
	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.
Y-BOCS	79	23.2	5.9	81	24.6	5.6	80	23.5	4.3	84	23.4	4.9
NIMH-OC	79	9.2	1.7	79	9.7	1.7	80	9.0	1.4	84	9.2	1.5
CGI-S	79	4.7	0.8	79	4.9	0.8	80	4.6	0.7	84	4.7	0.8
CGI-I												
MOC	75	17.1	3.0	78	17.0	3.2	74	16.7	3.7	78	17.5	3.0
HDRS	79	10.0	4.0	79	10.7	5.1	80	10.6	4.7	84	10.0	4.7

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 371/372 Dropouts

	Week							
	Baseline	1	2	4	6	8	10	12
Sertraline 50 mg		3	1	5	0	2	2	4
Sertraline 100 mg		3	5	3	4	5	1	6
Sertraline 200 mg		4	0	4	2	5	2	4
Placebo		0	5	0	8	7	3	1
Non-Randomized	17							

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 371/372 Reasons for Termination

n (percent)

	Sertraline 50 mg	Sertraline 100 mg	Sertraline 200 mg	Placebo
Completers	63 (78.8%)	54 (66.7%)	59 (73.8%)	60 (71.4%)
Adverse Effects	6 (7.5%)	11 (13.6%)	6 (7.5%)	5 (6.0%)
Lack of Effect	5 (6.2%)	7 (8.6%)	7 (8.. %)	11 (13.1%)
Other	6 (7.5%)	9 (11.1%)	8 (10.0%)	8 (9.5%)

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 371/372 Y-BOCS Score

Mean (S.D.)

Week

	Baseline	1	2	4	6	8	10	12
Sertraline 50 mg	23.2 (5.9)	21.7 (6.8)	20.4 (6.4)	19.2 (7.0)	18.0 (7.5)	17.3 (7.7)	16.7 (7.1)	16.1 (7.3)
Sertraline 100 mg	24.6 (5.6)	23.6 (6.2)	22.8 (6.4)	21.7 (7.2)	20.2 (7.3)	19.3 (7.3)	18.6 (6.4)	18.5 (7.0)
Sertraline 200 mg	23.5 (4.3)	22.4 (5.2)	21.5 (5.7)	20.1 (6.4)	18.5 (7.0)	17.6 (8.0)	16.6 (7.6)	15.9 (8.3)
Placebo	23.4 (4.9)	22.4 (5.4)	22.0 (5.7)	21.3 (5.5)	21.0 (5.3)	19.5 (6.5)	19.3 (6.7)	18.6 (7.3)

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 371/372 CGI-S

Mean (S.D.)

Week

	Baseline	1	2	4	6	8	10	12
Sertraline 50 mg	4.7 (0.8)	4.6 (0.9)	4.4 (1.0)	4.2 (1.1)	4.0	3.9 (1.2)	3.8 (1.2)	3.7 (1.2)
Sertraline 100 mg	4.9 (0.8)	4.8 (1.0)	4.7 (1.0)	4.5 (1.0)	4.3 (1.0)	4.1 (1.1)	3.9 (1.0)	4.0 (1.1)
Sertraline 200 mg	4.6 (0.7)	4.5 (0.8)	4.4 (0.8)	4.3 (0.9)	4.0 (1.1)	3.9 (1.3)	3.8 (1.1)	3.8 (1.2)
Placebo	4.7 (0.8)	4.5 (0.8)	4.5 (0.9)	4.5 (1.0)	4.4 (1.0)	4.2 (1.0)	4.2 (1.0)	4.0 (1.2)

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 371/372 NIMH-OC

Mean (S.D.)

Week

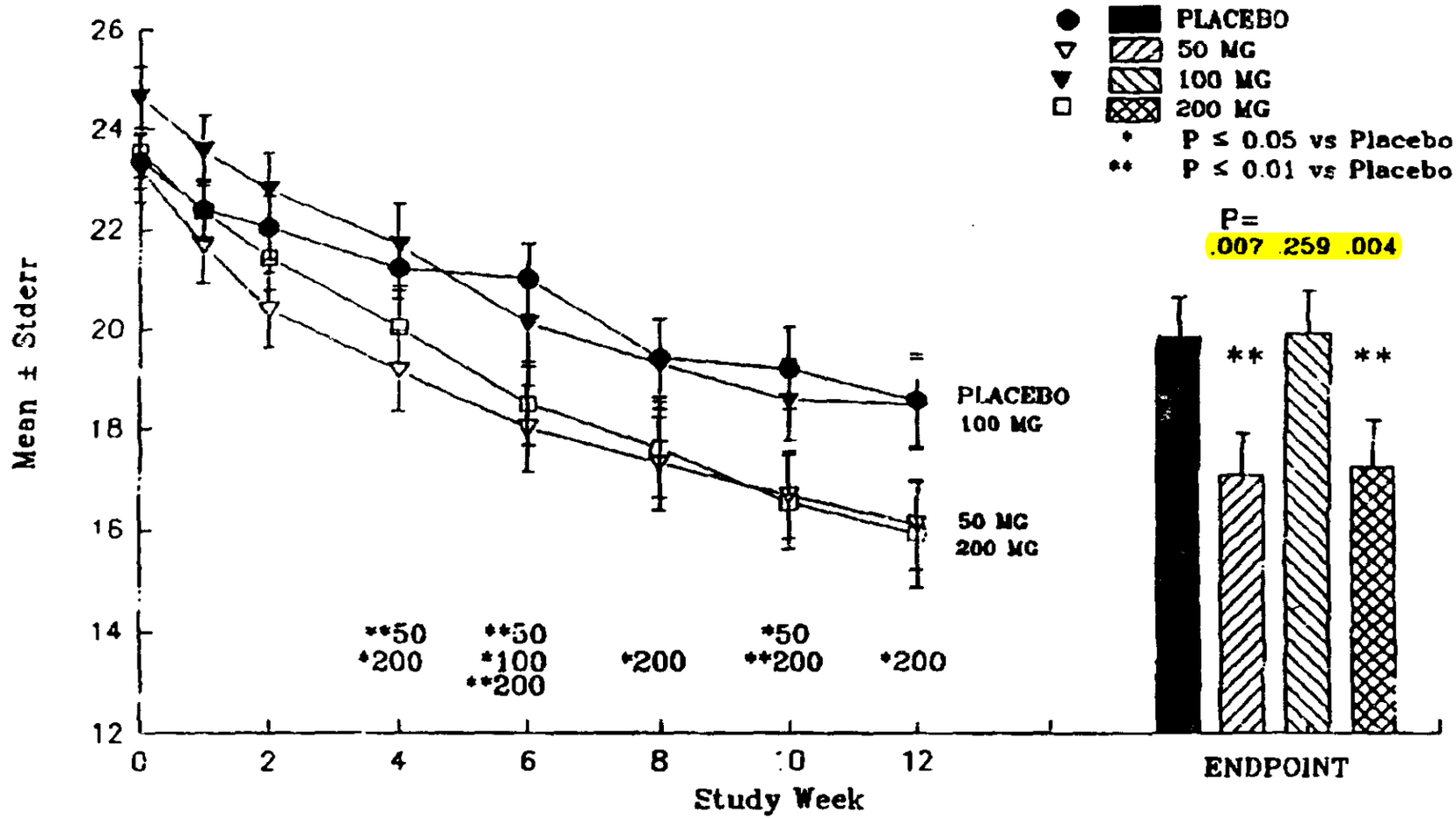
	Baseline	1	2	4	6	8	10	12
Sertraline 50 mg	9.2 (1.7)	9.0 (2.0)	8.4 (2.0)	8.0 (2.3)	7.6 (2.4)	7.4 (2.6)	7.2 (2.4)	7.0 (2.8)
Sertraline 100 mg	9.7 (1.7)	9.4 (2.0)	9.1 (2.0)	8.6 (2.1)	8.3 (2.1)	8.0 (2.2)	7.6 (2.2)	7.4 (2.2)
Sertraline 200 mg	9.0 (1.4)	8.7 (1.8)	8.5 (1.7)	8.1 (2.0)	7.6 (2.4)	7.4 (2.6)	7.1 (2.6)	6.9 (2.8)
Placebo	9.2 (1.5)	9.0 (1.8)	8.8 (2.0)	8.6 (1.9)	8.5 (2.0)	8.0 (2.1)	8.0 (2.0)	7.7 (2.4)

(Sample size chart for weekly graph for protocol 371/372.)

Sample Size				
Week	50mg	100mg	200mg	Plac.
0	79	81	80	84
1	79	81	80	83
2	77	78	76	82
4	75	73	74	79
6	72	70	71	77
8	71	65	70	71
10	69	60	65	65
12	67	60	63	61
Endpoint	79	81	80	84

NDA 19-839: Sertraline (Zoloft) Protocol 371/372

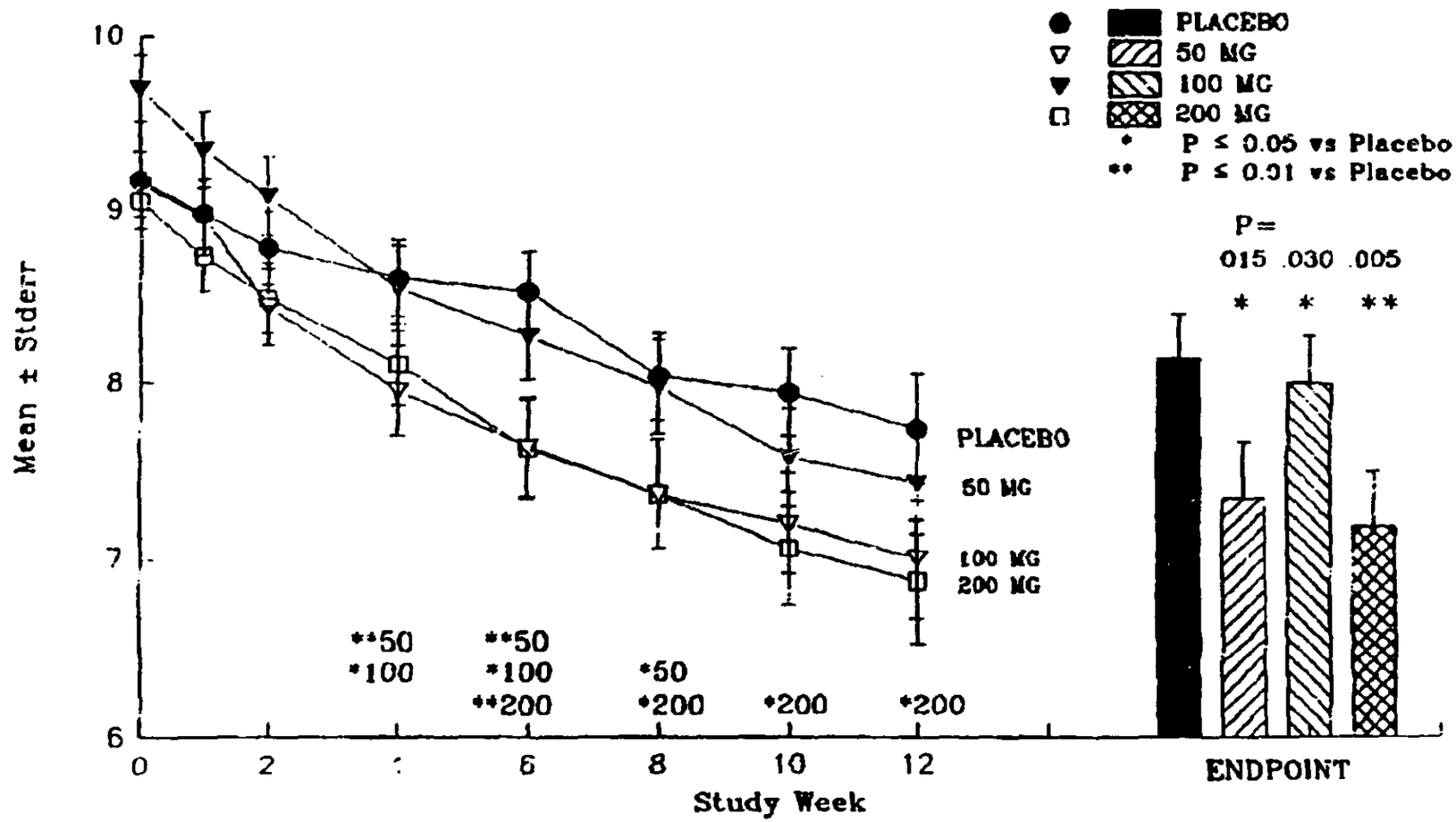
Y-BOCS



13

NDA 19-839 Sertraline (Zoloft) Protocol 371/372

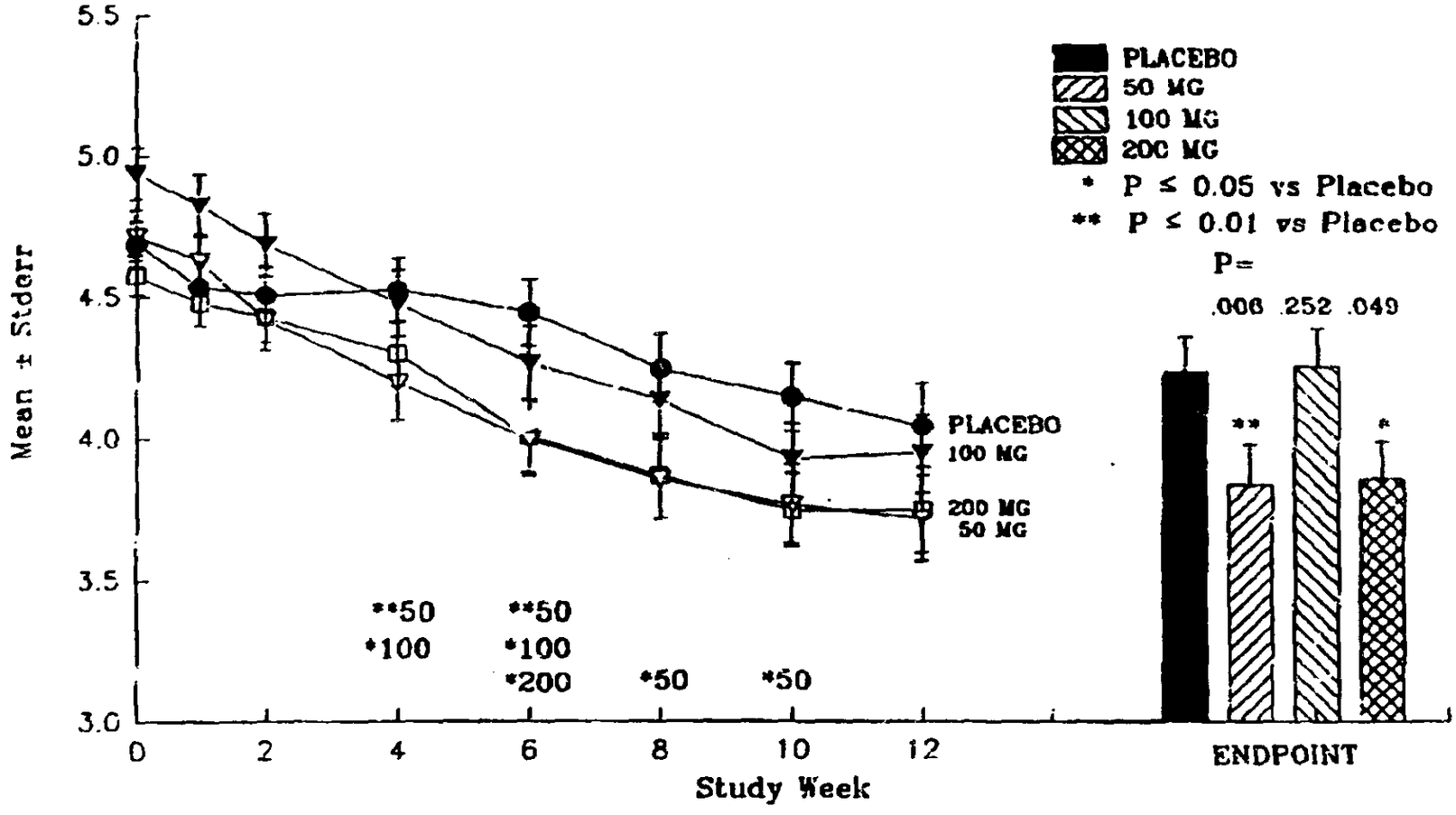
NIMH



32

NDA 19-839: Sertraline (Zoloft) Protocol 371/372

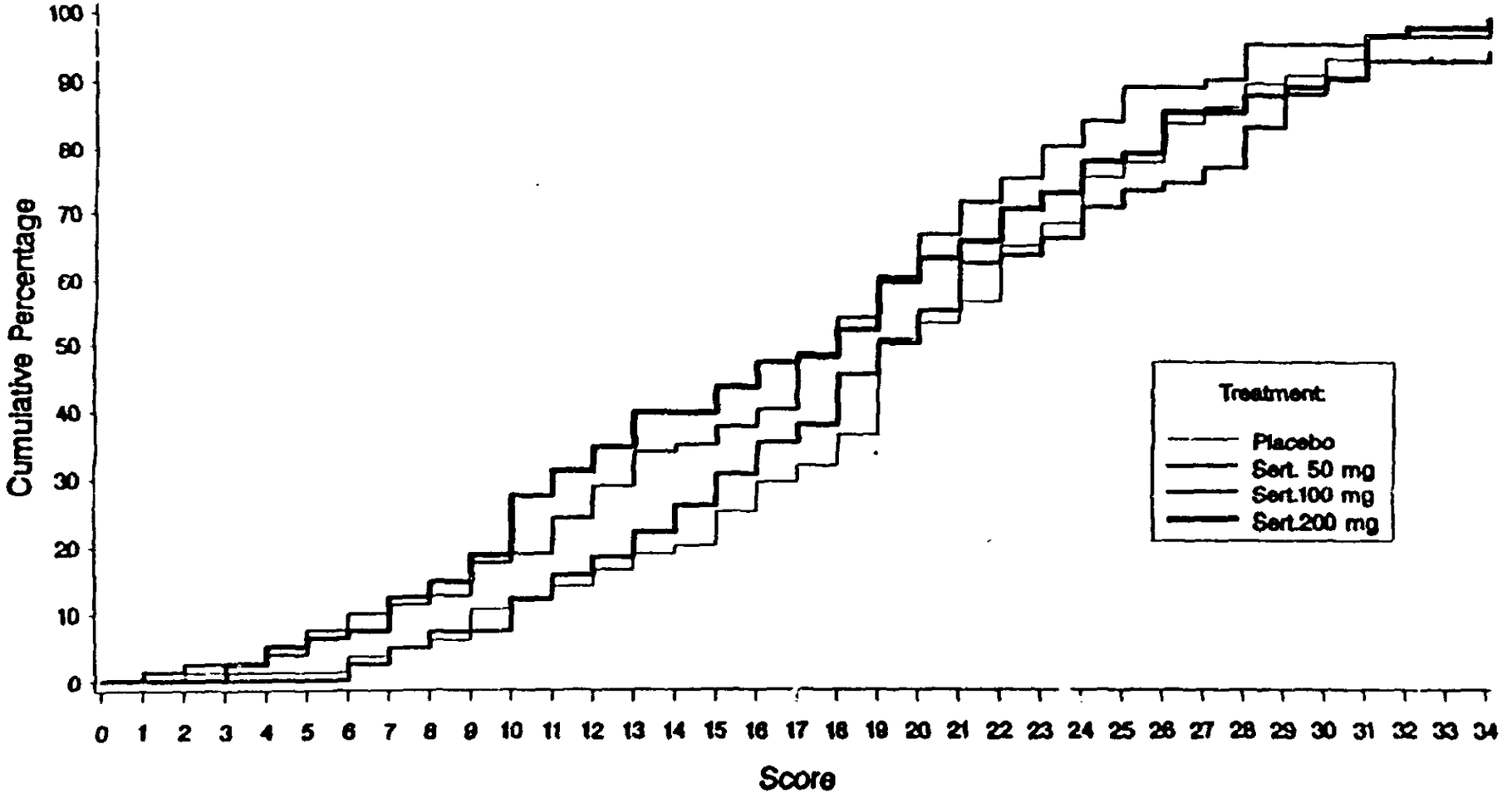
CGI Severity



33

NDA 19-839: Sertraline (Zoloft)
Protocol: 371/372

CUMULATIVE DISTRIBUTION FUNCTION OF Y-BOCS SCORES AT ENDPOINT



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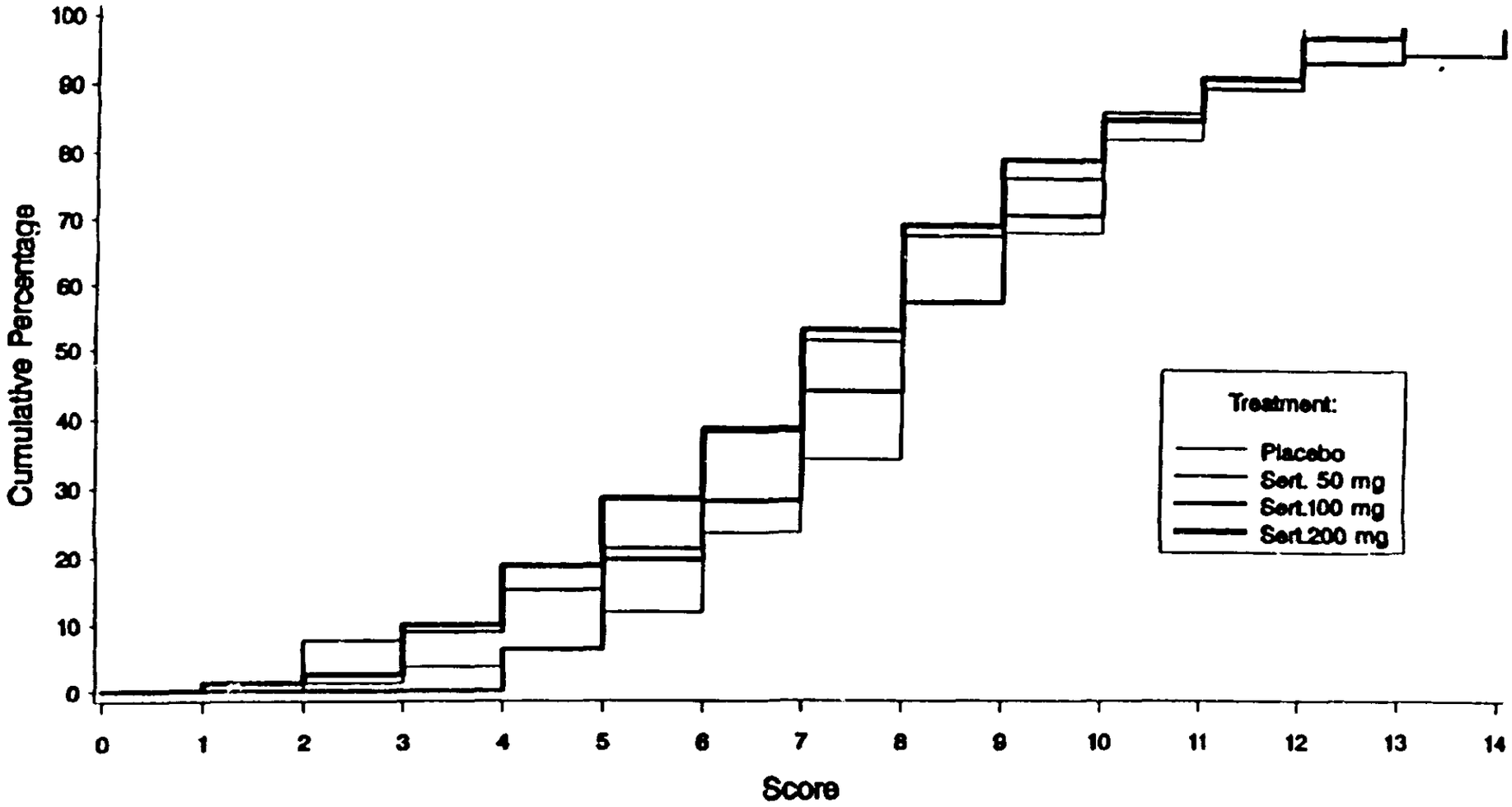
NDA 19-839: Sertraline (Zoloft)
Protocol: 371/372

CUMULATIVE DISTRIBUTION FUNCTION OF NIMH SCORES AT ENDPOINT



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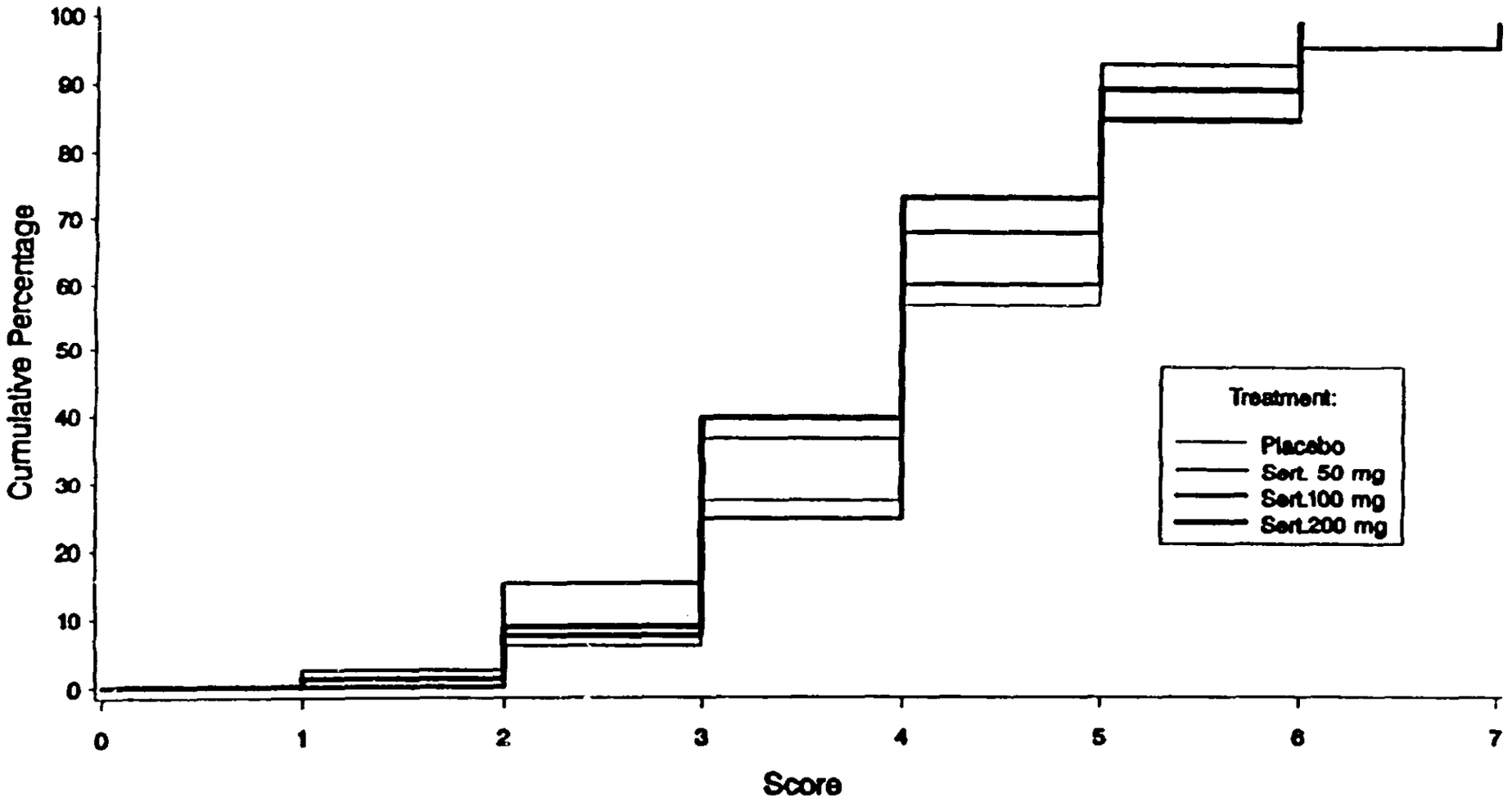
NDA 19-839: Sertraline (Zoloft)
Protocol: 371/372

CUMULATIVE DISTRIBUTION FUNCTION OF CGI SEVERITY AT ENDPOINT



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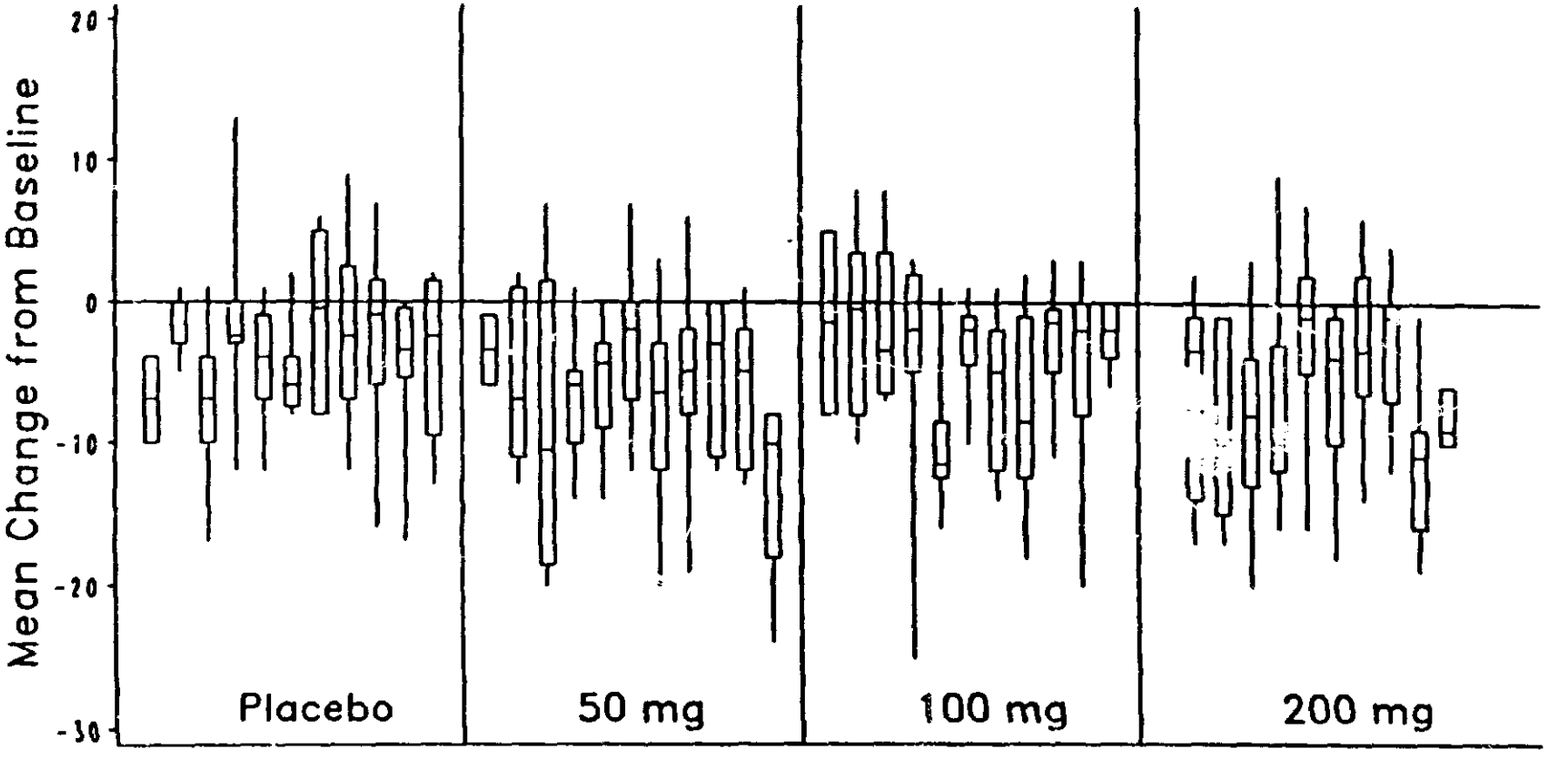
NDA 19–839: Sertraline (Zoloft)
Protocol 371/372

Y–BOCS TOTAL SCORE CHANGE FROM BASELINE TO ENDPOINT



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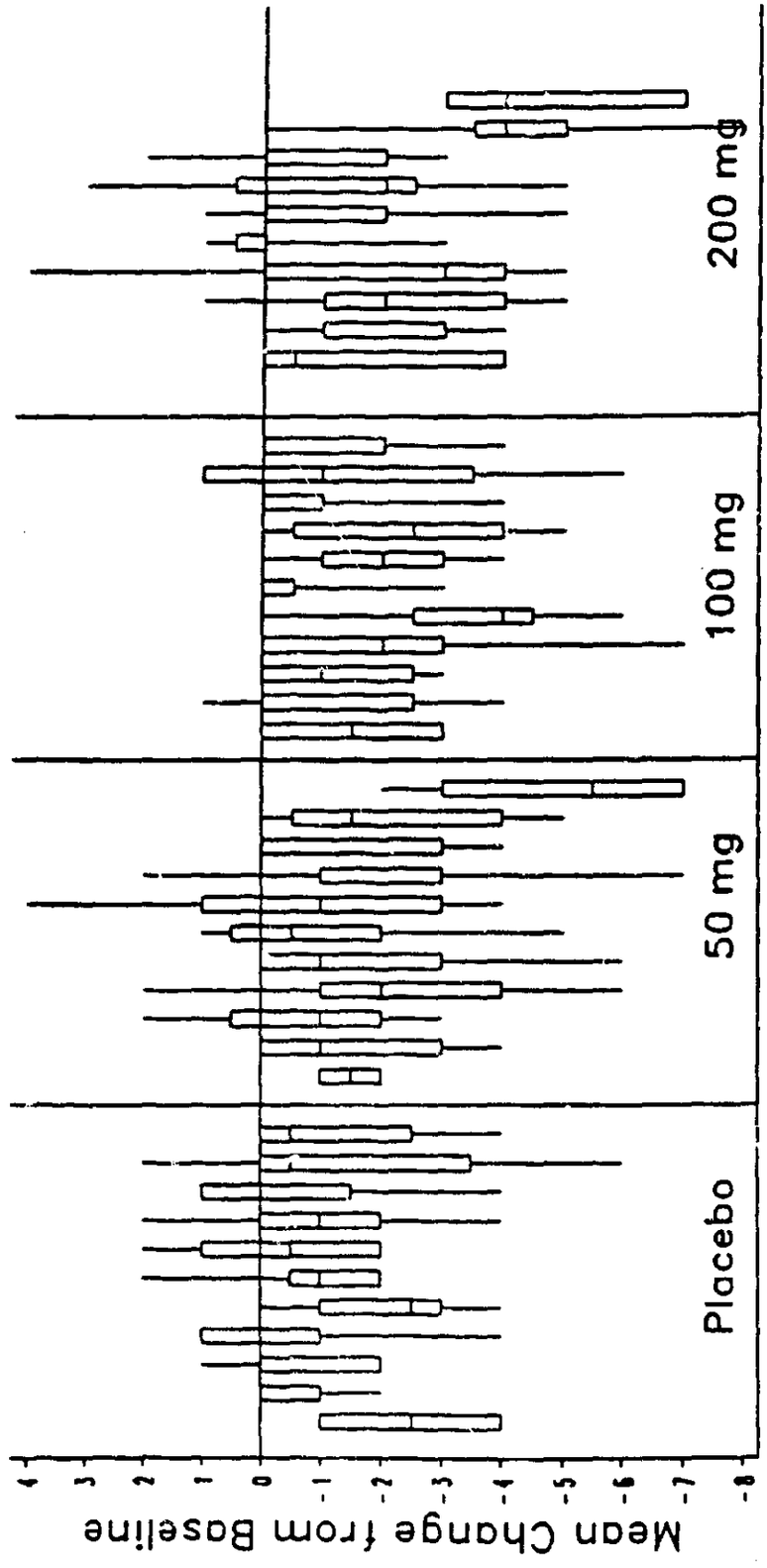
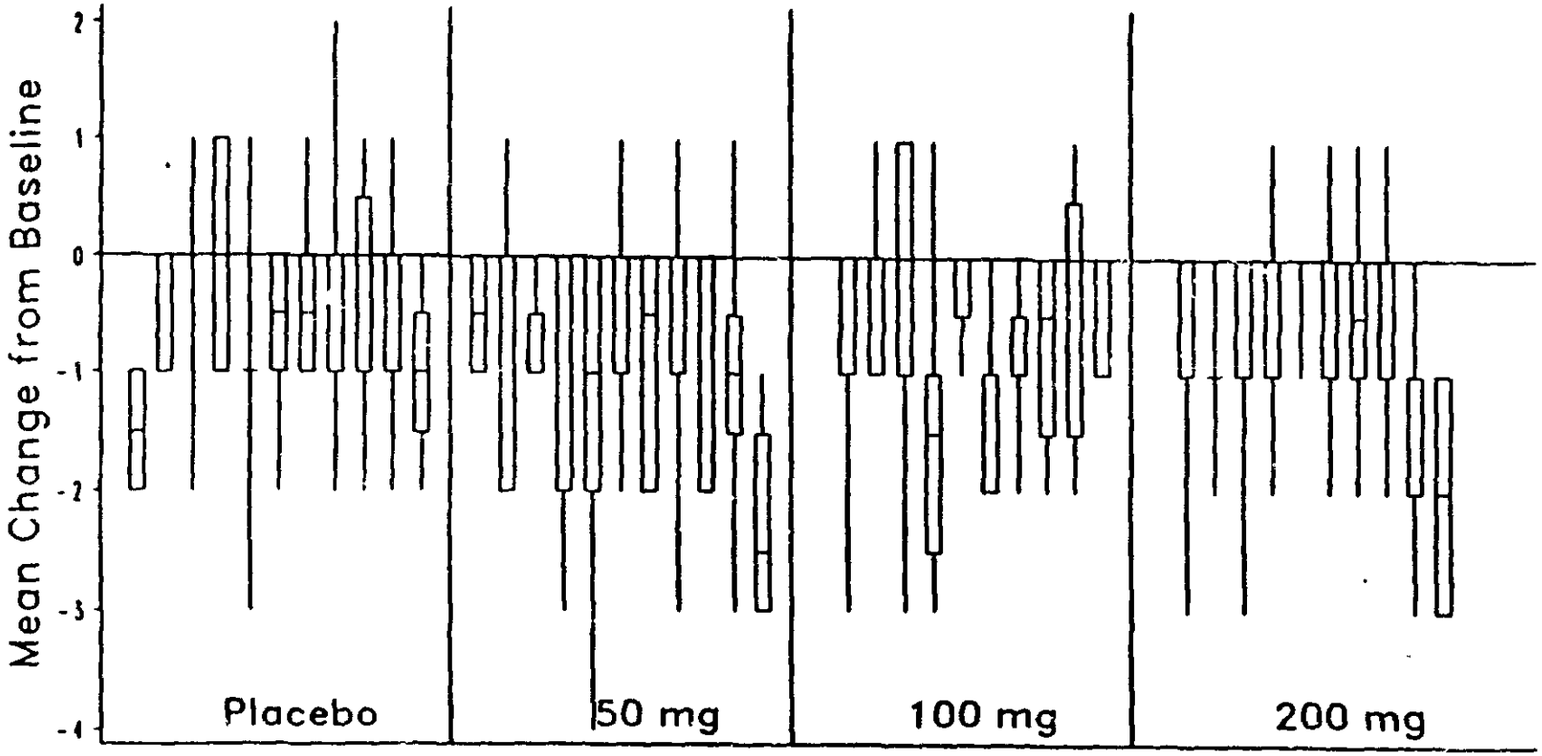
NDA 19-839: Sertraline (Zoloft)
Protocol 371/372

NIMH CHANGE FROM BASELINE TO ENDPOINT



NDA 19–839: Sertraline (Zoloft)
Protocol 371/372

CGI SEVERITY CHANGE FROM BASELINE TO ENDPOINT



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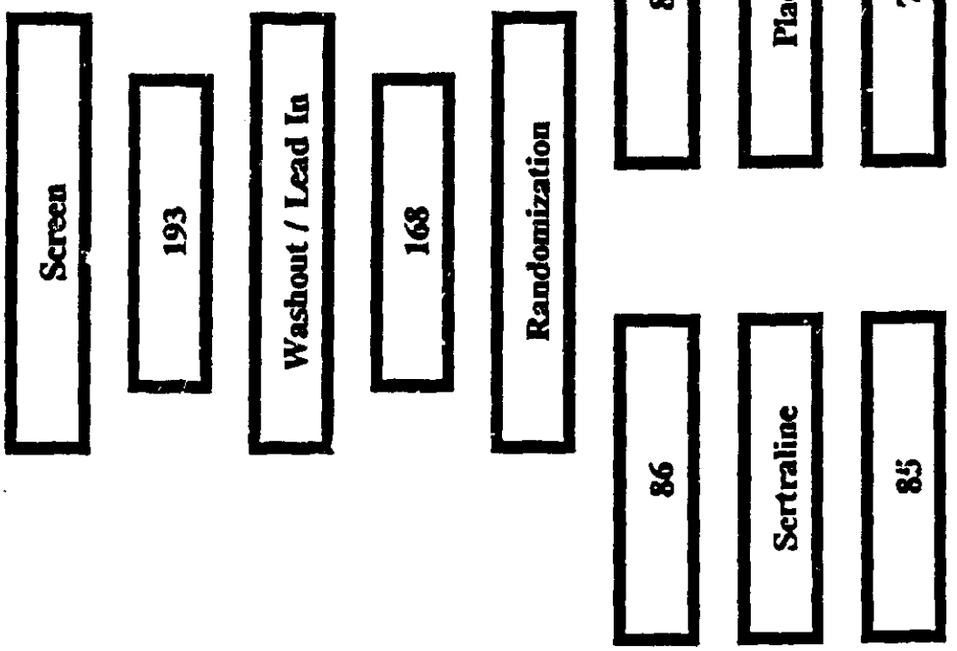
NDA 19-839: Sertraline (Zoloft) in OCD
Protocol 546 Number of Subjects



NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 546 Demographic Characteristics

N (Percent)

	Sertraline (N = 86)	Placebo (N = 81)
Sex		
Male	49 (57.0%)	43 (53.1%)
Female	37 (43.0%)	38 (46.9%)
Race		
Caucasian	83 (96.5%)	77 (95.1%)
Other	3 (3.5%)	4 (4.9%)
Mean Age (yrs)	35.3	38.1
Median Age	34.7	37.0
Age Range	18-62	18-71

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 546 Baseline Comparisons

	Sertraline			Placebo		
	n	Mean	S.D.	n	Mean	S.D.
Y-BOCS	85	25.2	3.8	79	25.0	4.1
NIMH-OC		9.0	1.2		9.1	1.6
CGI-S		4.6	0.6		4.7	0.7
CGI-I						
HDRS		8.2	4.5		7.7	4.0

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 546 Dropouts

	Week								
	Baseline	1	2	3	4	6	8	10	12
Sertraline		1	4	3	3	3	5	5	1
Placebo		4	4	1	3	5	5	3	0
Non-Randomized	25								

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 546 Reasons for Termination

n (percent)

	Sertraline	Placebo
Completers	61 (70.9%)	56 (69.1%)
Adverse Effects	9 (10.5%)	4 (4.9%)
Lack of Effect	6 (7.0%)	9 (11.1%)
Other	10 (11.6%)	12 (14.8%)

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 546 Y-BOCS

Mean (S.D.)

Week

	Baseline	1	2	3	4	6	8	10	12
Sertraline	25.2 (3.8)	24.0 (4.7)	23.2 (6.3)	21.3 (6.9)	21.6 (7.1)	19.7 (7.1)	17.9 (7.9)	17.0 (7.2)	16.1 (7.8)
Placebo	25.0 (4.1)	23.5 (5.4)	23.3 (5.4)	22.9 (5.6)	22.6 (6.0)	21.8 (7.0)	21.8 (6.5)	21.5 (7.5)	19.8 (8.1)

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 546 NIMH

Mean (S.D.)

Week

	Baseline	1	2	3	4	6	8	10	12
Sertraline	9.0 (1.2)	8.8 (1.4)	8.5 (2.0)	8.1 (2.0)	8.1 (2.3)	7.5 (2.2)	6.9 (2.5)	6.7 (2.3)	6.3 (2.6)
Placebo	9.1 (1.6)	8.8 (1.8)	8.6 (1.7)	8.4 (1.8)	8.4 (2.0)	8.2 (2.0)	8.2 (2.1)	8.0 (2.4)	7.4 (2.7)

NDA 19-839: Sertraline (Zoloft) in OCD

Protocol 546 CGI-S

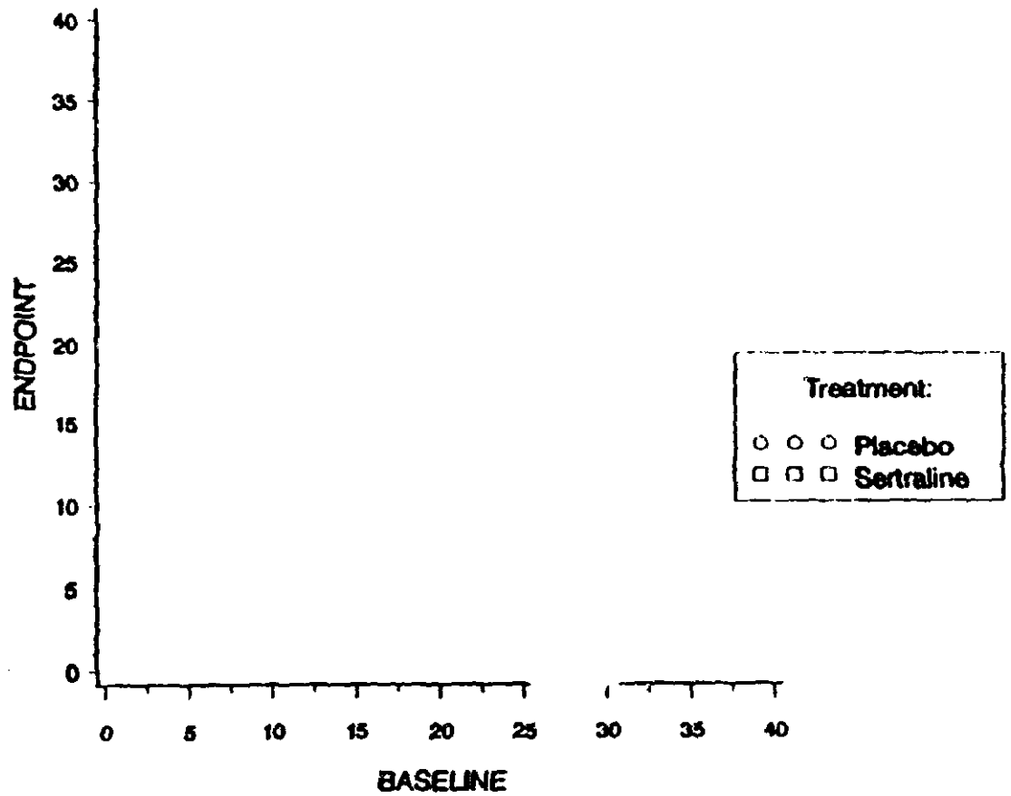
Mean (S.D.)

Week

	Baseline	1	2	3	4	6	8	10	12
Sertraline	4.6 (0.6)	4.5 (0.7)	4.4 (0.9)	4.2 (0.8)	4.2 (1.0)	3.9 (1.0)	3.7 (1.1)	3.6 (1.1)	3.4 (1.2)
Placebo	4.7 (0.7)	4.6 (0.8)	4.5 (0.7)	4.4 (0.8)	4.4 (0.9)	4.2 (0.9)	4.3 (0.9)	4.2 (1.0)	3.9 (1.2)

NDA 19-839: Sertraline (Zoloft)
Protocol: 546

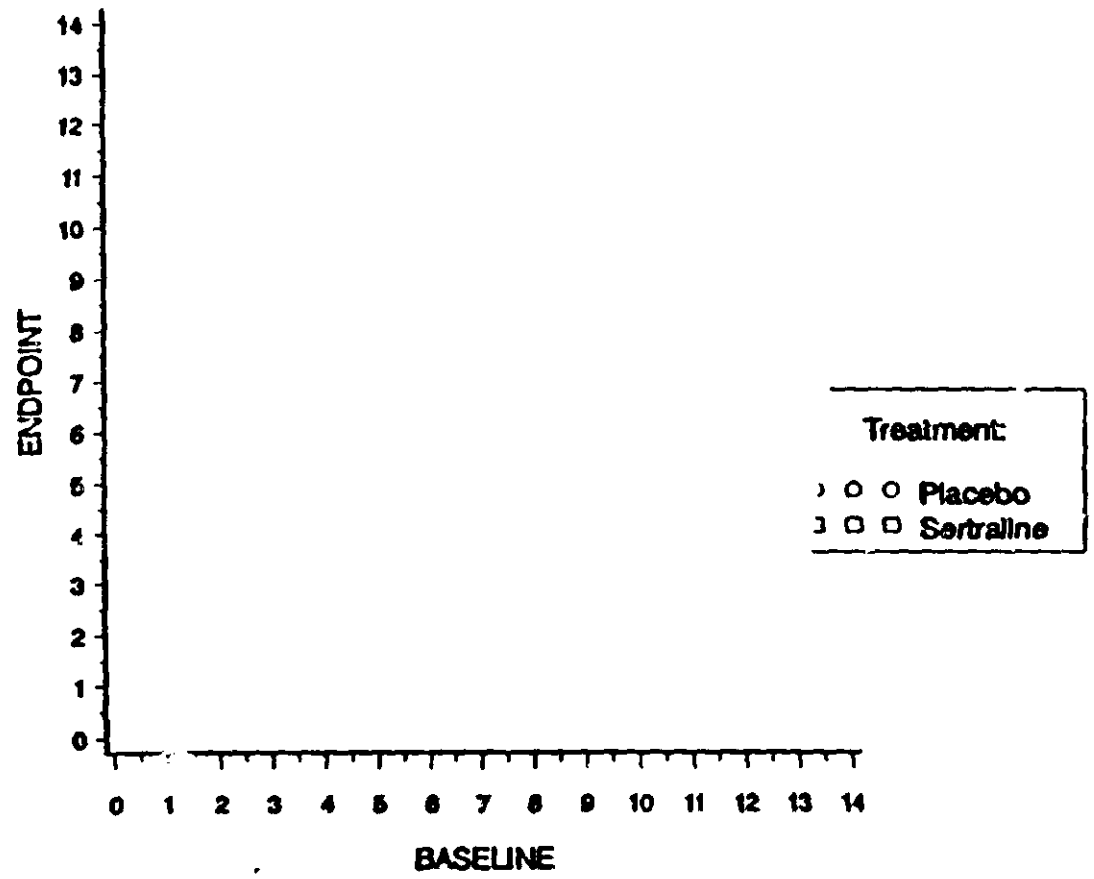
Y-BOCS AT BASELINE
BY Y-BOCS AT ENDPOINT



C:\S546\SCATYB.SAS,JEF 08MAR94

NDA 19-839: Sertraline (Zoloft)
Protocol: 546

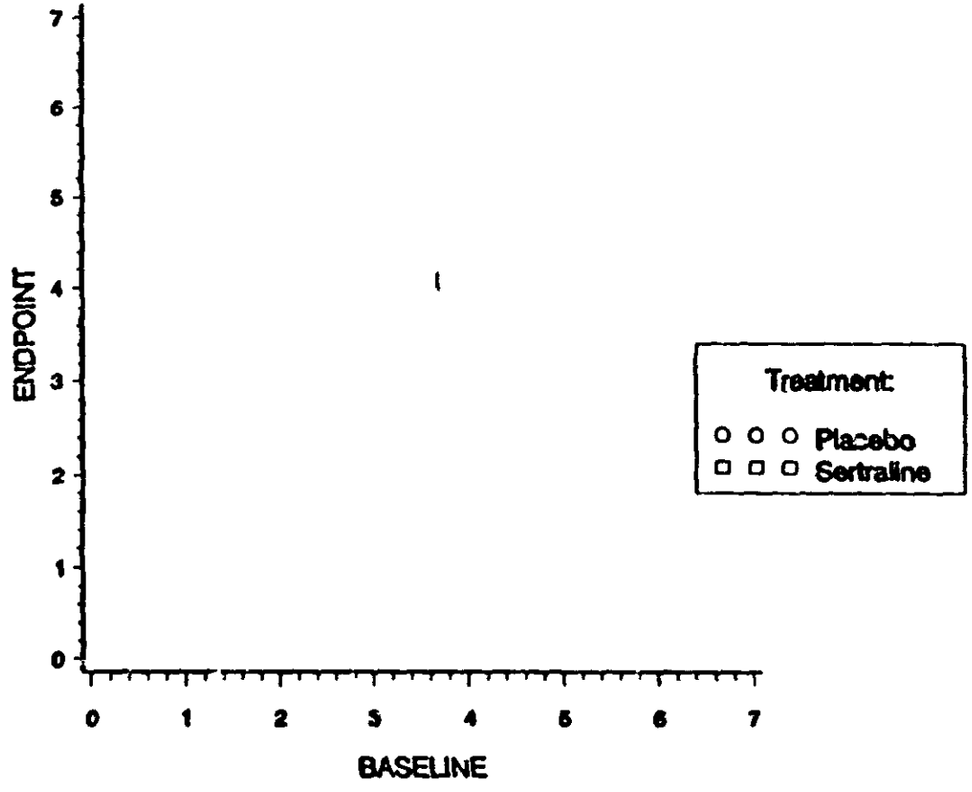
NIMH SCORE AT BASELINE
BY NIMH SCORE AT ENDPOINT



C:\S546\SCATNIMH.SAS,JEF 23FEB04

NDA 19-839: Sertraline (Zoloft)
Protocol: 546

CGI SEVERITY AT BASELINE
BY CGI SEVERITY AT ENDPOINT



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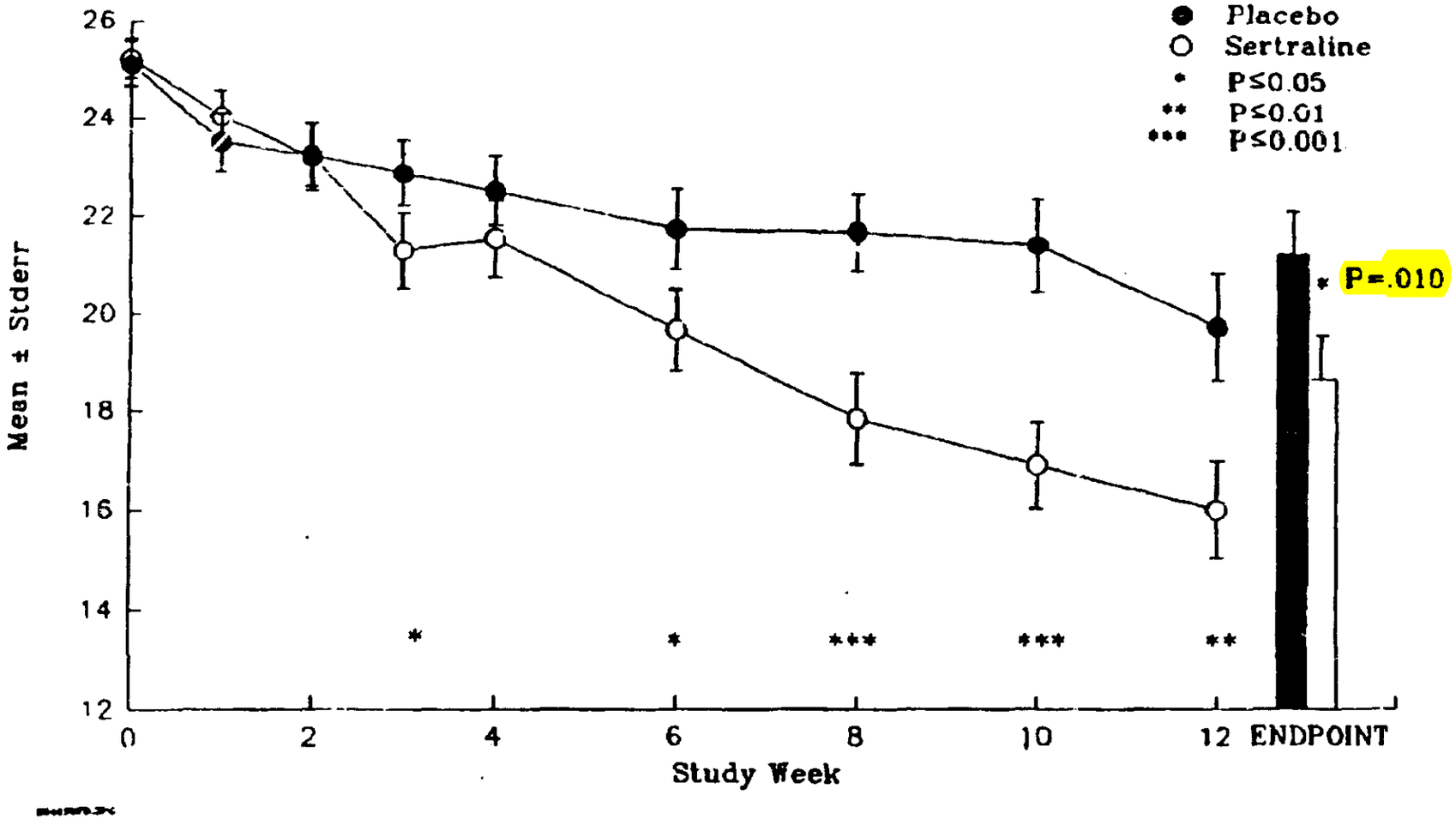
Sample Size		
Week	Sert.	Plac.
0	85	79
1	85	79
2	84	75
3	79	74
4	79	70
6	73	69
8	70	64
10	66	58
12	61	55
Endpoint	85	79

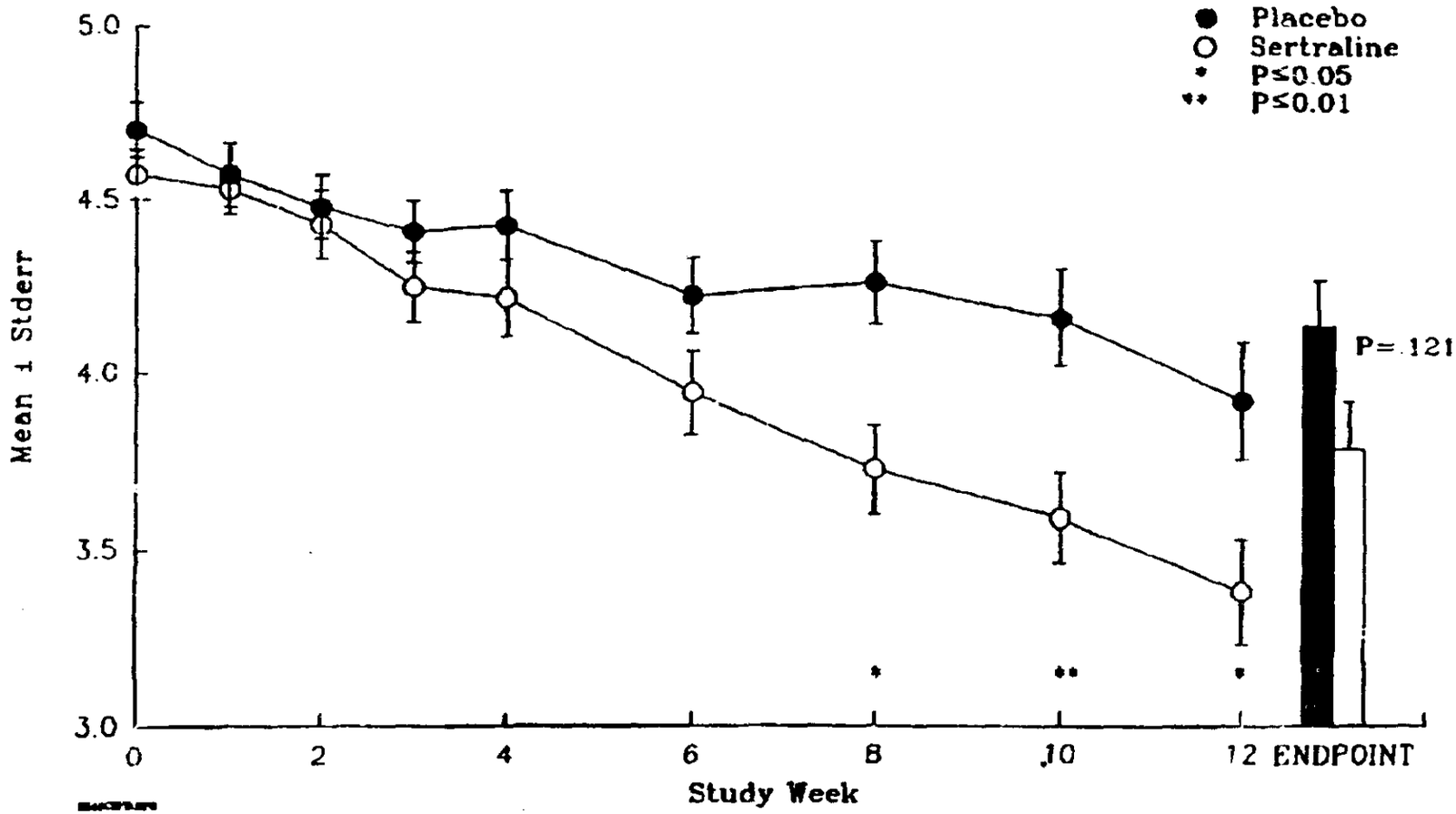
(Sample size chart for weekly graph for protocol 546.)

NDA 19-839: Sertraline (Zoloft) Protocol 546
Y-BOCS



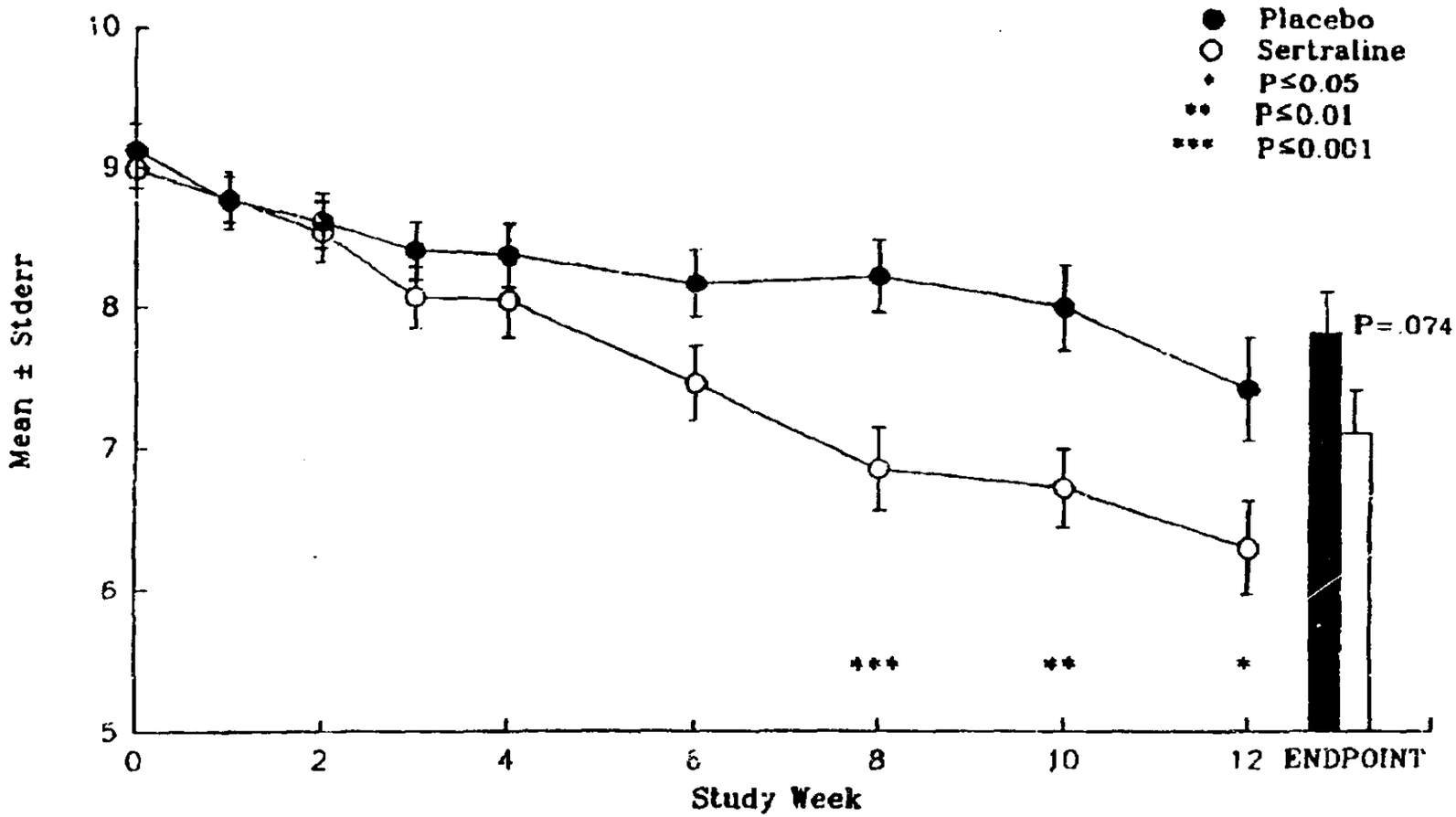
S1

NDA 19-839: Sertraline (Zoloft) Protocol 546
CGI Severity



52

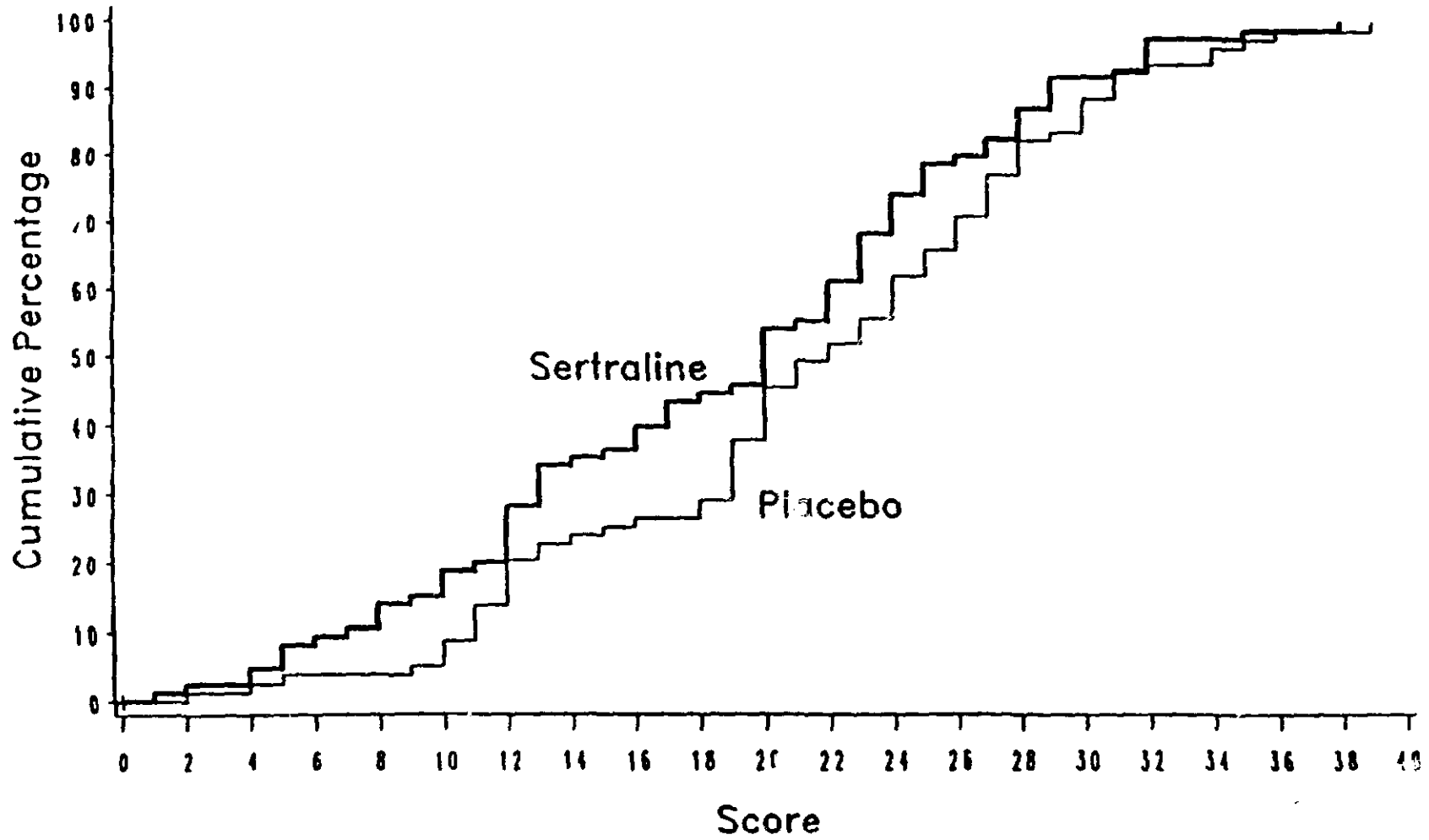
NDA 19-839: Sertraline (Zoloft) Protocol 546
NIMH



S-2

NDA 19-839: Sertraline (Zoloft)
Protocol: 546

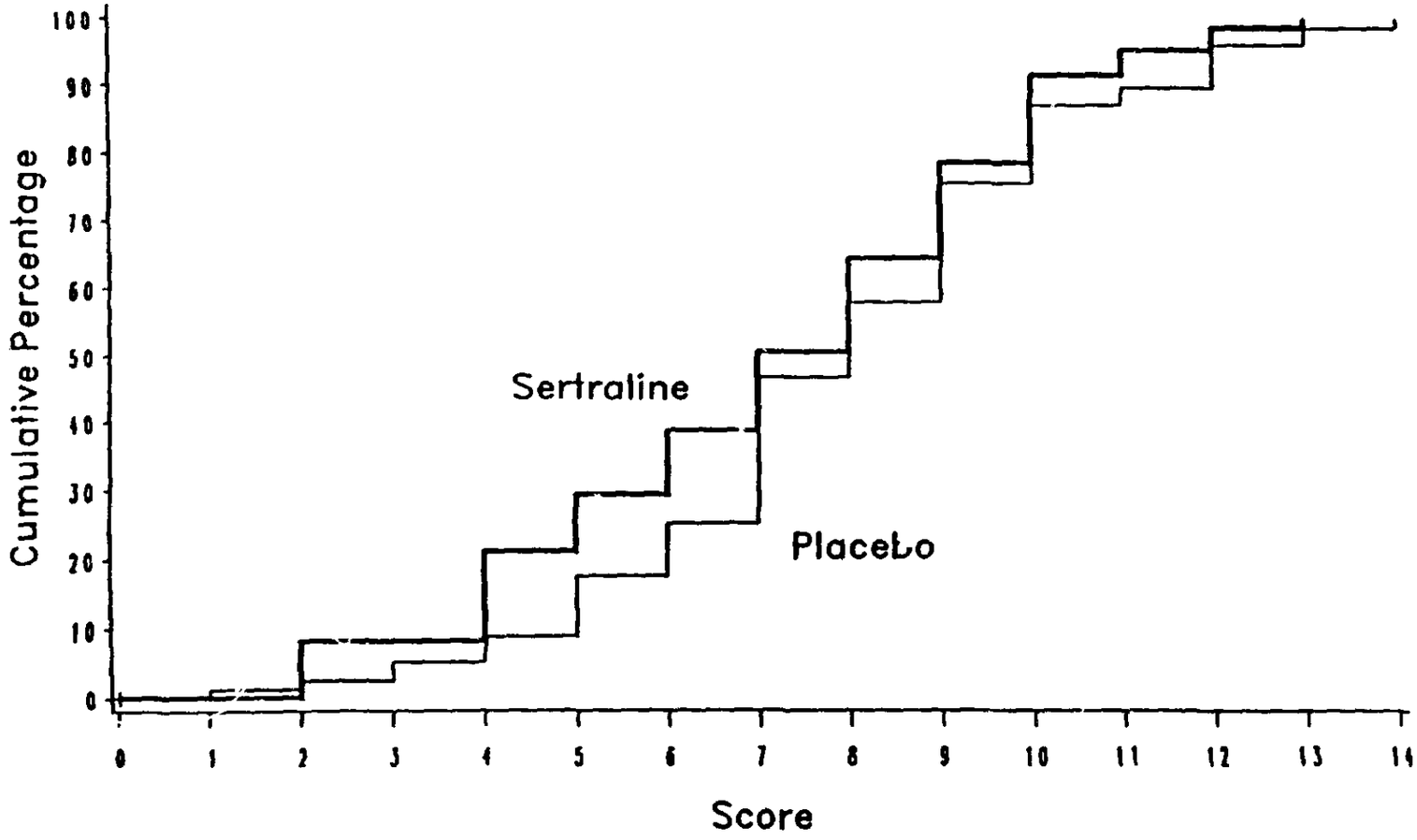
CUMULATIVE DISTRIBUTION FUNCTION OF Y-BOCS SCORES AT ENDPOINT



C: SASUZ S237 CUMDEP.SAS,LAL 08MAR94

NDA 19-839: Sertraline (Zoloft)
Protocol: 546

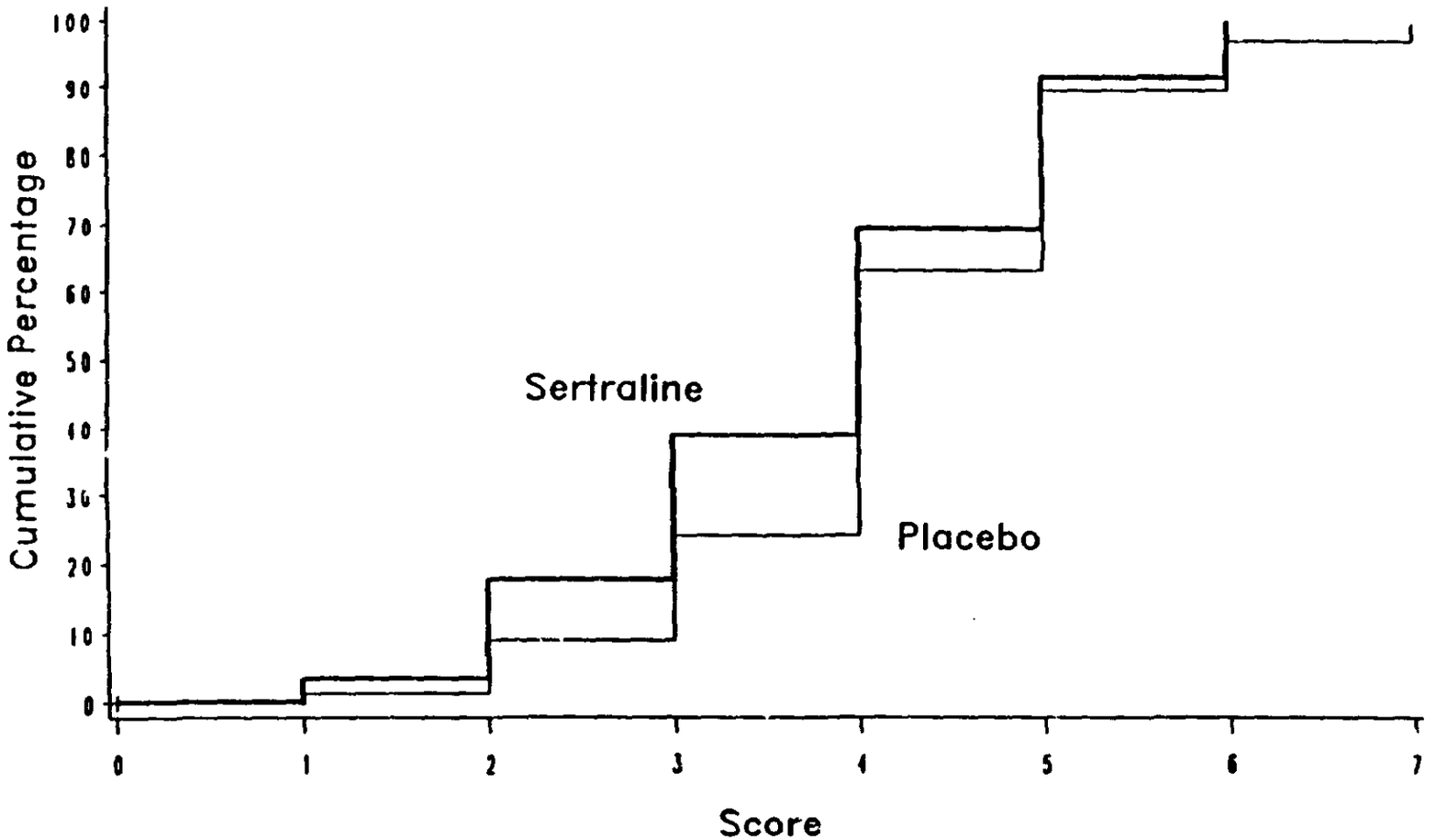
CUMULATIVE DISTRIBUTION FUNCTION OF NIMH SCORES AT ENDPOINT



C: SASUZ S237 CUMDEP.SAS,LAL 01MAR94

NDA 19-839: Sertraline (Zoloft)
Protocol: 546

CUMULATIVE DISTRIBUTION FUNCTION OF CGI SEVERITY AT ENDPOINT



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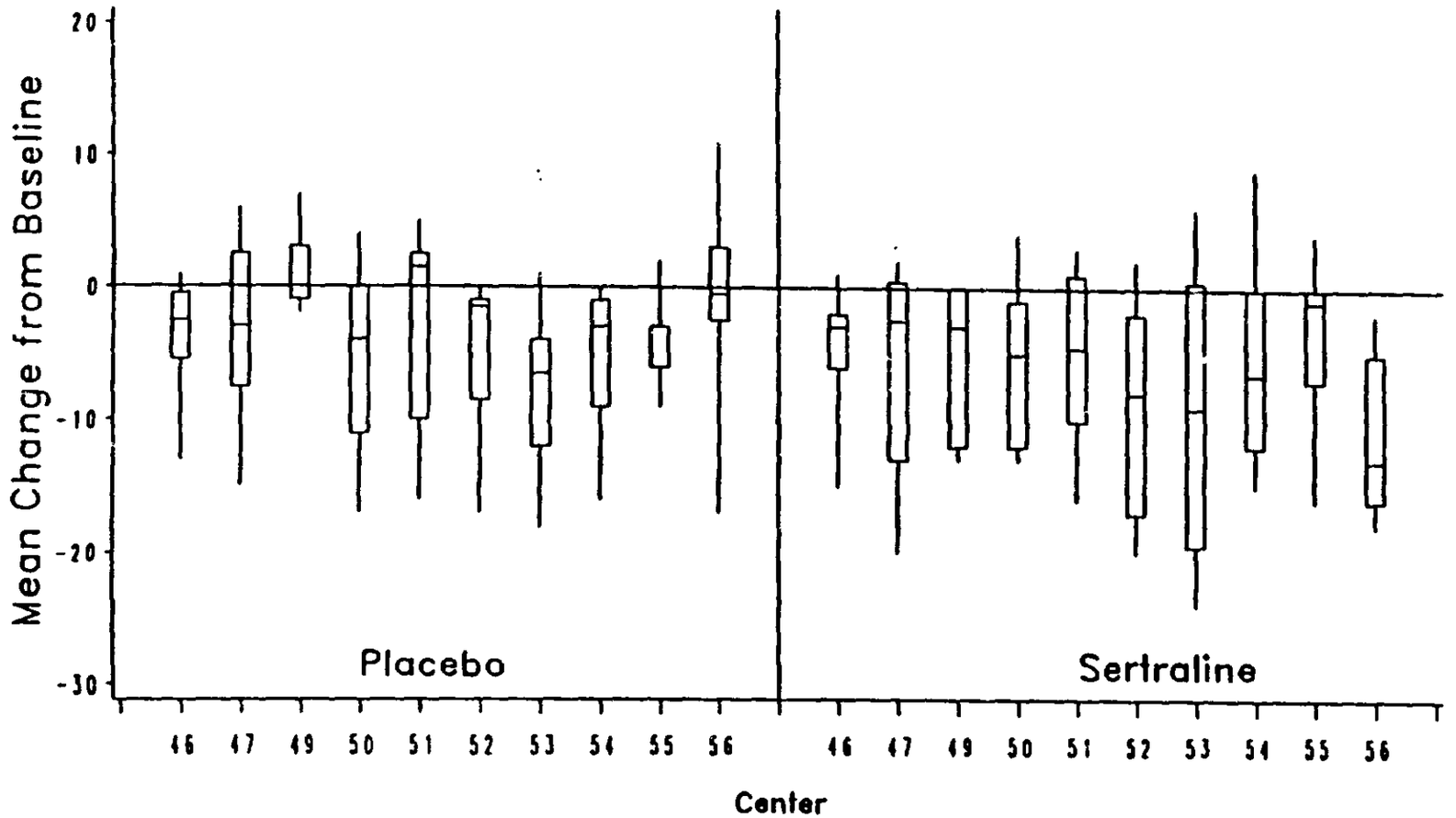
NDA 19-839: Sertraline (Zoloft)
Protocol 546

Y-BOCS CHANGE FROM BASELINE TO ENDPOINT



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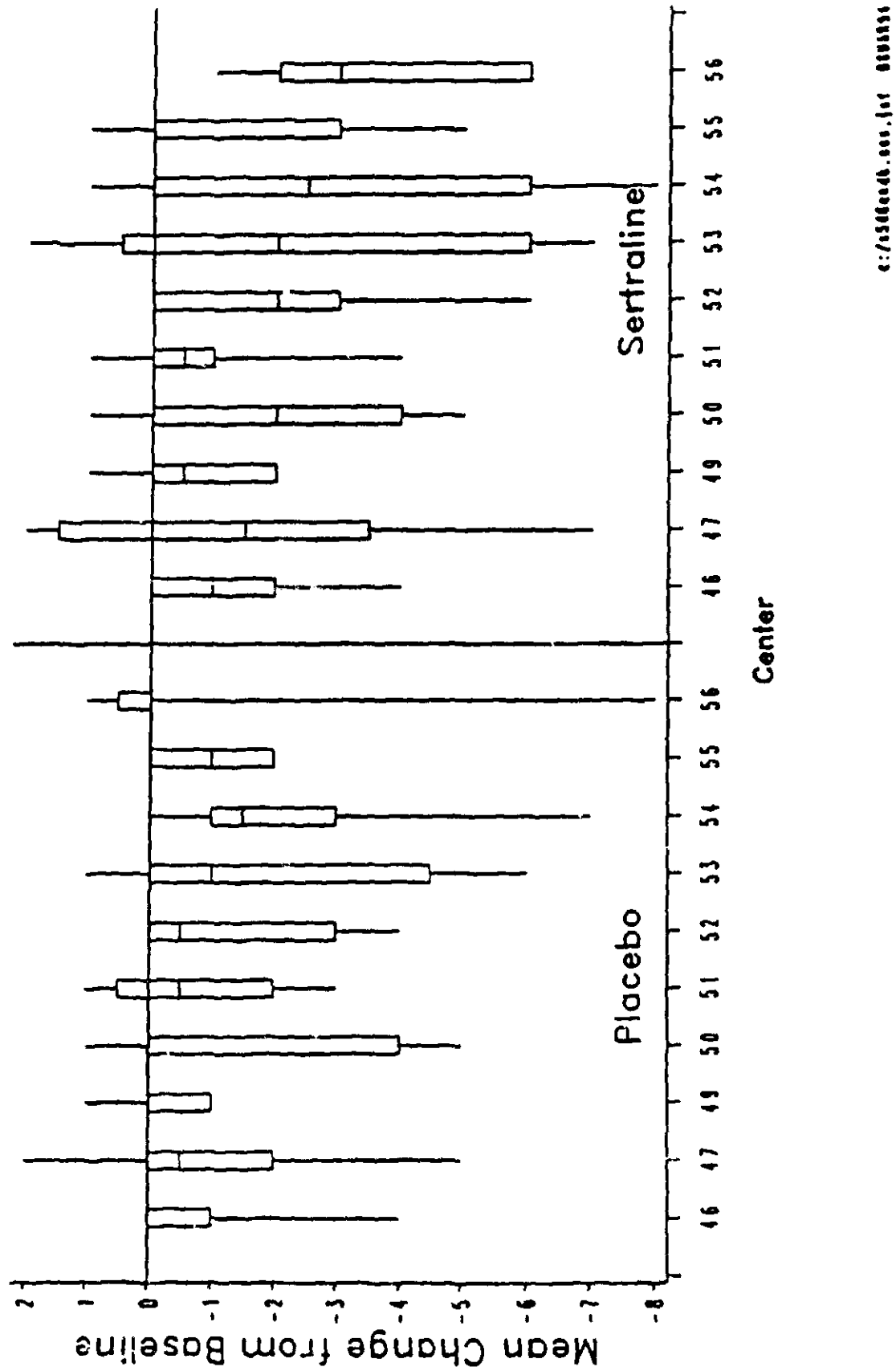
NDA 19-839: Sertraline (Zoloft)
Protocol 546

NIMH CHANGE FROM BASELINE TO ENDPOINT



NDA 19-839: Sertraline (Zoloft)
Protocol 546

CGI SEVERITY CHANGE FROM BASELINE TO ENDPOINT