CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-839/S-044

20-990/S-010

MEDICAL REVIEW

Review of Clinical Data

NDA:	19-839, 20-990
Drug Name:	Generic Name: Sertraline
	Trade Name: Zoloft
Sponsor:	Pfizer
Material Reviewed:	Submissions dated 6/26/03, 7/28/03, 8/12/03
	Andrew Mosholder's Review dated 8/13/02
Reviewer:	Gerard Boehm, MD, MPH
Date Completed:	9/3/03

The purpose of this memo is to review sertraline weight data analyses

Background

To assess growth during pediatric depression sertraline studies, the division asked Pfizer to provide analyses of weight data. Specifically, the division asked for analyses that examine changes in mean weight z-scores. For these analyses, the division asked Pfizer to assign a z-score to each study subject for baseline and end of study. The z-score is the number of standard deviations from the population mean for a specific subject's weight, given their age and sex. This analysis uses population data from CDC growth charts and allows a determination about whether study subjects are growing along their predicted growth curve. No change in mean z-score would indicate that subjects are growing as predicted by data from age adjusted peers. Decreases in mean z-score would indicate that subjects are lagging behind in growth.

Pfizer responded with a series of tables and graphs summarizing the z-score analyses and an electronic data set with weight and z-score data. They provided no discussion of the results. Separately, Pfizer provided labeling describing the results of these analyses.

Studies reviewed

The weight data analyses submitted by Pfizer came from two randomized controlled trials in depression (1001, 1017), and one open label extension trial (1015). The controlled trials were identically designed, used flexible dose sertraline (50-200mg), and lasted ten weeks. The open label extension enrolled subjects from both controlled trials and lasted twenty-four weeks. Subjects who were randomized to sertraline in the placebo controlled trial and completed the open label extension were treated with sertraline for a total of 34 weeks. The controlled trials included 189 subjects exposed to sertraline and 184 exposed to placebo. The extension trial included 221 subjects. Pfizer noted that all but 4 weight measurements included in their analyses were taken within 7 days of sertraline discontinuation (Table 3.4 6/28/03 submission).

Results from RCTs

Pfizer Analyses

Pfizer's analysis of the RCT data included only an output table that provided the mean z-scores at baseline and end of study by treatment for all subjects and stratified by sex. The following table summarizes the results provided by Pfizer.

Overall and Sex-stratified Mean Change from Baseline Weight Z-Scores, from Sertraline Placebo Controlled Pediatric Depression Trials

	Mean Change in weight z-score	
	Sertraline	Placebo
Overall	-.122 (n=187)	-.005 (n=180)
Male	-.112 (n=79)	.004 (n=101)
Female	-.129 (n=108)	-.016 (n=79)

From Pfizer table 1.1, 6/28/03 submission

FDA Analyses

Using the submitted electronic data sets, I conducted additional analyses of the weight data from the sertraline placebo controlled pediatric depression trials. The mean duration of treatment in the placebo controlled trials was similar in both treatment groups, 62 days for sertraline and 65 days for placebo. In the randomized placebo controlled trials, the mean change in weight for the sertraline group was -0.4kg compared to +0.8kg in the placebo group. The weight findings were similar when viewed separately for each study. In study 1001, sertraline subjects lost 0.3kg and placebo subjects gained 0.7kg and in study 1017, sertraline subjects lost 0.5kg and placebo subjects gained 0.8kg.

There were slight differences in the weight change results when stratified by sex. Male sertraline subjects had a mean decrease in weight of 0.12kg while male placebo subjects had a mean increase in weight of 1.04kg. Female sertraline subjects had a mean decrease in weight of 0.56kg while female placebo subjects had a mean increase in weight of 0.45kg.

When examined by last dose, there appeared to be some evidence of dose response for weight loss except for those subjects in the highest last dose group. The 50mg group lost 0.2kg (n=40), the 100mg group lost 0.3kg (n=56), the 150mg group lost 0.9kg (n=38) and the 200mg group lost 0.5kg (n=53). This finding may be confounded by duration of treatment because the 50mg group had the shortest duration (mean 53 days) followed by the 100mg group (mean 59 days), the 150mg group (mean 68 days), and the 200mg group (mean 70 days).

Results from Open label study

Pfizer Analyses

In their presentation of the open label study results, Pfizer used two groupings of the data, subjects who received sertraline in the preceding controlled trials (sertraline/sertraline) and subjects who received placebo in the preceding controlled trials (placebo/sertraline). Using only the data for those subjects who continued into open label treatment, Pfizer reported that the sertraline/sertraline subjects experienced an increase in mean z-score of 0.1 from the beginning of the open label phase (Pfizer table 2.1, 6/28/03 submission). The subjects who received sertraline for the first time during the open label phase experienced a mean decrease in z-score of -0.06 (Pfizer table 2.1, 6/28/03 submission). Pfizer also calculated the mean change in weight z-score using the baseline from the placebo

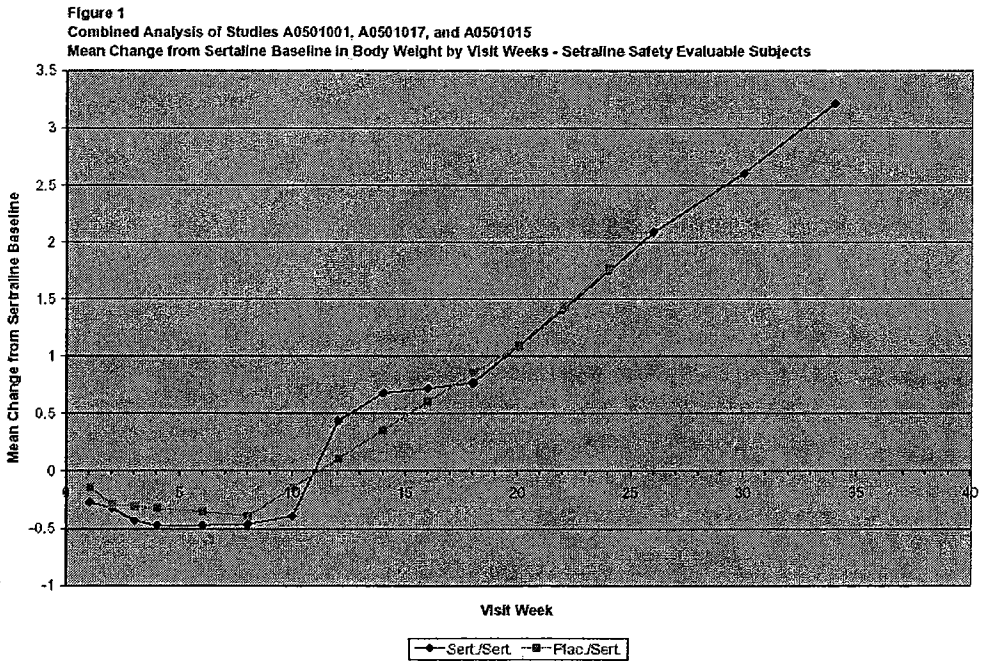
controlled trials for subjects who participated in the open label trial. For this analysis the sertraline/sertraline subjects had a mean decrease in z-score of .002 and the placebo/sertraline subjects had a mean decrease in z-score of .054 (Pfizer table 2.2, 6/28/03 submission).

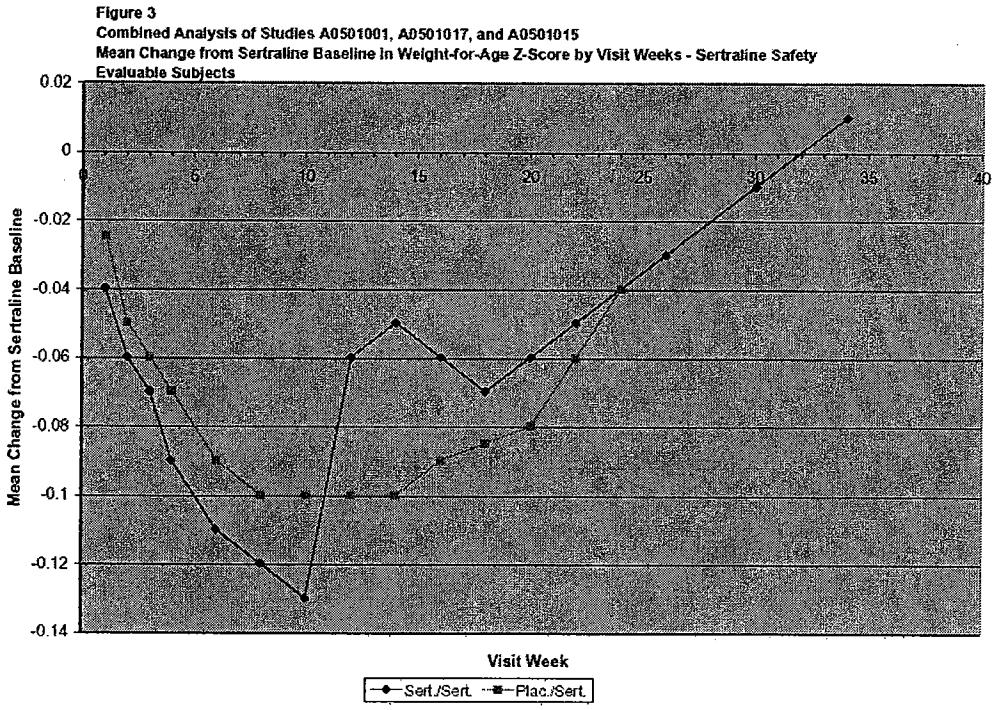
Results from Pooled Data

Pfizer Analyses

Pfizer pooled the sertraline exposure data from the randomized controlled trials (sertraline exposed) with the open label data to calculate mean changes in z-score. For these analyses they used all sertraline exposure experience (placebo controlled trial data and open label data) for the sertraline/sertraline subjects and calculated the mean change in weight z-score at endpoint. For the placebo/sertraline subjects, this analysis is identical to the above analysis which used the placebo controlled baseline weight for placebo/sertraline subjects who participated in the open label trial. In this analysis the mean change from baseline to endpoint for weight z-scores among the sertraline/sertraline subjects was -0.07 and -0.06 for the placebo/sertraline subjects.

Pfizer also provided a series of tables that provided the mean changes in weight (kg), weight percentile, and weight z-score by study week for the sertraline/sertraline group and the placebo/sertraline group. They also provided graphs that displayed these data. I provide those graphs below.





The graphs above are survivor analyses, where the number of subjects in each group declines over time. At baseline, there are 188 subjects in the sertraline/sertraline group and 121 subjects in the placebo/sertraline group. By week twelve, there are 95 subjects in the sertraline/sertraline group and 100 subjects in the placebo/sertraline group. At week 24 there are 75 subjects in the placebo/sertraline group (last available data for this group). At week 34 there are 68 subjects remaining in the sertraline/sertraline group.

FDA Analyses

Since there appeared to be a change around week ten in the above graphs I examined the impact of the discontinuing subjects on the weight change for the sertraline/sertraline group. One potential explanation for the observed results is that those subjects who discontinued early were different from the rest of the population and experience greater weight loss and that the trend change in the curve occurred when those subjects no longer contributed data. For the sertraline/sertraline group, I identified those subjects who had less than ten weeks duration of treatment. I then calculated the endpoint mean change from baseline for weight, z-score, and weight percentile for this group. I then identified the subjects who had at least 10 weeks duration of treatment. For these subjects, I calculated the mean change in weight at week ten from baseline. The purpose of this analysis was to determine if the subjects discontinuing before week ten had a markedly greater weight loss than survivors, and that their discontinuation accounted for the change in slope for the graph. The results of this analysis are included in the table below.

A comparison of mean weight change, weight z-score change and weight percentile change for sertraline/sertraline subjects who discontinued before week ten (endpoint – baseline) and those that continued through week ten (week ten-baseline)

Parameter	Discontinued before week 10 (n=43)	Continued through at least week 10 (n=142)
	Endpoint - baseline	Week 10 - baseline
Mean weight change	-0.5kg	-0.38kg
Mean weight z-score change	-0.1	-0.13
Mean weight percentile change	-2.83	-2.65

I conducted a separate analysis to look at the impact of the early discontinuations on the changes observed at week 10. I removed the subjects who discontinued prior to week ten from the sertraline/sertraline group. I then looked at the mean change in weight, weight z-score, and weight percentile by study week for the subjects with at least ten weeks of exposure that remained. I compared the results after removing the early discontinuations to the analysis including all subjects. Following removal of the early discontinuers there did not appear to be a marked difference in the mean change in weight, weight z-scores, or weight percentile by study week compared to the overall group through the first ten weeks. The results for the mean weight change and z-score are presented in the table below.

A comparison of mean weight change from baseline and mean weight z-score change from baseline for all sertraline/sertraline subjects and the sertraline/sertraline subjects with at least 10 weeks of exposure by study week, pediatric sertraline depression trials

Study week	Weight Mean Change from baseline		Weight mean z-score change from baseline	
	All Subjects	Only Subjects ≥10 weeks	All Subjects	Only Subjects ≥10 weeks
1	-0.28 (n=180)	-0.30 (n=141)	-0.04	-0.04
2	-0.32 (n=178)	-0.28 (n=144)	-0.06	-0.05
3	-0.45 (n=172)	-0.42 (n=142)	-0.08	-0.07
4	-0.48 (n=169)	-0.44 (n=144)	-0.09	-0.08
6	-0.51 (n=157)	-0.50 (n=144)	-0.11	-0.10
8	-0.47 (n=150)	-0.45 (n=145)	-0.12	-0.13
10	-0.38 (n=142)	-0.38 (n=142)	-0.13	-0.13

Discussion

The submitted data are limited and do not allow for a complete understanding of the impact of sertraline on weight gain. In placebo controlled trials of ten weeks duration, the sertraline exposed subjects lost almost 0.5 kg while the placebo subjects gained almost 1 kg. Since there is a placebo comparison group in these studies, comparisons using population data are unnecessary. Interestingly, when compared to population data, the placebo subjects in these trials had a negligible decline in the mean z-score (-0.005) supporting that these subjects had weight changes similar to those expected. The sertraline subjects had a mean decrease in z-score of -0.112 suggesting that their weight lagged behind weight gain predicted by population data.

Electrocardiograms: Only qualitative results were presented in the original submission; i.e., there was no analysis of clinically significant changes or mean changes in intervals. One sertraline subject showed QTc prolongation from 399 ms at baseline to 453 ms on sertraline.

In response to a request from this Division, the sponsor submitted additional analyses of ECG data on 7-12-02. For this analysis the sponsor focused exclusively on the QTc interval, using data from the two controlled trials. For this analysis, ECG interval data was obtained from the ECG tracings in the following manner. If the investigator or a cardiologist had read the ECG, those values were used. If not, the automated interval values generated by the ECG machine were used. If there was no such data from the ECG machine, Dr. Christopher Wohlberg of Pfizer read the ECG tracing (this applied to some 30 subject's tracings). The results were as follows:

Treatment group	Sertraline	Placebo
N	164	165
Mean change from baseline in msec, QTc Fridericia	+2.9	+2.6
Standard deviation	18.4	22.3
p-value (ANCOVA)	0.69	

In addition, there were no significant differences between treatment groups for the numbers of patients exceeding clinically significant QTc threshold values (such as endpoint value > 500 msec, increase from baseline >30 msec, etc.).

The sponsor submitted further ECG analyses on 8-7-02. This submission contained data on other ECG parameters (PR, QRS, and heart rate) for the same subjects (164 sertraline patients and 165 placebo patients). There were no statistically significant differences between treatment groups for mean changes from basline in length of the QRS or PR intervals, or for heart rate. This was true whether the analysis included all subjects, children alone, or adolescents alone. Pfizer also reported the numbers of patients exceeding the upper limit of normal for age on PR or QRS intervals. For PR interval, there were 4/164 sertraline treated patients with treatment-emergent prolongation of the PR interval, compared to 0/165 placebo patients. For the QRS duration, the number of patients with treatment-emergent QRS > 100 msec was 2/164 for sertraline and 3/165 for placebo.

Finally, the sponsor provided a literature reference describing the effects of sertraline on the ECG parameters of children and adolescents (Wilens et al., 1999).[1] This was a non-IND study, funded by NIH and Pfizer, of sertraline in the treatment of pediatric OCD. The trial was a randomized, double blind, placebo controlled, parallel group study, 12 weeks in duration; 92 subjects received sertraline and 95 placebo. The study employed a flexible dose design, with a mean final dose of sertraline of 167 mg/day. The authors found no statistically significant differences between the sertraline and placebo groups with respect to mean changes from baseline in the PR, QRS, or QTc intervals.

[1] Wilens TE, Biederman J, March JS, et al. Absence of cardiovascular effects of sertraline in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999;38:573-577.

If one views the weight data for the first ten weeks of exposure for sertraline subjects exposed in the RCTs and the first ten weeks of open label sertraline exposure for subjects who received placebo in the preceding controlled trial, the weight loss, declines in weight percentiles and declines in weight z-scores appear consistent.

Uncertainty about sertraline's effect on weight in pediatric patients arises from the lack of controlled data beyond ten weeks. The mean weight change curve suggests that the weight loss trend changed between weeks eight and ten for those continuing in this trial, with the group beginning to gain weight at this point. To examine if this change was due to the discontinuation of subjects with greater weight loss, I conducted additional analyses. The weight endpoint change from baseline for the subjects who discontinued before week 10 was similar to weight change at week ten from baseline for those who continued for at least 10 weeks. Furthermore, when the data from subjects who discontinued early was removed, the weight change, z-score change and weight percentile changes by study week were not markedly different from the results that included data from the subjects who discontinued early. This seems to support that the trend change observed at week ten is not due to discontinuation of patients with greater weight loss.

The data suggest that subjects continuing treatment begin to gain weight again around week ten and weight gain at the end of the study was near what population data would have predicted based on study subjects' baseline weights. There are no data to allow comment on long term sertraline use and impact on weight.

Pfizer had proposed the following labeling to describe the weight changes observed in these trials (some of the wording reflects changes proposed by the division and agreed to by Pfizer, while other wording has been newly proposed by Pfizer):

As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. In a pooled analysis of two 10-week, double-blind, placebo-controlled, flexible dose (50-200mg) outpatient trials for major depressive disorder (n=373), there was a difference in weight change between sertraline and placebo of roughly 1 kilogram, for both children (ages 6- —11) and adolescents (ages 12—17 in both cases representing a slight weight loss for sertraline compared to a slight gain for placebo. At baseline the mean weight for children was 39.0kg for sertraline and 38.5kg for placebo. At baseline the mean weight for adolescents was 61.4kg for sertraline and 62.5kg for placebo. There was a bigger difference between sertraline and placebo in the proportion of outliers for clinically important weight loss in children than in adolescents. For children, about 7% had a weight loss > 7% of body weight compared to none of the placebo patients; for adolescents, about 2% had a weight loss > 7% of body weight compared to about 1% of placebo patients.

patterns from their age-adjusted peers. Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.

Recommendations

I recommend removing the following labeling text suggested by Pfizer:

I recommend replacing the above deleted text with the following labeling:

A subset of these patients who completed the randomized controlled trials (sertraline n=100, placebo n=121) were continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5kg was seen during the first eight weeks of treatment for subjects with first exposure to sertraline during the open-label extension study, similar to the mean weight loss observed among sertraline treated subjects during the first eight weeks of the randomized controlled trials. The subjects continuing in the open label study began gaining weight compared to baseline by week 12 of sertraline treatment. Those subjects who completed 34 weeks of sertraline treatment (10 weeks in a placebo controlled trial + 24 weeks open label, n=68*, had weight gain that was similar to that expected using data from age-adjusted peers.

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/s/

Jerry Boehm
9/3/03 10:51:24 AM
MEDICAL OFFICER

Judith Racoosin
9/3/03 01:11:41 PM
MEDICAL OFFICER

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REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 19-839 SE5-044 and 20-990 SE5-010
SPONSOR: Pfizer
DRUG: Sertraline
MATERIAL SUBMITTED: Pediatric Exclusivity Supplement
DATE SUBMITTED: 12-14-01
DATE RECEIVED: 12-17-01
PDUFA DUE DATE: 10-17-02
REVIEWER: Andrew D. Mosholder, M.D., M.P.H.
REVIEW COMPLETION DATE: 8-13-02

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The sponsor's proposed claim for the treatment of pediatric major depressive disorder is not supported by the data in this submission. Both pivotal studies failed to distinguish sertraline from placebo on the primary outcome measures. The sponsor has proposed pooling the data from the two trials to yield a statistically significant result, on the basis that the trials were conducted under identical protocols. This, however, would be a major departure from our usual policies discouraging pooling of efficacy data.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps If Approvable: This is not applicable.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program: The sponsor conducted two randomized, double blind, placebo controlled, parallel group trials, designated 1001 and 1017. Each trial involved approximately 200 children and was 8 weeks in duration. The protocols for both trials were identical. In addition to these double blind studies, there were 3 open label safety studies, one of which was ongoing at the time of submission.

B. Efficacy: If the data from the two trials are pooled then the results show statistical superiority for sertraline over placebo. However, neither trial by itself showed superiority of sertraline to placebo on the a priori primary outcome measures.

C. Safety: The most important safety finding is the degree of weight loss observed with sertraline in comparison to placebo. Weight loss was particularly prominent among children, with 7.1% of the children on sertraline loosing at least 7% of their baseline weight, compared to no children on placebo having such weight loss.

D. Dosing: The dosages studied were identical to those for adults; i.e., 50-200 mg daily.

E. Special Populations: This supplement is limited to pediatric data.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Pfizer is seeking labeling for use of Zoloft in the treatment of major depressive disorder (MDD) in pediatric patients.

B. State of Armamentarium for Indication(s)

Zoloft is already among the drugs approved for pediatric obsessive-compulsive disorder (OCD). No drug is labeled for pediatric MDD, although the sponsor of Prozac (fluoxetine) has received an approvable letter for this indication.

C. Important Milestones in Product Development

The agency issued a pediatric Written Request (WR) for Zoloft on 4-28-99. The original WR asked for pediatric efficacy data in MDD, pediatric pharmacokinetic data, and long term pediatric safety data. However, since Pfizer had already gained approval for sertraline in the treatment of pediatric OCD, the requested pediatric pharmacokinetic and long term safety data had already been submitted. Accordingly, Pfizer asked the agency to remove these portions of the WR, and the agency agreed, amending the WR in a letter dated 2-28-00. Thus, to fulfill the terms of the WR, Pfizer needed to submit only the study reports of two pediatric efficacy trials in MDD. Pfizer was granted pediatric exclusivity for the submission of this supplement by the Pediatric Exclusivity Board, effective 2-1-02.

D. Important Issues with Pharmacologically Related Agents

In the Prozac pediatric clinical trials, adverse reactions that were unique to this population included decreased growth velocity, and a very high frequency of hypomania.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are no such findings to report.

III. Human Pharmacokinetics and Pharmacodynamics

Please refer to the approved labeling for Zoloft for a description of pediatric pharmacokinetics. Based on a study of 61 children and adolescents administered sertraline for 6 weeks, AUC and Cmax mean values are slightly lower than those for adults when adjusted for body weight. The current labeling suggests use of lower doses for smaller children.

IV. Description of Clinical Data and Sources

A. Overall Data

This supplement includes two randomized, double blind, placebo controlled studies that were identical in design, studies 1001 and 1017. In addition, study 1015 is an ongoing open label extension for these two double blind studies. Finally, Pfizer also included reports from two open label studies involving the use of sertraline in juvenile depression.

The cutoff date for including clinical trial safety data in this submission was 10-16-01. One hundred eight-nine subjects received sertraline in the double blind trials, and 80 received sertraline in the completed open label trials. Additionally, 126 subjects previously treated with placebo were newly exposed to sertraline when they entered the ongoing follow-up study 1015 (please refer to the email from Graydon Elliott at Pfizer, sent 3-20-02). Therefor, a total of 395 children and adolescents received sertraline in these clinical trials.

B. Tables Listing the Clinical Trials

The sponsor's table from section 3.5 of the submission, describing the clinical trials, is reproduced below.

Summary Information for Studies Included in Pediatric Depression Supplement

Protocol	Design	Doses	Treatment Duration	Total No. Treated	
				Sertraline	Placebo
Controlled Studies—Completed					
A0501001	Flexible dose	50-200 mg	10 weeks	97	91
A0501017	Flexible dose	50-200 mg	10 weeks	92	93
Uncontrolled Studies—Completed					
R-0246	Flexible dose	50-200 mg	10 weeks followed by 12 weeks of a continuation phase for responders	53	
STL-CDN-94-002	Flexible dose	50-200 mg	24 weeks	27	
Uncontrolled Study—Ongoing					
A0501015	Flexible dose	50-200 mg	24 weeks	226*	

*Two hundred twenty-six subjects entered the study as of the cut-off date of 16 October 2001.

C. Postmarketing Experience

The submission does not include postmarketing surveillance data.

D. Literature Review

The sponsor identified and summarized a total of 24 literature reports concerning use of sertraline in the pediatric population.

V. Clinical Review Methods

A. Describe How Review was Conducted

The principle source of information for this review was the sponsor's submission. The individual study reports were examined to evaluate efficacy, and the combined summary was reviewed to evaluate safety.

B. Overview of Materials Consulted in Review

Primary source: Submission dated 12-14-01
Secondary sources: (1) Email from Graydon Elliott at Pfizer, sent 3-20-0; (2) Sponsor's response to inquiry regarding ECG data, submitted 7-12-02 and 8-7-02.

A. Overview of Methods Used to Evaluate Data Quality and Integrity:

The Division of Scientific Integrity (DSI) was to inspect the following sites for protocol A0501001.

Center 5016: H. Quintana, New Orleans (N=18)
Center 5024: P. Londborg, Seattle (N=14)

Please refer to the DSI reports for details of the findings. In addition, Pfizer excluded Dr. Frank's site from study 1001 because of GCP deficiencies that were disclosed during the sponsor's audit of the site.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards?

Yes. Investigators in the U.S. were subject to the usual IRB oversight with respect to ethical standards. In addition, each protocol stipulated that the trial was to be conducted according to ICH Good Clinical Practice Guidelines, the Declaration of Helsinki, and applicable local ethical regulations.

E. Evaluation of Financial Disclosure

5014 Craig Donnelly, MD
5015 Robert L. Hendren, DO
5016 Humberto Quintana, MD
5017 L. Matthew Frank, MD*
5019 Michael J. Rieser, MD
5020 Mark Rapaport, MD
5023 Jeffrey Danziger, MD
5024 Peter D. Londborg, MD
5025 Ron Steingard, MD
5026 Carmel A. Foley, MD
5027 John Walkup, MD
5028 Michael Liebowitz, MD
5029 Walter D. Rosenfeld, MD
5034 Vanshdeep Sharma, MD
5036 Elly R. Lee, MD / Julie Oldroyd, MD
5040 Moira Rynn, MD
5048 Michael S. Greenbaum, MD
5054 Randall Ricardi, DO
5056 Robert Brown, MD
5057 Maxine Minto, MD

India
5076 Sohan Derasari, MD
5077 Podila Satya Venkata Narsimha Sharma, MD
5078 Shubhangi Parkar, MD
5079 Krishnapillai Kumar Ayyappan, MD

*After an audit by Pfizer's Clinical Quality Assurance group, efficacy data from Dr. Frank's site (5017) was excluded from the analysis because of protocol and GCP violations.

Objectives: The purpose of this study was to evaluate the safety and efficacy of sertraline versus placebo in the treatment of pediatric patients with MDD.

Population: Subjects were to be outpatients, aged 6-17 years. Their diagnosis of MDD was to be confirmed by the K-SADS-PL. At entry, subjects were to have a score of at least 45 on the Children's Depression Rating Scale-revised (CDRS-R) and a score of at least 4 on the CGI-severity. Subjects were to discontinue all psychotropic medications at least 2 weeks before the study (4 weeks in the case of fluoxetine treatment). The following were among the exclusion criteria: ADHD, conduct disorder, OCD, panic disorder, bipolar disorder, psychosis, eating disorders, substance abuse, pregnancy, lactation, mental retardation, seizures, and dangerousness to self or others. A total of 160 subjects were to be randomized, at approximately 30 sites (the number of sites was increased to 30 in a protocol amendment dated 11-1-00, but the number of subjects remained the same).

Design: This was a randomized, double blind, parallel group, placebo controlled, flexible dose trial. Subjects were to be randomized to sertraline or placebo (1:1 ratio), with stratification according to age group (6-11 years versus 12-17 years). The dose of sertraline was to be 25 mg/day X 3 days, followed by 50 mg/day through the end of week 2. Subsequently, the dose could be titrated upward by 50 mg daily every 2 weeks at the investigator's discretion, with the upper limit being 200 mg/day. The minimum dose was to be 50 mg/day, and the drug could be

administered am or pm. The duration of treatment was 10 weeks. Concomitant diphenhydramine and chloral hydrate were permitted.

Assessments: Screening evaluations were to include history and physical examination, K-SADS-PL, CDRS, CGI, clinical laboratories, urine drug screen, pregnancy testing, and ECG. The CDRS-R and CGI were to be rated every 1-2 weeks during double blind treatment. The CDRS-R comprises 17 items, with 14 items rated by the investigator based on information from the subject, caregivers, and other sources as appropriate, and the final 3 items completed by the investigator based on observation of the subject. Severity is rated on a scale of 1-7 for most of the items (the scale is 1-5 for items 4, 5 and 16). At the baseline and final visit, the investigator was to complete separate CDRS-R ratings based on reports from the child, the parents/caregivers, and other sources as appropriate, and then provide a "best description" overall rating. The individual items of the CDRS-R are as follows:

1. Impaired Schoolwork
2. Difficulty Having Fun
3. Social Withdrawal
4. Sleep Disturbance
5. Appetite Disturbance
6. Excessive Fatigue
7. Physical Complaints
8. Irritability
9. Excessive Guilt
10. Low Self-Esteem
11. Depressed Feelings
12. Morbid Ideation
13. Suicidal Ideation
14. Excessive Weeping
15. Depressed Facial Affect
16. Listless Speech
17. Hypoactivity

Additional outcome measures that were to be completed at baseline and endpoint included a global assessment scale for children (CGAS), the Multidimensional Anxiety Scale for Children (MASC), and the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q). Note that the CDRS-R was the only assessment of depressive symptomatology. Also, the K-SADS-PL affective disorders module was to be completed at the final visit. Safety assessments were to include vital signs, clinical laboratories, ECG, and weight.

Analysis plan: The primary efficacy measure was to be the change in CDRS-R score from baseline to endpoint. The specified method was ANCOVA with treatment, age group and baseline terms. Other assessments, as listed above, were to be secondary outcome measures. A response analysis was planned comparing the proportion of subjects in each treatment group attaining a 40% decrease or greater in the CDRS-R adjusted score (adjusted by subtracting the minimum score of 17).

Results

The sponsor defined the intent-to-treat population as subjects with both baseline and post-randomization efficacy data.

The following table, adapted from the sponsor, provides a summary of the patient disposition. No information was provided on the number of subjects screened for this trial. The major difference between treatment groups was a higher number of sertraline patients who discontinued from adverse events (ten in the sertraline group versus no placebo patients), along with a higher number of "subject defaulted" in the sertraline group.

Category	Number of patients	
	Sertraline	Placebo
Randomized	97	91
Excluded for GCP issues (Dr. Frank)	3	3
Intent-to-treat	93	88
Completed	65	77
Discontinued (total)	32	14
Adverse Event	10	0
Lack of efficacy	3	2
Other	7	6
Subject defaulted	12	6

The number of patients completing each week of the trial, as reflected in the number of subjects with CDRS-R scores, is shown below.

Treatment	Randomized	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10
Sertraline	94	89	88	86	81	75	72	63
Placebo	88	88	85	82	82	81	75	75

Demographics

The following tables summarize the study sample of all randomized patients, according to treatment, age group and gender.

SERTRALINE	Male	Female	Total
Children (6-11 years)	23	20	43
Adolescents (12-17 years)	21	33	54
Total	44	53	97

PLACEBO	Male	Female	Total
Children (6-11years)	24	19	43
Adolescents (12-17 years)	25	23	48
Total	49	42	91

The table below summarizes the baseline patient characteristics for all randomized patients. Note that the subjects were predominantly white, with relatively few comorbid disorders. Most subjects had experienced only their current episode of major depression .

Characteristic	Sertraline (n=97)	Placebo (N=91)
Age (yrs)		
Mean	12	12
Range	6-17	6-17
Ethnic origin (n)		
White	76	72
Asian	7	4
African-American	6	8
Hispanic	4	5
Other	4	2
History of psychiatric disorder of any type other than depression (n)	33	28
History of depression prior to current episode (n)	9	14
Prior antidepressant therapy (n)	8	8
CDRS-R mean total score (p-value=0.76)	64.2	63.8

From the sponsor's SAS dataset listing efficacy data by site, this reviewer determined that only 3 placebo-treated patients and 6 sertraline-treated patients were from sites in India; the remainder were from the U.S. Also, it should be noted that although the vast majority of subjects had no previous episode of depression, among these patients the mean duration of their current, initial episode was rather lengthy (22.6 months for sertraline subjects; 17.8 months for placebo subjects).

Dosing: The mean final daily dose was 111 mg for sertraline subjects, and 137 mg (equivalent) for placebo subjects.

Efficacy Measures: The results for the primary outcome measure are shown below.

Treatment Group Sertraline Placebo

according to Dr. Siddiqui's analysis, but it was not nearly as

Conclusions

Study 1017

Investigators/sites: The following is the sponsor's list of investigators, reproduced from the study report. Sites that did not randomize any patients have been omitted.

USA
5003 Karen Weihs, MD
5005 Mark E. Bangs, MD
5006 Louise Beckett, MD
5007 Doug Geenens, DO/W. Rory Murphy, MD
5008 M. Patricia Solbach, PhD
5009 Paul Ambrosini, MD
5010 Michael Levin, MD/Kathleen Toups, MD
5021 Keith Saylor, PhD
5022 Carrie Borchardt, MD
5038 Steven Dubovsky, MD
5042 Karen D. Wagner, MD, PhD
5049 Ann Childress, MD
5050 Shara Kronmal, MD, PhD
5055 Craig Wronski, DO

Canada
5030 William Fleisher, MD
5033 Anne Duffy, MD
5035 Jane Garland, MD

Costa Rica
5074 Yasmin Jaramillo-Borges, MD

Mexico
5060 Alfonso Ontiveros, MD

India
5061 Thomas John, MD
5062 Shoba Srinath, MD
5064 Davinder Mohan, MD
5065 Gowri Devi Mandadi, MD
5067 Nagesh Brahmavar Pai, MD

Objectives, Population, Design, Assessments, and Analysis Plan: identical to Protocol 1001

Results

The following tables summarize the study sample of all randomized patients, according to treatment, age group and gender.

SERTRALINE	Male	Female	Total
Children (6-11 years)	20	23	43
Adolescents (12-17 years)	17	32	49
Total	37	55	92

PLACEBO	Male	Female	Total
Children (6-11years)	32	16	48
Adolescents (12-17 years)	22	26	48
Total	54	42	96

The table below summarizes the baseline patient characteristics for all randomized patients.

Characteristic	Sertraline (n=92)	Placebo (N=96)
Age (yrs) Mean Range	 12 6-17	 12 6-17
Ethnic origin (n) White Asian African-American Hispanic Other	 59 19 1 11 2	 58 19 1 14 4
History of other psychiatric disorder (n)	33	35
History of depression prior to current episode (n)	9	12

Prior antidepressant therapy (n)	8	24
CDRS-R mean total score (p-value=0.57)	64.4	65.4

From the sponsor's SAS dataset listing patient demographic data by site, there were 16 subjects from Costa Rica, 5 subjects from Mexico, 35 subjects from India, and 132 subjects from the U.S. Also, as in study 1001, while a substantial majority of subjects had no previous episode of depression, the mean duration of their current, initial episode was rather lengthy (over 20 months in both treatment groups).

Dosing: The mean final daily dose was 128 mg for sertraline subjects, and 134 mg (equivalent) for placebo subjects.

Efficacy Measures: The results for the primary outcome measure are shown below.

Treatment Group	Sertraline	Placebo

Combined analysis: Pfizer performed a pooled analysis of efficacy data from studies 1001 and 1017, which was part of their statistical analysis plan (see "Combined Analysis of Pediatric Depression Studies A0501001 and A0501017," dated 5-5-00).

The combined analysis is shown here:

Treatment Group	Sertraline	Placebo

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

B. Description of Patient Exposure (i.e., number of patients at given duration, dose, demographic, distribution, country)

Please refer to section IV (Description of Clinical Data and Sources) above. The cutoff date for including clinical trial safety data in this submission was 10-16-01. The table below summarizes the numbers of patients exposed in these trials.

Type of study	Sertraline patients	Placebo patients
Double-blind trials	189	184
Completed open label trials	80	
Ongoing open label trials	126*	
Total patients exposed	395	184

*an additional 100 subjects in ongoing open label trials had already received sertraline in a double blind trial

As of the cutoff date of 10-16-01, the total duration of exposure in person-years was as follows, according to the sponsor's 5-22-02 submission:

	N	Person-years
Sertraline	395	136.3
Placebo	184	32.5

C. Methods and Specific Findings of Safety Review

For assessment of the common adverse event profile, and of changes in safety parameters (vital signs, clinical laboratories, and ECGs), the combined data from the two double-blind placebo controlled trials was the primary source. These data provide a readily available comparison to placebo. For serious but less frequent adverse events, the entire set of safety data (from all 395 pediatric subjects exposed) was considered.

Deaths and Serious Adverse Events: There were no deaths in these trials. With respect to serious adverse events, the following is the sponsor's tabulation of such events from all relevant studies (total n =395 for sertraline, 184 for placebo).

Serious Adverse Events Reported in AEM as of 16 October 2001
(A0501001, A0501017, R-0246, STL-CDN-94-002, and A0501015)

	Sertraline	Placebo
Suicidal Ideation	5	0
Suicide Attempt	2	2
Progression of Depression	2	0
Worsening of Depression	2	0
Aggressive Reaction	1	0
Intentional Overdose	1	0
Left Great Toe Abscess	1	0
Multi-drug Overdose	1	0
Oppositional Behavior	1	0
Parent-child Conflict	1	0
Pneumonia*	1	1
Progression of Conduct Disorder	1	0
Seizure	1	0
Self-inflected Injury	1	0
Suicidal Gesture	1	0
Threatening Behavior	1	0
Upper Respiratory Infection	1	0
Acute Appendicitis	0	2
Ruptured Ovarian Cyst	0	1

Subjects may have had more than one adverse event.

*Same subject (1017). Subject took placebo in study A0501001 and sertraline in open-label extension (A0501015). Same event is captured in both studies.

Many of the events were psychiatric in nature. Because the sponsor's tabulation permitted more than one adverse event term per patient, this reviewer examined the narrative summaries for the serious adverse events. There were a total of 4 sertraline patients and 2 placebo patients who engaged in self injurious behaviors of some kind, and there were a total of 6 sertraline subjects

(but no placebo subjects) who developed suicidality requiring hospitalization. For suicidal ideation or overt self-injury combined, there were 10 patients with such events for sertraline and 2 for placebo, representing 2.5% and 1.1% of the total number of sertraline and placebo patients, respectively. Expressed as a rate per 100 person years, the incidence was 7.3 suicidal events per 100 person years for sertraline, and 6.2 per 100 person years for placebo.

Adverse Dropouts

The following table, reproduced from the submission, summarizes the adverse events more frequently associated with discontinuation in the double-blind trials. Specifically, the events listed occurred in more than one sertraline patient, and in no more than one placebo patient.

PANEL 2: MOST COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION IN SERTRALINE-TREATED SUBJECTS

Adverse Event	Percent Discontinued [n/N]
Aggressive Reaction	1.6% [3/189]
Agitation	1.6% [3/189]
Suicidal Ideation	1.6% [3/189]
Depression Aggravated	1.1% [2/189]
Hyperkinesia	1.1% [2/189]
Suicide Attempt	1.1% [2/189]

Common adverse event profile: To assess the profile of common adverse drug reactions, the combined data from the two placebo-controlled trials was used. The adverse events meeting the usual definition of common and drug-related (i.e., absolute incidence $\geq$5% and relative risk $\geq$ 2) are shown below.

	Incidence by treatment group	
Adverse event	Sertraline (n=189)	Placebo (n=184)
Diarrhea	10.6%	3.8%
Vomiting	8.5%	3.8%
Anorexia	7.4%	2.2%
Agitation	6.3%	2.2%

Clinical laboratories: One patient (#3005) discontinued double blind sertraline treatment for elevated SGPT (approximately 2x ULN); this resolved after discontinuation. Patient #0001 in open label study R-0246 discontinued treatment because of hypokalemia which may have been related to diarrhea.

The two placebo controlled trials provide the most informative data, by virtue of including a control group for comparison. In the placebo-controlled trials, most of the clinically significant laboratory abnormalities were from urine dipstick tests, although 3 sertraline patients (versus one placebo patient) had low hematocrit. With respect to changes in mean laboratory values, the following comparisons were statistically significant:

Parameter	Mean Change from Baseline	
	Sertraline	Placebo
Hct	-0.3	+0.2
Total bilirubin (mg/dl)	0.0	0.0 (sic)
Uric acid (mg/dl)	-0.7	+0.1

These changes are of unclear clinical significance, in my opinion.

Vital signs: As with clinical laboratories, the results from the two placebo controlled trials will be emphasized here because they allow comparisons to a placebo control.

There were only a few instances of clinically significant changes in vital signs in the double blind trials. For changes in weight, however, there were the following results:

	Sertraline (n=187)	Placebo (n=187)
Weight Decrease $\geq$ 7%	4.3%	0.6%
Weight Increase $\geq$ 7%	3.2%	5.6%

When examined separately for children and adolescents, the weight change discrepancy between sertraline and placebo is greater for children:

Children	Sertraline (n=84)	Placebo (n=86)
Weight Decrease $\geq$ 7%	7.1%	0
Weight Increase $\geq$ 7%	3.6%	7.0%

Adolescents	Sertraline (n=103)	Placebo (n=94)
Weight Decrease $\geq$ 7%	1.9%	1.1%
Weight Increase $\geq$ 7%	2.9%	4.3%

With respect to mean changes in vital signs, there were no statistically significant differences between sertraline and placebo with respect to blood pressure or pulse in the double blind trials. In open label study R0246 mean blood pressure increased slightly by the end of treatment. However, mean change in weight at endpoint differed between treatments in both age groups:

Children	Sertraline (n=84)	Placebo (n=86)
Mean change in weight (kg)	-0.17	+0.98 (p-value =0.001)

Adolescents	Sertraline (n=103)	Placebo (n=94)
Mean change in weight (kg)	-0.55	+0.61 (p-value =0.001)

[For comparison, as noted in the clinical review of the pediatric OCD supplement (Supplement 17 submitted 12-19-96), in Study 498, the number of subjects having a weight loss of at least 7% was 5 of 92 for sertraline, and zero out of 95 for placebo.]

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/s/

Andy Mosholder
8/13/02 01:36:39 PM
MEDICAL OFFICER

Thomas Laughren
8/23/02 01:48:37 PM
MEDICAL OFFICER
I agree that a claim for pediatric MDD has not been supported, but also that the weight loss information should be added to labeling; see memo to file for more detailed comments.--TPL

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REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 19-839 SE5-044 and 20-990 SE5-010
SPONSOR: Pfizer
DRUG: Sertraline
MATERIAL SUBMITTED: Pediatric Exclusivity Supplement Addendum
DATE SUBMITTED: 12-19-02
DATE RECEIVED: 12-20-02
REVIEWER: Roberta L. Glass, M.D.
REVIEW COMPLETION DATE: 4-24-03

I. Background

This current submission is the sponsor's response to labeling changes (FDA letter 9/20/02) based on the pediatric supplement (for pediatric exclusivity) originally submitted on December 14, 2001. At this point in time, the sponsor and FDA appear to be in agreement that the data does not support an efficacy claim for major depressive disorder in the pediatric population. Safety data concerning weight decreases were noted in the two 10 week placebo controlled trials submitted in the December 14, 2001 submission. As can be seen in the following table below (extracted from Dr. Laughren's review of 7/23/02), weight loss ≥ 7% was observed with the greatest frequency in the subgroup of children (aged 6-11) :

Children	**Sertraline (n=84)**	**Placebo (n=86)**
Weight Decrease ≥ 7%	7.1%	0
Weight Increase ≥ 7%	3.6%	7.0%
Mean change in weight (kg)	-0.17	+0.98 (p=0.001)
Adolescents	**Sertraline (n=103)**	**Placebo (n=94)**
Weight Decrease ≥ 7%	1.9%	1.1%
Weight Increase ≥ 7%	2.9%	4.3%
Mean change in weight (kg	-0.55	+0.61 (p=0.001)

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In this current submission, the sponsor has submitted a study report for Study A0501015, a 24 week open label extension study of sertraline in children and adolescent outpatients diagnosed with major depressive disorder. The sponsor also submitted a revised version of labeling; unfortunately, rather than propose their changes based on FDA proposed labeling from the FDA 9/20/02 correspondence, the sponsor merely revised their submitted version from their 12/14/01 proposal. This review will be utilizing the FDA version from 9/20/02, incorporating some of the sponsor's proposed changes based on the submitted study report.

II. Findings from Study Report A0501015

This study was an open-label, flexible dose, 24-week, outpatient study designed to evaluate the longer-term safety and efficacy of sertraline in outpatient children and adolescents aged 6-18 years old who were previously diagnosed with major depressive disorder and who had completed 10 weeks of double-blind treatment in Study A0501001 ("Study 1001") or Study A0501017 ("Study 1017"). There were 221 patients who received at least one dose of open-label study medication, and were included in the sponsor's "primary safety evaluation." The following sponsor table summarizes the early withdrawals during this study:

	Sert/Sert (N=99)	Pbo/Sert (N=122)
Children (6-11 years)	2 subjects discontinued due to: Vomiting (1 subject) [a] Nervousness (1 subject)	5 subjects discontinued due to: Agitation (1 subject) [a] Nervousness (2 subjects) [a] Suicidal ideation (1 subject) [b, c] Hyperkinesia (1 subject)
Adolescents (12-17 years)	2 subjects discontinued due to: Abdominal pain (1 subject) [a] Syncope, nausea, vomiting (1 subject)	4 subjects discontinued due to: Diarrhea (1 subject) [a, b] ↑ Hepatic enzymes (1 subject) [a] Somnolence (1 subject) [a] Headache (1 subject) [b]

***[Sert/Sert indicates that patients were in active control group in the feeder study
Pbo/Sert indicates that patients were in the placebo group in the feeder study]

Of note, there was one 16 year old male (Subject #5048-2129) who was reported to have elevated liver function study tests during treatment with 50 mg/day Zoloft®. His SGOT reached a maximum of 139 IU/L (NL: 0-41 IU/L) on day 42, and normalized at discharge (day 56) and during follow up (up to 102 days). However, the SGPT values increased up to 78 U/L (NL: 5-30 U/L) on Day 42, with a maximum values of 80 U/L at Day 63 (7 days after discontinuation), and continued to be elevated by Day 102 (57 U/L).

Otherwise, there were no unexpected findings in this study report; the safety findings were consistent with the labeling or described in previous reviews of pediatric data.

Because the finding of significant weight loss was identified in the placebo controlled studies, the following table was created to summarize the weight changes reported in this open label study:

	Sertraline/Sertraline	Placebo/Sertraline
All Children/Adolescents (combined):	N=96	N=118
Weight Decrease ≥ 7%	0	2 (1.7%)
Weight Increase ≥ 7%	34 (35.4%)	24 (20.3%)
SEPERATED BY AGE GROUP		

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Children (Aged 6-11 years)	N=42	N=61
Weight Decrease ≥ 7%	0	1 (1.6)
Weight Increase ≥ 7%	16 (38.1)	14 (23%)
Adolescents	n=54	n=57
Weight Decrease ≥ 7%	0	1 (1.8)
Weight Increase ≥ 7%	18 (33.3)	10 (17.5)

From the data in the table above, it appears that there were little to no weight decreases ≥ 7% observed in this 24 week open label study; however, it must be kept in mind that there were no placebo or other comparator groups. Therefore, any conclusions are quite limited and difficult to generalize.

III. Comments regarding labeling

The sponsor did not modifying the FDA proposed labeling in this submission; instead, they proposed language by merely modifying their previously submitted labeling. Therefore, it is difficult to discern the source of some of their proposed labeling changes. The sponsor appears to have accepted the changes proposed by FDA for the two sections of **Other Adverse Events in Pediatric Patients, Adverse Reaction**, and **Dosage and Administration**. The following is proposed language for the **Pediatric Use** section of labeling (based on FDA's proposed labeling to the sponsor from 9/20/02 with some modified changes):

Pediatric Use–The efficacy of ZOLOFT for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6-17 (see Clinical Trials under CLINICAL PHARMACOLOGY). The efficacy of ZOLOFT in pediatric patients with major depressive disorder, panic disorder, PTSD or PMDD has not been established.

Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age with major depressive disorder or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight (see Pharmacokinetics under CLINICAL PHARMACOLOGY).

Approximately —— 600 patients with major depressive disorder or OCD between 6 and 17 years of age have received ZOLOFT in clinical trials, both controlled and uncontrolled. The adverse event profile observed in these patients was generally similar to that observed in adult studies with ZOLOFT (see ADVERSE REACTIONS). As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. In a pool of two placebo-controlled trials, there was a difference in weight change between sertraline and placebo of roughly 1 kilogram, for both children and adolescents, in both cases representing a slight weight loss for sertraline compared to a slight gain for placebo. There was a bigger difference between sertraline and placebo in the proportion of outliers for clinically important weight loss in children than in

adolescents. For children, about 7% had a weight loss ≥ 7% of body weight compared to none of the placebo patients; for adolescents, about 2% had a weight loss ≥ 7% of body weight compared to about 1% of placebo patients. When a subset of these patients was continued into a 24 week open extension study, no consistent pattern was noted for weight change. ~~Consequently,~~ Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established.

The risks, if any, that may be associated with Zoloft's use beyond 1 year in children and adolescents with OCD or major depressive disorder have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from clinical studies that were 12 to 52 weeks in duration and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term sertraline use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use.

IV. Conclusion

The sponsor has submitted additional data including a 24 week open label study in which a significant effect on weight loss was not observed in the 271 patients enrolled. Because there was no placebo control, this data is not able to be generalized to a larger population. Please see Section III (above) for recommendations regarding labeling changes.

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/s/

Roberta Glass
4/24/03 11:28:26 AM
MEDICAL OFFICER

Paul Andreason
5/16/03 10:09:41 AM
MEDICAL OFFICER
I agree with Dr Glass's interpretation of the sponsor's data. I also agree with Dr Glass's proposed draft labeling changes.

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