CLINICAL REVIEW

NDA: 20-031
SUPPLEMENT: S-037
SPONSOR: GlaxoSmithKline
DRUG: Paroxetine HCl (Paxil)
MATERIAL SUBMITTED: Pediatric Exclusivity Supplement
DATE SUBMITTED: 4-11-02
PDUFA DUE DATE: 10-11-02
REVIEW COMPLETION DATE: 10-7-02
REVIEWER: Andrew D. Mosholder, M.D., M.P.H.

Executive Summary

I. Recommendations

A. Recommendation (b) (4)

B. Recommendation on Phase 4 Studies and/or Risk Management Steps: In my opinion, no particular Phase IV commitments are necessary.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

This supplement included data from three acute treatment randomized controlled trials in pediatric major depressive disorder (MDD), one acute treatment trial in pediatric obsessive compulsive disorder (OCD), one relapse prevention trial in OCD, and open label treatment. Preliminary safety findings from a recent study in pediatric social phobia were also included. The table below lists the trials.

Study	Description
Social Phobia	
676	Randomized, double blind, placebo controlled, parallel group, 16-week trial; paroxetine 10-50 mg/day versus placebo; n=328 children and adolescents with social phobia. Study completed but only data on serious adverse events available for this submission.
MDD	
329	Randomized, double blind, placebo controlled, parallel group, 8 week trial; paroxetine 20-40 mg/day versus placebo; n=275 adolescents aged 12-18 years with MDD. Continuation phase allowed for up to 6 months of additional double blind medication.
377	Randomized, double blind, placebo controlled, parallel group, 12 week international trial; paroxetine 20-40 mg/day versus placebo; n= 275 adolescents aged 13-18 years with MDD
701	Randomized, double blind, placebo controlled, parallel group, 8 week trial; paroxetine 10-50 mg/day versus placebo; n=203 children and adolescents with MDI

Obsessive Compulsive Disorder	
453	Randomized, double blind, placebo controlled, 16 week relapse prevention trial; 16 week open label treatment with paroxetine followed by randomization of responders to placebo or paroxetine 10-60 mg/day; n= 335 children and adolescents with OCD (in double blind phase)
704	Randomized, double blind, placebo controlled, parallel group, 10 week trial; paroxetine 10-50 mg/day versus placebo; n=203 children and adolescents with OCD
Open label safety	
716	Open label, 6 month extension for subjects in studies 701, 704 or 715; paroxetine 10-15 mg/day; n= 261 children and adolescents with MDD or OCD. Study ongoing as of 10-1-01 cutoff date.
Pharmacokinetic	
715	Open lablel, multiple rising dose pharmacokinetic study; paroxetine 10-30 mg for up to 10 weeks; n=62 children and adolescents with either MDD or OCD

The integrated safety database for this supplement included data on 932 pediatric patients treated with paroxetine, for a total exposure of 283 patient-years.

B. Efficacy

The three randomized, controlled trials in MDD, listed above, all failed to show a separation of paroxetine treatment from placebo on their primary efficacy measures.

Study 377: There were a total of 33 sites in 10 different countries (Belgium, Italy, Spain, U.K., Holland, Canada, South Africa, United Arab Emirates, Argentina, and Mexico). The objective of this study was to evaluate the safety and efficacy of paroxetine in the treatment of adolescent unipolar major depression. The initial phase of the study was a 2-week placebo washout. Following this, subjects were to be randomized to 12 weeks of treatment with either paroxetine or placebo; dosing of paroxetine was flexible (20, 30 or 40 mg daily). Subjects were then tapered off study medication over a 2 week period. The sample was to be 264 outpatients with unipolar major depression, aged 13-18 years. The two primary outcome measures were (1) the proportion of subjects with at least a 50% reduction from baseline in their Montgomery Asberg Depression Rating Scale (MADRS) score, and (2) change from baseline in the K-SADS-L depression subscale. A total of 182 subjects received paroxetine and 93 received placebo. The sample was predominantly female (gender ratio approximatley 2:1) and Caucasian, with a mean age of approximately 15 years. There were no obvious imbalances between treatment groups with respect to demographic characteristics. The results for the primary outcome measures failed to distinguish between paroxetine and placebo. The proportion of patients meeting the response criterion was 60% for paroxetine and 58% for placebo (p-value = 0.62). The mean change from baseline in K-SADS-L depression subscale was –9.3 for paroxetine and –8.9 for placebo (p-value = 0.70). Conclusions: This trial did not provide any evidence that paroxetine is active in the treatment of adolescent MDD.

Study 701: There were 40 U.S. sites and one Canadian site for this trial. The objective of this trial was to compare the safety and efficacy of paroxetine and placebo in the treatment of children and adolescents with MDD. This was a randomized, double blind, placebo controlled, parallel group, flexible dose study. Subjects were to have a screening evaluation followed by a baseline evaluation approximately one week later, and if eligible were then randomized to receive either paroxetine 10-50 mg/day or placebo, for a duration of 8 weeks. Randomization was to be stratified by age group (7-11 years, and 12-17 years). The initial dose was to be 10 mg

daily for all subjects, with dose increases permitted weekly in increments of 10 mg, up to the maximum of 50 mg. At the end of the study the dosage was down-titrated by10 mg/day every 7 days, with discontinuation after subjects received 10 mg for one week. The protocol specified the following as the primary outcome measure: "Change from baseline in Children's Depression Rating Scale – Revised (CDRS-R) total score at the Week 8 LOCF endpoint." The intended sample size was 192. Subjects were to have MDD, with a CDRS-R socre of at least 45 at both baseline and screening. Three hundred five subjects were screened, and 206 were randomized (104 to paroxetine and 102 to placebo). There were slightly more premature discontinuations in the paroxetine group (31) than in the placebo group (23). On the mean change from baseline at endpoint in CDRS-R total score, which was the primary outcome measure, the result for the placebo group was numerically superior to that for the paroxetine group (-23.4 versus –22.6 for placebo and paroxetine, respectively). With respect to secondary outcome measures, there were no results showing statistical superiority of paroxetine over placebo. Conclusions: This trial did not provide any evidence that paroxetine is effective in the treatment of pediatric MDD.

Study 329

There were 13 U.S. sites for this trial. The purpose of this trial, as stated in the protocol, was to "compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression." This was a multicenter, randomized, double-blind, placebo controlled, three-arm, parallel group study. The duration of acute treatment was to be 8 weeks, with the option of a 6-month extension of double blind treatment for subjects who had responded. After a 7-10 day screening period eligible subjects were to be randomized to imipramine, paroxetine, or placebo. The randomization ratio was 1:1:1, with randomization in blocks of 6 subjects. The titration scheduled specified an initial daily dose of imipramine of 50 mg, with titration to 200 mg by the beginning of the fourth week. The dosage of paroxetine was 20 mg which was to be initiated without titration. In the event of inadequate response by the end of 4 weeks, the medication could be titrated up to 300 mg of imipramine or 40 mg of paroxetine. Medication was administered in divided doses on a BID schedule. Concomitant psychotropic medications were prohibited. There were two primary outcome measures specified: the change in HAMD 17 item total score at endpoint, and the proportion of responders at endpoint. A subject was to be considered a responder at week 8 if he or she had a HAMD-17 score $\leq$ 8, or a decrease from baseline in the HAMD-17 of at least 50%. The subjects were to be 300 adolescents, aged 12-18 years, with MDD according to DSM-III-R criteria, and a minimum HAMD-17 score of 12. The current episode of major depression was to be at least 8 weeks in duration. Ninety patients were randomized to paroxetine, 94 to imipramine, and 87 to placebo. Adverse events were the most frequent reason for discontinuation from the imipramine arm; otherwise there were not major differences in the disposition of subjects between treatment groups. Over 70% of paroxetine and placebo patients completed the trial. The result on the HAMD for the paroxetine arm was numerically superior to the other treatment groups, but the difference was not statistically significant. For the second primary outcome measure, the proportion of patients who met the aforementioned criteria for response (HAMD-17 score $\leq$ 8, or a decrease from baseline in the HAMD-17 $\geq$ 50%), the proportion of responders at endpoint was greater for paroxetine than placebo, but this difference was not statistically significant. The difference in the proportion of responders was, however, marginally statistically significant using an observed cases analysis. On the secondary outcome measure of remission, the percentage of patients with a HAMD score $\leq$ 8 at endpoint, the result was 63.3% for paroxetine, 50.0% for imipramine, and

46.0% for placebo. On this outcome the difference from placebo was statistically significant for paroxetine (p-value = 0.019) but not for imipramine. On the CGI-Improvement scale, the results showed superiority of paroxetine over placebo by a statistically significant margin for the observed cases analysis, but not for the LOCF analysis. Conclusions: Although there was some evidence of activity of paroxetine on the secondary outcome measures, the paroxetine treatment group did not separate statistically from placebo on the a priori primary efficacy measures in this trial. There was no evidence that impramine was more effective than placebo in this trial. On balance, this trial should be considered as a failed trial, in that neither active treatment group showed superiority over placebo by a statistically significant margin.

OCD Study 704:
Please refer to the study report for a complete list of investigators. The purpose of this study was to detemine the safety and efficacy of paroxetine for the treatment of pediatric OCD. This was a randomized, double blind, multicenter, parallel group, flexible dose study. Subjects were to have a screening assessment, followed in approximately one week by a baseline assessment. If subjects met the entry criteria at the baseline evaluation, they were randomized to either paroxetine or placebo. Randomization was to be stratified by 2 age subgroups (7-11 years of age versus 12-17 years of age). The initial dosage of paroxetine was to be 10 mg daily, which could be increased by 10 mg/day at weekly intervals as needed, up to a maximum of 50 mg/day. Placebo patients could receive one to five tablets of matching placebo per day. The duration of the acute treatment phase was to be 10 weeks. There was to be no concomitant psychotropic medication, or concomitant psychotherapy. When discontinuing treatment, subjects were to be down-titrated by increments of 10 mg per week until they had remained on 10 mg/day for 7 days; at that point the medication was stopped. Optional open label treatment, up to 6 months in duration, was to be made available to subjects following the trial (under Protocol 716). Subjects were to be assessed every 1-2 weeks during the acute treatment phase of the trial; efficacy assessments included CY-BOCS and CGI (Severity and Improvement). Subjects were to be between 7 and 17 years old, with OCD for at least 2 month's duration. The goal was to randomize roughly equal numbers of children (aged 7-11 years) and adolescents (aged 12-17 years), with a total of 204 subjects. OCD was to be the primary psychiatric diagnosis, and the CY-BOCS score was to be at least 16 at both the screening and baseline visits. The change from baseline in the CY-BOCS (LOCF at week 10) was designated the primary outcome variable. The study was conducted from January 2000 through July 2001. Of the 265 subjects who were screened, a substantial majority (207) were randomized, 98 to paroxetine and 105 to placebo. Overall, the sample was predominantly male (117 males and 86 females). The mean age of the children was approximately 9 years for both paroxetine and placebo groups, and the mean age of the adolescents was approximately 14 years. The sample was predominantly Caucasian (88%); 6% of subjects were African-American, and the remainder "other." There were no Asian subjects in the trial. The median duration of OCD was 3 years. Psychiatric comorbidity of some type was present in 31% of paroxetine patients and 40% of placebo subjects. The mean daily dose of paroxetine at endpoint was 30.1 mg/day for the entire sample, and was slightly higher for adolescents (36.5 mg/day) than for children (25.4 mg/day). On the primary outcome variable, the week 10 LOCF mean change from baseline in CYBOCS for the intent-to-treat sample, the results were as follows.

	Paroxetine	Placebo
N (ITT sample)	91	98

Baseline LS mean	24.2	25.1
Mean change, LOCF, wk 10	-9.3	-5.5
p-value (ANCOVA)	<0.001*	

* adjusted for baseline score, age group, gender, and psychiatric comorbidity

Conclusions: This trial provides evidence that paroxetine is active in the treatment of pediatric OCD.

OCD Study 453: There were a total of 26 investigators for this trial. All sites were in the U.S. The purpose was to assess the effect of paroxetine treatment on relapse in pediatric OCD patients. This was a multicenter, randomized, double blind, placebo controlled trial. The first phase of the study was to be an open label, 16 week period of treatment with paroxetine. Subjects were administered a starting dose of 10 mg/day, and the dose could be increased to a maximum of 60 mg/day. At the end of the 16 weeks of treatment, subjects were to be randomized to either placebo or paroxetine if they met the following criteria: at least a 25% improvement from baseline on the CYBOCS total score, and a CGI-improvement score of 1 or 2. The dosage during the double blind portion of the trial was not to be adjusted. Subjects who were randomized to placebo were to be down-titrated blindly in increments of 10 mg per week. At the end of double blind treatment, subjects were down-titrated in a similar fashion. The duration of double blind treatment was to be 16 weeks. During the double blind portion of the trial, a subject was to be withdrawn from the trial and referred for treatment if they met any of these criteria: worsening of CGI-improvement score by 1 point for 2 consecutive visits, worsening of CGI-improvement score by >2 points at any visit, or CGI-improvement score >5. The subjects were to be aged 8-17 years, with OCD by DSM-IV criteria as their primary diagnosis, confirmed by the K-SADS-L. The goal was to enroll 375 subjects in open label treatment, with the expectation that 180 of these subjects could subsequently be randomized. Subjects were to have a score of at least 16 on the CYBOCS at both screening and baseline. The primary outcome measure was the proportion of patients who relapsed (according to the criteria above) during double blind treatment. Time to relapse was specified as a secondary analysis. A total of 339 subjects entered the open label treatment phase, and 194 of these subjects were subsequently randomized, 95 to paroxetine and 98 to placebo. The median age was 10 for the paroxetine subjects and 9 for placebo subjects. The sample was over 90% Caucasian. There was a slight gender imbalance between treatment groups; 51% of the paroxetine subjects were female, while only 41% of the placebo patients were female. The intent-to-treat sample included 193 subjects. The percentage of patients who relapsed was 35% for paroxetine and 45% for placebo; this difference was not statistically significant, however (p-value = 0.14). The results varied by age subgroup: subjects under 12 years of age showed a lower percentage of relapsers for paroxetine compared to placebo, while the percentage of relapsers was essentially equal between treatment groups for the adolescents. For time to relapse, the hazard ratio of 1.5 favored paroxetine over placebo, but this was not statistically significant (p-value = 0.10). Conclusions: This trial failed to show that paroxetine is effective in the prevention of OCD relapse in pediatric patients.

C. Safety

The most prominent adverse reactions (b) (4) appear to involve behavioral effects; these events were coded with terms such as hostility and emotional lability. As previously noted, the sponsor's method of coding these events was potentially confusing, and thus additional information will be helpful for the purpose of definitively assessing the potential behavioral toxicity of paroxetine treatment in pediatric patients.

There was one postmarketing spontaneous report that described a fatal allergic reaction in an 11 year old boy following a single dose of paroxetine.

Further assessment of the safety profile will have to await the sponsor's reply to requests for additional information, such as the request regarding ECG data.

D. (b) (4)

(b) (4)

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

Clinical Review

I. Introduction and Background

A. Drug Established (b) (4)

Paroxetine hydrochloride (Paxil) is a selective serotonin reuptake inhibitor (SSRI) that is marketed with indications for MDD (MDD), obsessive compulsive disorder (OCD), panic disorder, social anxiety disorder, generalized anxiety disorder, and post-traumatic stress disorder. (b) (4)

B. State of Armamentarium for Indication(s)

Currently, fluvoxamine, sertraline and clomipramine are labeled for pediatric OCD. No drugs are presently indicated for pediatric depression. However, a supplement for fluoxetine (Prozac) adding claims for both pediatric MDD and pediatric OCD recently received an approvable letter.

C. Important Milestones in Product Development

GlaxoSmithKline (GSK) submitted this supplement in response to the agency's Pediatric Written Request (WR) letter dated 4-28-02. The WR was amended at the sponsor's request in a letter dated 2-28-00. The Pediatric Exclusivity Board has granted GSK pediatric exclusivity for this supplement.

D. Other Relevant Information

There is nothing to report.

E. Important Issues with Pharmacologically Related Agents

The pediatric supplement for fluoxetine (Prozac), which has received an approvable action but is not yet approved, included data that showed reduced growth velocity relative to placebo with longer-term use. Additionally, data from pediatric trials with other SSRIs suggest that behavioral activiation (e.g., hyperactivity, mania) may be associated with SSRI use.

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

There is nothing to report.

III. Human Pharmacokinetics and Pharmacodynamics

As noted in the Paxil labeling, paroxetine is extensively absorbed after oral administration, and displays non-linear pharmacokinetics suggesting that the compound inhibits its own metabolic clearance. Consistent with this observation is that fact that paroxetine is both a substrate and an inhibitor of CYP 2D6. (b) (4)

This submission includes a pediatric pharmacokinetic trial, Study 715. In this trial, 27 children and 35 adolescents received paroxetine for a total of six weeks, at doses of 10 mg/day for the first two weeks, 20 mg/day for the next two weeks, and then 30 mg/day.

Pharmacokinetic parameter [units]		**Children** *(8-11 years)*			**Adolescents** *(12-17 years)*		
		10 mg [n=23]	**20 mg** [n=23]	**30 mg** [n=21]	**10 mg** [n=33]	**20 mg** [n=29]	**30 mg** [n=27]
Cmax [ng/mL]	**Geom. mean** CVb	**14.0** 109%	**50.0** 63%	**105.5** 68%	**6.6** 191%	**35.0** 70%	**82.4** 56%
AUC(0-24) [ng.h/mL]	**Geom. mean** CVb	**188** 131%	**772** 60%	**1711** 66%	**94** 227%	**570** 82%	**1395** 60%
CL/F [L/h]	**Geom. mean** CVb	**53.2** 131%	**25.9** 60%	**17.5** 66%	**106.6** 227%	**35.1** 82%	**21.5** 60%
CL/F (weight-normalized) [(L/h)/kg]	**Geom. mean** CVb	**1.31** 117%	**0.64** 58%	**0.42** 66%	**1.64** 202%	**0.54** 76%	**0.33** 53%

Data are presented as geometric mean and between-subject coefficient of variation

As seen above, there was considerable nonlinearity for the pharmacokinetic parameters (b) (4) As described in the OCPB review by Dr. Jackson, it was found that clearance in male children was 1.6 times higher than in female children (data not shown here).

Plasma drug concentration measurements were also obtained in clinical trials 676, 701 and 704. According to the sponsor's cover letter for their 7-3-02 amendment to this supplement, the pharmacokinetic data from these three trials are still being analyzed.

IV. Description of Clinical Data and Sources

A. Overall Data: The clinical data reviewed was that submitted in the sponsor's 4-11-02 supplement; there was no other source of data.

B. Table Listing the Clinical Trials

Study	Description
	Social Phobia
676	Randomized, double blind, placebo controlled, parallel group, 16-week trial; paroxetine 10-50 mg/day versus placebo; n=328 children and adolescents with social phobia. Study completed but only data on serious adverse events available for this submission.
	MDD
329	Randomized, double blind, placebo controlled, parallel group, 8 week trial; paroxetine 20-40 mg/day versus placebo; n=275 adolescents aged 12-18 years with MDD. Continuation phase allowed for up to 6 months of additional double blind medication.
377	Randomized, double blind, placebo controlled, parallel group, 12 week international trial; paroxetine 20-40 mg/day versus placebo; n= 275 adolescents aged 13-18 years with MDD
701	Randomized, double blind, placebo controlled, parallel group, 8 week trial; paroxetine 10-50 mg/day versus placebo; n=203 children and adolescents with MDI
	Obsessive Compulsive Disorder
453	Randomized, double blind, placebo controlled, 16 week relapse prevention trial; 16 week open label treatment with paroxetine followed by randomization of responders to placebo or paroxetine 10-60 mg/day; n= 335 children and adolescents with OCD (in double blind phase)

704	Randomized, double blind, placebo controlled, parallel group, 10 week trial; paroxetine 10-50 mg/day versus placebo; n=203 children and adolescents with OCD
Open label safety	
716	Open label, 6 month extension for subjects in studies 701, 704 or 715; paroxetine 10-15 mg/day; n= 261 children and adolescents with MDD or OCD. Study ongoing as of 10-1-01 cutoff date.
Pharmacokinetic	
715	Open lablel, multiple rising dose pharmacokinetic study; paroxetine 10-30 mg for up to 10 weeks; n=62 children and adolescents with either MDD or OCD

C. Postmarketing Experience

GSK searched their postmarketing database for adverse event reports involving patients under 17 years of age; the cutoff date was 12-12-01. This search yielded a total of 926 case reports, which are described in the submission.

D. Literature Review

The sponsor conducted a literature search on the topic of pediatric use of paroxetine, covering the period from January 1980 to October 2001, and using the following databases: SBLINE, MEDLINE, EMBASE, the Derwent Drug File, SciSearch and BIOSIS. This search identified publications of 7 open label studies, 4 case series and 23 case reports. Note that the results of study 329 have been published.[1]

V. Clinical Review Methods

A. How the Review was Conducted: All clinical trials were considered in the evaluation of paroxetine's pediatric safety profile. For the review of efficacy, since only the acute treatment OCD trial (704) was capable of supporting an efficacy claim, that study was the only one reviewed in detail. The other trials were summarized in one or two pages for informational purposes.

B. Overview of Materials Consulted in Review: The sponsor's 4-11-02 submission was the only material reviewed.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Two sites in study 704, Dr. Harshawat and Dr. Ricardi, were inspected by the Division of Scientific Investigation. No deficiencies were found.

[1] Keller MB, Ryan ND, Strober M et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 2001 40(7):762-772.

In addition, GSK performed their own audit of the following sites:

Study 329
Graham Emslie, MD / Dallas, TX
(b) (4) / Pittsburgh, PA

Study 453
Jon Bell, MD / Denver, CO
(b) (4) / Los Angeles, CA
Laura Sanchez, MD / Philadelphia, PA
Humberto Quintana, MD / Omaha, NB

Study 701
Paras Harshawat, MD / Terre Haute, IN
Saul Helfing, MD / Lake Oswego & Salem, OR
Scott Hoopes, MD / Boise, ID
Teresa Varanka, MD / Prairie Village, KS
Vivek Kusamaker, MD / Halifax & Sydney, NS, Canada

Study 704
Daniel Geller, MD / Belmont. MA
Paras Harshawat, MD / Terre Haute, IN
M. Carmen Palazzo, MD / New Orleans, LA*
Randall Ricardi, MD / Phoenix, AZ

---

*site terminated by sponsor because of compliance violations

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

GSK reported that the trials conducted in the U.S. (studies 329, 453, 701, 704, 715, and 716) were carried out with appropriate Institutional Review Board oversight. GSK stated that the foreign study (377) was conducted according to the Declaration of Helsinki and Good Clinical Practices, and that there was either an Institutional Review Board or an Ethics Committee for each site. No information on ethical standards was provided for study 676; however, the study report for this trial was incomplete at the time of the submission.

E. Evaluation of Financial Disclosure

Dr. David Wheadon, Senior Vice President for U.S. Regulatory Affairs, certified on Form FDA 3454 that GSK made no financial arrangements with investigators that depended upon the results of the clinical studies. The following investigators received payments or honoraria from the sponsor that were disclosable under 21 CFR 54: (b) (6) $138,700; (b) (6) $252,442; (b) (6) $30,645.

In my view, there were no financial arrangements that were likely to have biased the results of these trials.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The sponsor conducted three acute treatment studies in pediatric major depression, one acute treatment trial in pediatric OCD, and one relapse prevention trial in pediatric OCD. Of these, the only trial that demonstrated efficacy of paroxetine relative to placebo was the acute treatment OCD trial. [redacted] (b) (4)

B. General Approach to Review of the Efficacy of the Drug

None of the three randomized, controlled trials in MDD yielded results that distinguished paroxetine from placebo on a priori primary outcome variables. Accordingly, these three trials (studies 377, 701 and 329) will only be briefly summarized in this review.

For OCD, there were two randomized controlled trials, one of which was an acute treatment trial (study 704) and the other of which was a relapse prevention trial (study 453). Of the two, study 704 showed a positive result [redacted] (b) (4) This trial will be presented in the most detail, and is the only trial reviewed by our Biometrics team.

C. Detailed Review of Trials by Indication

1. Major Depressive Disorder

Study 377

Investigators/sites: There were a total of 33 sites in 10 different countries (Belgium, Italy, Spain, U.K., Holland, Canada, South Africa, United Arab Emirates, Argentina, and Mexico). Please refer to the study report for a complete list of the investigators.

Purpose: The objective of this study was to evaluate the safety and efficacy of paroxetine in the treatment of adolescent unipolar major depression

Design: The initial phase of the study was a 2-week placebo washout. Following this, subjects were to be randomized to 12 weeks of treatment with either paroxetine or placebo; dosing of paroxetine was flexible (20, 30 or 40 mg daily). Subjects were then tapered off study medication over a 2 week period.

Population: The sample was to be 264 outpatients with unipolar major depression, aged 13-18 years.

Assessments: The two primary outcome measures were (1) the proportion of subjects with at least a 50% reduction from baseline in their Montgomery Asberg Depression Rating Scale (MADRS) score, and (2) change from baseline in the K-SADS-L depression subscale. Safety monitoring included clinical laboratories and vital signs (but ECGs were obtained only at screening).

Results: The sponsor's table below displays the numbers of patients enrolled by treatment group, and their disposition.

	Treatment Group	
Study Conclusion Reason	Paroxetine n=182	Placebo n=93
COMPLETED STUDY	127 (69.8)	69 (74.2)
Withdrawal Reason		
Adverse Experiences	20 (11.0)$	7 (7.5)*
Lack of efficacy	9 (4.9)	6 (6.5)
Protocol Violation	7 (3.8)	4 (4.3)*
Lost to Follow-up	13 (7.1)	6 (6.5)
Other	6 (3.3)	1 (1.1)
TOTAL WITHDRAWN	55 (30.2)	24 (25.8)

As seen above, there were no great discrepancies between treatment groups with respect to the numbers of patients discontinuing for specific reasons.

With respect to demographic characteristics, the sample was predominantly female (gender ratio approximatley 2:1) and Caucasian, with a mean age of approximately 15 years. There were no obvious imbalances between treatment groups with respect to demographic characteristics.

The results for the primary outcome measures failed to distinguish between paroxetine and placebo. The proportion of patients meeting the response criterion was 60% for paroxetine and 58% for placebo (p-value = 0.62). The mean change from baseline in K-SADS-L depression subscale was –9.3 for paroxetine and –8.9 for placebo (p-value = 0.70).

Conclusions: This trial did not provide any evidence that paroxetine is active in the treatment of adolescent MDD.

Study 701

Investigators/sites: There were 40 U.S. sites and one Canadian site. Please refer to the study report for a complete list of the investigators. The study was conducted from March 2000 through January 2001.

Purpose: The objective of this trial was to compare the safety and efficacy of paroxetine and placebo in the treatment of children and adolescents with MDD.

Design: This was a randomized, double blind, placebo controlled, parallel group, flexible dose study. Subjects were to have a screening evaluation followed by a baseline evaluation approximately one week later, and if eligible were then randomized to receive either paroxetine 10-50 mg/day or placebo, for a duration of 8 weeks. Randomization was to be stratified by age group (7-11 years, and 12-17 years). The initial dose was to be 10 mg daily for all subjects, with dose increases permitted weekly in increments of 10 mg, up to the maximum of 50 mg. At the end of the study the dosage was down-titrated by10 mg/day every 7 days, with discontinuation after subjects received 10 mg for one week.

Assessments: Screening assessments included the K-SADS-PL interview, medical and psychiatric history, physical exam, clinical laboratories, urine drug screen, pregnancy testing, and ECG. Safety monitoring included vital signs, with ECGs and clinical laboratories at the end of the 8 weeks of treatment. The protocol specified the following as the primary outcome measure: "Change from baseline in Children's Depression Rating Scale – Revised (CDRS-R) total score at the Week 8 LOCF endpoint."

Population: The intended sample size was 192. Subjects were to be divided into two age groups, as noted above, and neither age group was to be less than 40% of the total sample. Subjects were to have MDD, with a CDRS-R socre of at least 45 at both baseline and screening.

Results: Three hundred five subjects were screened, and 206 were randomized (104 to paroxetine and 102 to placebo). There were slightly more premature discontinuations in the paroxetine group (31) than in the placebo group (23). The numbers of patients who dropped out for each specific reason for premature discontinuation are summarized below.

Reason	Paroxetine (n=104)	Placebo (n=102)
Adverse event	10	2
Lack of efficacy	7	11
Protocol deviation	3	3
Lost to follow up	8	4
Other	3	3

On the mean change from baseline at endpoint in CDRS-R total score, which was the primary outcome measure, the result for the placebo group was numerically superior to that for the paroxetine group (-23.4 versus –22.6 for placebo and paroxetine, respectively). With respect to secondary outcome measures, there were no results showing statistical superiority of paroxetine over placebo.

Conclusions: This trial does not provide any evidence that paroxetine is effective in the treatment of pediatric MDD.

Study 329

Investigators/sites: The table below, reproduced from the sponsor's submission, lists the investigators for this trial.

Center	Investigator	Affiliated Institution	City/State/Provence
001	Barbara Geller, MD	Washington University School of Medicine	St. Louis, MO
002	Martin B. Keller, MD	Brown University School of Medicine	Providence, RI
003, Site 1	Rachel Klein, PhD Jorge Armenteros, MD	New York State Psychiatric Institute	New York, NY
003, Site 2	Harold Koplewicz, MD	Long Island Jewish Medical Center	New Hyde Park, NY
004	Stan Kutcher, MD* G. Papatheodorou, MD	Sunnybrook Health Science Center	Toronto, Ontario, Canada
005	Neal Ryan, MD Boris Birmaher, MD	University of Pittsburgh School of Medicine	Pittsburgh, PA
006	Michael Strober, PhD David Feinberg, MD	University of California Los Angeles Medical Center	Los Angeles, CA
007	Karen Wagner, MD, PhD	University of Texas Medical Branch	Galveston, TX
008	Greg Clarke, PhD William Sack, MD	Oregon Health Sciences University	Portland, OR
009	Graham Emslie, MD	University of Texas Southwestern at Dallas	Dallas, TX
010	Elizabeth Weller, MD	Ohio State University Medical Center	Columbus, OH
011	Gabrielle Carlson, MD	State University of New York at Stony Brook	Stony Brook, NY
012	Vivek Kusumakar, MD Stan Kutcher, MD*	Izaak Walton Killam Children's Hospital	Halifax, Nova Scotia, Canada

Source: Appendix A contains the curriculum vitae (or biographical sketch) of each principal investigator

* Dr. Kutcher participated at site 004 from March 1994 through April 1995, and at site 012 from May 1995 through study completion.

Purpose: The protocol states that the purpose of this trial was, "To compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression."

Design: This was a multicenter, randomized, double-blind, placebo controlled, three-arm, parallel group study. The duration of acute treatment was to be 8 weeks, with the option of a 6-month extension of double blind treatment for subjects who had responded. After a 7-10 day screening period eligible subjects were to be randomized to imipramine, paroxetine, or placebo. The randomization ratio was 1:1:1, with randomization in blocks of 6 subjects. The titration scheduled specified an initial daily dose of imipramine of 50 mg, with titration to 200 mg by the beginning of the fourth week. The dosage of paroxetine was 20 mg which was to be initiated without titration. In the event of inadequate response by the end of 4 weeks, the medication could be titrated up to 300 mg of imipramine or 40 mg of paroxetine. Medication was administered in divided doses on a BID schedule. Concomitant psychotropic medications were prohibited.

Assesments: Screening assessments included history and physical exam, clinical laboratories, pregnancy testing, ECG, and complete K-SADS-L. Monitoring of subjects during the study was to include vital signs, ECGs, and repeat clinical laboratories at the end of 8 weeks. Pharmacokinetic blood samples were to be obtained at weeks 4 and 8. There were two primary

outcome measures specified: the change in HAMD 17 item total score at endpoint, and the proportion of responders at endpoint. A subject was to be considered a responder at week 8 if he or she had a HAMD-17 score $\leq$ 8, or a decrease from baseline in the HAMD-17 of at least 50%.

Population: The subjects were to be 300 adolescents, aged 12-18 years, with MDD according to DSM-III-R criteria, and a minimum HAMD-17 score of 12. The current episode of major depression was to be at least 8 weeks in duration.

Results: The study was conducted between April 1994 and February 1998. The following table, reproduced from the submission, displays the disposition of the subjects in the trial. Adverse events were the most frequent reason for discontinuation from the imipramine arm; otherwise there were not major differences in the disposition of subjects between treatment groups. Note that over 70% of paroxetine and placebo patients completed the trial. The table also shows the mean dose for paroxetine and imipramine.

Patient Disposition			
	Paroxetine	**Imipramine**	**Placebo**
Entered	93	95	87
Completed 8 weeks	72%	60%	76%
Reason for Withdrawal			
Adverse Event	10%	32%	7%
Lack of efficacy	4%	1%	7%
Other reason+	14%	7%	10%
Mean dose (mg) (S.D.)	28.0 (8.5)	206 (64.0)	0

+ Other includes patients withdrawn for protocol violations and lost to follow-up

The results for the HAM-D are shown in the following table.

Treatment	N	Baseline	Mean change from BL at endpoint	SE	p-value vs pbo
Paroxetine	90	18.98	-10.74	0.81	0.133
Imipramine	94	18.11	-8.91	0.81	0.873
Placebo	87	18.97	-9.09	0.83	-

The result for the paroxetine arm was numerically superior to the other treatment groups, but the difference was not statistically significant.

For the second primary outcome measure, the proportion of patients who met the aforementioned criteria for response (HAMD-17 score $\leq$ 8, or a decrease from baseline in the HAMD-17 $\geq$ 50%), the results are shown in the following table.

Treatment	N	Responders (%)	p-value vs. pbo
Paroxetine	90	60 (66.7)	0.112
Imipramine	94	55 (58.5)	0.612
Placebo	87	48 (55.2)	-

The proportion of responders at endpoint was greater for paroxetine than placebo, but this difference was not statistically significant. The difference in the proportion of responders was, however, marginally statistically significant using an observed cases analysis (data not shown).

Secondary outcome measures: The percentage of patients with a HAMD score $\leq$ 8 at endpoint, which the sponsor termed "remission," was 63.3% for paroxetine, 50.0% for imipramine, and 46.0% for placebo. On this outcome the difference from placebo was statistically significant for paroxetine (p-value = 0.019) but not for imipramine. On the CGI-Improvement scale, the results showed superiority of paroxetine over placebo by a statistically significant margin for the observed cases analysis, but not for the LOCF analysis.

Conclusions: Although there was some evidence of activity of paroxetine on the secondary outcome measures, the paroxetine treatment group did not separate statistically from placebo on the a priori primary efficacy measures in this trial. There was no evidence that impramine was more effective than placebo in this trial. On balance, this trial should be considered as a failed trial, in that neither active treatment group showed superiority over placebo by a statistically significant margin.

2. Obsessive Compulsive Disorder

Study 704

Investigators/sites

The following table, reproduced from the submission, lists the investigators in the trial.

Table 1 Investigators, the SB Assigned Center Number and the Investigator Hospital or University Affiliation and Location

Investigator	Center	Affiliated Institution	City	State
United States				
Gail Bernstein, M.D.	002	University of Minnesota Medical School	Minneapolis	MN
Graham Emslie, M.D.	004	UT Southwestern Medical Center, Children's Medical Center of Dallas	Dallas	TX
Daniel Geller, M.D. Joseph Biederman, M.D.	005	McLean Hospital	Belmont	MA
James Lee, M.D. Thomas Gualtieri, M.D.	006	North Carolina Neuropsychiatry	Charlotte	NC
James Grimm, M.D.	008	Oregon Center for Clinical Investigations, Inc.	Salem	OR
Robert Hendren, M.D.	009	UMDNJ-Robert Wood Johnson Medical School	Piscataway	NJ
Rakesh Jain, M.D.	010	R/D Clinical Research, Inc.	Lake Jackson	TX
Ricks Warren, Ph.D. Ajit Jetmalani, M.D.*	011	Westover Heights Clinic	Portland	OR
Hugh Johnston, M.D.	012	University of Wisconsin Medical School-WISPIC	Madison	WI
Michael Labellarte, M.D.	013	Johns Hopkins Medical Institutions	Baltimore	MD
Scott Hoopes, M.D.	014	315 North Allumbaugh	Boise	ID
Michael Rieser, M.D.	015	3046 Rio Dosa Drive	Lexington	KY
Randall Ricardi, D.O.	016	Phoenix Children's Hospital	Phoenix	AZ
Floyd Sallee, M.D.	017	Univ. of Cincinnati College of Medicine	Cincinnati	OH
Karen Wagner, M.D.	019	Univ. of Texas Medical Branch	Galveston	TX
Tanya Murphy, M.D. Wayne K. Goodman, M.D.	020	University of Florida Faculty Group Practice	Gainesville	FL
Robert Hoehn, M.D.	021	Research Memphis	Memphis	TN
Laura Rocker, M.D.	022	Health Research Associates, LLC	Cleveland	OH
Anthony Machi, M.D.*	023	Milwaukee Center for Clinical Research	Milwaukee	WI
Paras Harshawat, M.D.	025	4733 South 7th Street	Terre Haute	IN
Rakesh Ranjan, M.D.	026	Rakesh Ranjan, MD and Associates, Inc.	Medina	OH

* Patients were screened but not randomized.

Table 1 Investigators, the SB Assigned Center Number and the Investigator Hospital or University Affiliation and Location (continued)

Investigator	Center	Affiliated Institution	City	State
United States				
Adelaide Robb, M.D.	027	Children's National Medical Center	Washington	DC
Padmini Atri, M.D. John Gilliam, M.D.	028	Westbrook Behavioral Associates, LLC	Richmond	VA
Robert Reichler, M.D. Syed Mustafa, M.D.	029	Pacific Institute of Mental Health	Seattle	WA
Robert Lehman, M.D. Alan Jonas, M.D.	040	Pharmapsych Research, Inc.	Baltimore	MD
Judith Fallon, M.D.	041	NeuroScience, Inc.	Bethesda	MD
Jeffrey Hirshfield, M.D.	043	Clinical Research of West Florida	Clearwater	FL
Frank Lopez, M.D.	044	Children's Developmental Center	Maitland	FL
Anne Macek, M.D.	047	The Institute for Advanced Clinical Research	Elkins Park	PA
Teresa Varanka, M.D.	048	CTT Consultants, Inc.	Prairie Village	KS
Stuart Kaplan, M.D. Joan Busner, Ph.D.	049	Penn State University College of Medicine	Hershey	PA
Lourdes Quiray, M.D.	051	Child, Adolescent, and Adult Psychiatry.	Fort Walton Beach	FL
Daniel Becker, M.D.	052	Discovery Alliance, Inc.	Mobile	AL
Timothy Soundy, M.D.	053	University Physicians-Psychiatry Associates	Sioux Falls	SD
M. Carmen Palazzo, M.D.	055	GGS Psychiatric Clinic of New Orleans	New Orleans	LA
Giancarlo Ferruzzi, M.D.	056	San Antonio Center for Clinical Research	San Antonio	TX
Michael Greenbaum, M.D.*	058	Neuropsychiatric Associates of Illinois, S.C.	Vernon Hills	IL
Canada				
Aidan Stokes, M.D.	031	IWK Grace Health Centre	Halifax	Nova Scotia
Lorne Warneke, M.D.	033	Grey Nuns Hospital	Edmonton	Alberta

* Patients were screened but not randomized.

Purpose: The purpose of this study was to determine the safety and efficacy of paroxetine for the treatment of pediatric OCD.

Design: This was a randomized, double blind, multicenter, parallel group, flexible dose study. Subjects were to have a screening assessment, followed in approximately one week by a baseline assessment. If subjects met the entry criteria at the baseline evaluation, they were randomized to

either paroxetine or placebo. Randomization was to be stratified by 2 age subgroups (7-11 years of age versus 12-17 years of age). The initial dosage of paroxetine was to be 10 mg daily, which could be increased by 10 mg/day at weekly intervals as needed, up to a maximum of 50 mg/day. Placebo patients could receive one to five tablets of matching placebo per day. The duration of the acute treatment phase was to be 10 weeks. There was to be no concomitant psychotropic medication, or concomitant psychotherapy. When discontinuing treatment, subjects were to be down-titrated by increments of 10 mg per week until they had remained on 10 mg/day for 7 days; at that point the medication was stopped. Optional open label treatment, up to 6 months in duration, was to be made available to subjects following the trial (under Protocol 716).

Assessments: The screening evaluations included a psychiatric interview with the complete K-SADS-PL instrument, medical history, physical exam, ECG, height and weight, clinical laboratories, and pregnancy testing. Baseline evaluations were to include CY-BOCS and CGI. Subjects were to be assessed every 1-2 weeks during the acute treatment phase of the trial; efficacy assessments included CY-BOCS and CGI (Severity and Improvement). The sponsor's table showing the schedule of events is shown here.

	Scrn Visit Day -7	Base-Line Visit Day 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Early W/D	Taper End Visit	14-Day Study F/U[a]
Screen/Baseline Evaluations												
Informed Consent/Assent	X											
Patient Demography	X											
Inclusion/Exclusion Criteria	X	X										
Psychiatric Interview	X											
Full K-SADS-PL Interview	X											
OCD criteria (DSM-IV)	X											
OCD History/Med History	X											
Medical/Surgical History	X											
Patient Randomization		X										
Efficacy Parameters												
CY-BOCS	X	X		X		X	X	X	X	X		
CGI (Severity of Illness)		X	X	X	X	X	X	X	X	X		
CGI (Global Improvement)			X	X	X	X	X	X	X	X		
GAF		X		X		X	X	X	X	X		
Safety Evaluations												
12 Lead ECG	X	X[b]							X	X	X[b]	X[b]
Vital Signs[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Height and Weight	X								X	X		
Adverse Experience		X	X	X	X	X	X	X	X	X	X	X
Laboratory Evaluation	X	X[e]							X	X	X[e]	X[e]
Urine Drug Screen	X											
Physical Examination	X								X	X		
Serum Pregnancy Test[d]	X[d]								X[d]	X[d]		
Blood draw for PK[g]						X			X	X		
Miscellaneous Records												
Prior and Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Medication		X	X	X	X	X	X	X	X[f]	X[f]		
Medical Procedures		X	X	X	X	X	X	X	X	X	X	X
Study Medication Record		X	X	X	X	X	X	X	X	X	X	
Study Conclusion Record									X	X		

K-SADS-PL – Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime Version

GAF – Global Assessment of Functioning Scale; CY-BOCS – Childen's Yale-Brown Obsessive-Compulsive Scale

a – Follow-up visit to be completed 14-days after last dose of study medication for all patients except those continuing into the open label extension study, 29060/716.

b – Repeat ECG if results at previous visit are clinically significantly abnormal. Screen results must be interpreted prior to randomization.

c – 3-minutes sitting systolic and diastolic blood pressure and heart rate

d – For females of child-bearing potential

e – Repeat Laboratory Evaluations to be performed only if clinically significantly abnormal results and with the investigator's agreement. Results of repeat evaluation must be interpreted prior to randomization. Hematology (hemoglobin, hematocrit, WBC with differential, RBC, and platelet count); Blood Chemistry (creatinine, BUN, total bilirubin, alkaline phosphatase, SGPT [ALT], SGOT[AST], electrolytes, TSH, T_3, T_4[thyroid tests at Screening Visit only]; dipstick urinalysis (if positive for blood or protein, full microscopy will be performed).

f - Taper Medication dispensed for all patients ending Treatment phase or withdrawing at Dosage Level 2-5.

g – PK sampling is optional and patient consent is required.

Population: Subjects were to be between 7 and 17 years old, with OCD for at least 2 month's duration. The goal was to randomize roughly equal numbers of children (aged 7-11 years) and adolescents (aged 12-17 years), with a total of 204 subjects. The diagnosis was to be according to DSM-IV criteria and the K-SADS-PL; also, OCD was to be the primary psychiatric diagnosis. The CY-BOCS score was to be at least 16 at both the screening and baseline visits. Patients with major depression, bipolar disorder, psychosis, mental retardation, seizures, or substance abuse were to be excluded, as were patients dangerous to themselves or others. In addition, pregnancy, psychotherapy, or previous poor response to an SSRI were also to be grounds for exclusion.

Analysis plan: The change from baseline in the CY-BOCS (LOCF at week 10) was designated the primary outcome variable. The statistical method specified in the protocol was ANOVA with treatment, age category, gender, comorbidity category, and baseline score as covariates. The planned analysis did not include center as a covariate (because of the small number of patients per site). The intent-to-treat sample (ITT) was defined in the usual manner; i.e., those subjects who received one or more doses of study medication and had one or more post-baseline evaluations. Among the secondary outcome measures was a response variable, with response defined as $\geq$25% improvement from baseline to endpoint on the CY-BOCS total score.

Results: The study was conducted from January 2000 through July 2001. Of the 265 subjects who were screened, a substantial majority (207) were randomized.

Patient completion rates: The number of patients for each visit is shown in the table below (adapted from the sponsor's study report). It will be seen that the completion rate was higher for the placebo group.

Visit	Paroxetine (N=98)		Placebo (N=105)	
	n	(%)	n	(%)
Baseline	98	(100.0)	105	(100.0)
Week 1	95	(96.9)	101	(96.2)
Week 2	92	(93.9)	98	(93.3)
Week 3	88	(89.8)	96	(91.4)
Week 4	83	(84.7)	92	(87.6)
Week 6	72	(73.5)	86	(81.9)
Week 8*	69	(70.4)	81	(77.1)
Week 10**	63	(64.3)	78	(74.3)

Subject disposition: The sponsor's table showing the reason for premature discontinuation is shown on the next page. The reasons for discontinuing differed by age group: in the adolescent group, discontinuation for lack of efficacy was more frequent with placebo, while this was not the case for younger subjects; on the other hand, among children, an adverse event was a more frequent reason for discontinuing paroxetine than placebo, but this was not the case for adolescents.

	Age Group: Total			Age Subgroups			
				Age Group: Children		Age Group: Adolescents	
Reason for Study Conclusion	**Paroxetine** (N = 98) n (%)	**Placebo** (N = 105) n (%)	**Total** (N = 203) n (%)	**Paroxetine** (N = 58) n (%)	**Placebo** (N = 57) n (%)	**Paroxetine** (N = 40) n (%)	**Placebo** (N = 48) n (%)
Adverse Event	10 (10.2)	3 (2.9)	13 (6.4)	8 (13.8)	1 (1.8)	2 (5.0)	2 (4.2)
Lack of efficacy	5 (5.1)	14 (13.3)	19 (9.4)	3 (5.2)	4 (7.0)	2 (5.0)	10 (20.8)
Protocol deviation (including non-compliance)	5 (5.1)	3 (2.9)	8 (3.9)	1 (1.7)	1 (1.8)	4 (10.0)	2 (4.2)
Lost to Follow-up	6 (6.1)	3 (2.9)	9 (4.4)	5 (8.6)	2 (3.5)	1 (2.5)	1 (2.1)
Other *	7 (7.1)	2 (1.9)	9 (4.4)	5 (8.6)	1 (1.8)	2 (5.0)	1 (2.1)
Total withdrawn	33 (33.7)	25 (23.8)	58 (28.6)	22 (37.9)	9 (15.8)	11 (27.5)	16 (33.3)
Completed study **	65 (66.3)	80 (76.2)	145 (71.4)	36 (62.1)	48 (84.2)	29 (72.5)	32 (66.7)

* Includes non-study-related personal reasons: family decided not to start medication, although it was dispensed (1 patient); patient required excluded medication (1 patient); withdrew consent (3 patients); patient sexually molested (1 patient); wrong medication dispensed (1 patient); patient did not wish to continue (1 patient); mother took patient off study, seeking other treatment (1 patient).

** Patients were considered to have completed the study if they completed the Week 10 visit. The total of 145 completers includes 3 patients who completed at Week 8 and 1 patient who completed post-Week 10.

Source: Table 13.3.1b, Section 11; Listing 13.3.1b, Appendix B

Demographic characteristics: The following tables display the numbers of patients by age group, gender, and randomized treatment. There were more males than females in the trial, and more children than adolescents.

CHILDREN	Females	Males	Total
Paroxetine	27	31	58
Placebo	22	35	57
Total	49	66	115

ADOLESCENTS	Females	Males	Total
Paroxetine	18	22	40
Placebo	19	29	48
Total	37	51	88

Overall, the sample was predominantly male (117 males and 86 females). The mean age of the children was approximately 9 years for both paroxetine and placebo groups, and the mean age of the adolescents was approximately 14 years. The sample was predominantly Caucasian (88%); 6% of subjects were African-American, and the remainder "other." There were no Asian subjects in the trial. The median duration of OCD was 3 years. Psychiatric comorbidity of some type was present in 31% of paroxetine patients and 40% of placebo subjects.

Examination of the frequency of use of concomitant medications did not reveal any discrepancies between groups. The most commonly used concomitant medication was acetaminophen, used by approximately one-fourth of subjects in either group.

Dose: The mean daily dose of paroxetine at endpoint was 30.1 mg/day for the entire sample, and was slightly higher for adolescents (36.5 mg/day) than for children (25.4 mg/day).

Efficacy analyses: Dr. Palazzo's site (number 055) was excluded from the analysis because of compliance violations, resulting in 14 fewer subjects for the efficacy analysis. On the primary outcome variable, the week 10 LOCF mean change from baseline in CYBOCS for the intent-to-treat sample, the results were as follows.

	Paroxetine	Placebo
N (ITT sample)	91	98
Baseline LS mean	24.2	25.1
Mean change, LOCF, wk 10	-9.3	-5.5
p-value (ANCOVA)	<0.001*	

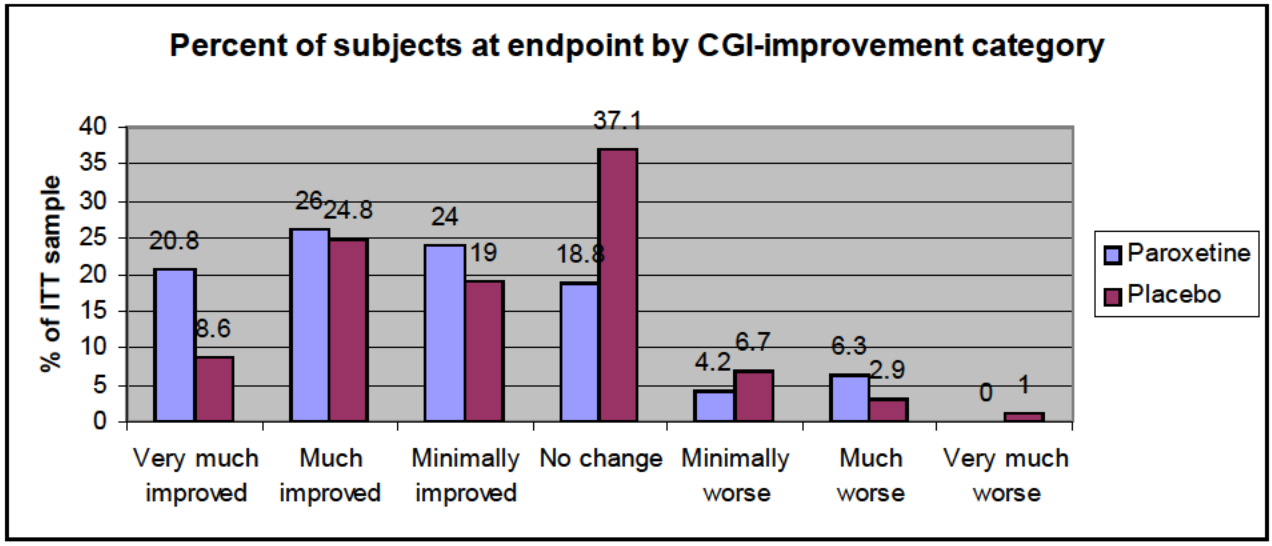
* adjusted for baseline score, age group, gender, and psychiatric comorbidity

For the covariates that were included in the model (baseline score, age group, gender, and psychiatric comorbidity), there were no statistically significant interactions with treatment. Although the sponsor did not re-analyze this excluding site 055, one would not expect that to change the analysis substantially.

With respect to secondary outcome measures, the submission did not provide analyses that omitted site 055. On the proportion of responders (with response defined as at least a 25%

reduction in the CYBOCS total score), the results favored paroxetine over placebo, with 65% of paroxetine patients meeting the criterion for response at endpoint compared to only 41% of placebo patients (p-value = 0.002). On the CGI-severity score change from baseline, paroxetine was not statistically significantly different from placebo.

The chart below shows the CGI-Improvement results at endpoint. Note that the greatest discrepancies between treatments are in the "very much improved" and "no change" categories.



Conclusions: This trial provides evidence that paroxetine is active in the treatment of pediatric OCD.

Study 453

Investigators/sites: There were a total of 26 investigators for this trial. All sites were in the U.S. The interested reader is referred to the study report for a complete list (table 1 in the study report).

Purpose: To assess the effect of paroxetine treatment on relapse in pediatric OCD patients.

Design: This was a multicenter, randomized, double blind, placebo controlled trial. The first phase of the study was to be an open label, 16 week period of treatment with paroxetine. Subjects were administered a starting dose of 10 mg/day, and the dose could be increased to a maximum of 60 mg/day. At the end of the 16 weeks of treatment, subjects were to be randomized to either placebo or paroxetine if they met the following criteria: at least a 25% improvement from baseline on the CYBOCS total score, and a CGI-improvement score of 1 or 2. The dosage during the double blind portion of the trial was not to be adjusted. Subjects who were randomized to placebo were to be down-titrated blindly in increments of 10 mg per week. At the end of double blind treatment, subjects were down-titrated in a similar fashion. The duration of double blind treatment was to be 16 weeks.

Assessments: During the double blind portion of the trial, a subject was to be withdrawn from the trial and referred for treatment if they met any of these criteria: worsening of CGI-improvement score by 1 point for 2 consecutive visits, worsening of CGI-improvement score by ≥2 points at any visit, or CGI-improvement score ≥5. Other scheduled assessments included the CYBOCS, HAMA, HAMD, and Yale Global Tic scale. Subjects were to be assessed every 2 weeks during the double blind phase. Safety assessments included ECGs, clinical laboratories, pregnancy testing, vital signs, and weight (but not height).

Population: The subjects were to be aged 8-17 years, with OCD by DSM-IV criteria as their primary diagnosis, confirmed by the K-SADS-L. The goal was to enroll 375 subjects in open label treatment, with the expectation that 180 of these subjects could subsequently be randomized. Subjects were to have a score of at least 16 on the CYBOCS at both screening and baseline.

Analysis plan: The primary outcome measure was the proportion of patients who relapsed (according to the criteria above) during double blind treatment. Time to relapse was specified as a secondary analysis.

Results: A total of 339 subjects entered the open label treatment phase, and 194 of these subjects were subsequently randomized, 95 to paroxetine and 98 to placebo. The median age was 10 for the paroxetine subjects and 9 for placebo subjects. The sample was over 90% Caucasian. There was a slight gender imbalance between treatment groups; 51% of the paroxetine subjects were female, while only 41% of the placebo patients were female. The intent-to-treat sample included 193 subjects.

There were more subjects who withdrew (for any reason) from the placebo group (66%) than from the paroxetine group (56%). Lack of efficacy was the primary reason for withdrawal in the double blind phase, in both groups.

The percentage of patients who relapsed was 35% for paroxetine and 45% for placebo; this difference was not statistically significant, however (p-value = 0.14). The results varied by age subgroup: subjects under 12 years of age showed a lower percentage of relapsers for paroxetine compared to placebo, while the percentage of relapsers was essentially equal between treatment groups for the adolescents. For time to relapse, the hazard ratio of 1.5 favored paroxetine over placebo, but this was not statistically significant (p-value = 0.10).

Conclusions: This trial failed to show that paroxetine is effective in the prevention of OCD relapse in pediatric patients.

E. Efficacy Conclusions

None of the three randomized, controlled trials in pediatric major depression demonstrated efficacy for paroxetine. The acute treatment trial in pediatric OCD did indicate that paroxetine is active in short term treatment of this disorder, but the relapse prevention trial failed to

demonstrate efficacy. (b) (4)

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The most prominent adverse reactions (b) (4) appear to involve behavioral effects; these events were coded with terms such as hostility and emotional lability. As previously noted, the sponsor's method of coding these events was potentially confusing, and thus additional information will be helpful for the purpose of definitively assessing the potential behavioral toxicity of paroxetine treatment in pediatric patients.

There was one postmarketing spontaneous report that described a fatal allergic reaction in an 11 year old boy following a single dose of paroxetine.

B. Description of Patient Exposure

The following table, reproduced from the submission, depicts the patient exposure by demographic subgroups, for subjects who received paroxetine. The submission did not provide such information for subjects who received placebo.

	Paroxetine	
	N	**Exposure (yrs)***
All OCD and MDD Studies (combined)		
Total	932	282.81
Age Group (yrs)		
<12**	345	106.60
≥12†	587	176.22
12-14	274	88.65
≥15	313	87.57
Gender		
Male	473	140.34
Female	459	142.47
Race		
White	778	240.09
Other††	154	42.72

The following table shows the number of subjects by their maximum paroxetine dose, for all paroxetine subjects in these trials (from ISS table 18.6). The most frequent maximum dose for both children and adolescents was 20 mg. Although ISS table 18.6 displayed the number of patients exposed to each dose by trial week, the submission did not include the more usual

display showing the numbers of subjects according to their mean daily dose and total duration of exposure.

Max. dose/day (mg)	Children (n=345)	Adolescents (n=587)	All patients (n=932)
10	44	15	59
20	109	184	293
30	95	160	255
40	46	131	177
50	38	62	100
60	13	35	48

C. Methods and Specific Findings of Safety Review

For assessment of the common adverse event profile, and of changes in safety parameters (vital signs and clinical laboratories), the combined data from the double-blind placebo controlled trials was the primary data source. These data provide a readily available comparison between drug and placebo. I have chosen to emphasize the combined data set rather than merely the OCD controlled trial for the purpose of having a larger sample size of controlled data; of course, this requires an assumption that any differences in the safety profile between OCD and MDD subjects are ignorable. For serious but less frequent adverse events, the entire set of safety data (from all 932 pediatric subjects exposed to paroxetine) was considered. GSK classified adverse event terms according to the WHOART standard dictionary.

In addition to the clinical trial data, GSK's literature review and summary of postmarketing reports were also reviewed, and will be described separately following the description of the clinical trial safety findings.

GSK defined the "intent-to-treat" (ITT) population as all subjects who received study medication (open label or double blind) and for whom post-baseline data is available. However, some of the integrated safety data is presented for the "all patients" population, which is slightly larger; for paroxetine, there were 943 subjects in the all patients sample and 942 subjects in the ITT sample. Similarly, there were 387 placebo patients in the ITT sample (for acute studies, excluding the relapse prevention study 453), while there were 396 placebo patients in the all patients population.

Disposition of patients: The following table, adapted from the sponsor's submission, summarizes the disposition of all 932 paroxetine-treated subjects in these trials.

Disposition	n (%)
Completed Study	344 (36.9)
Adverse Event	145 (15.6)
Lack of Efficacy	156 (16.7)
Protocol Deviation	73 (7.8)
Lost to Follow-up	67 (7.2)

Other	121 (13.0)
Total Withdrawn	562 (60.3)
Ongoing	26 (2.8)

This table, adapted from the sponsor, shows the corresponding data from the subset of acute controlled trials for the purpose of comparisons between paroxetine and placebo:

Disposition	% of Paroxetine pts (n=470)	% of Placebo pts (n=387)
Completed Acute Phase/Study	69.4%	73.9%
Adverse Experience	10.4%	4.4%
Lack of Efficacy	5.5%	11.4%
Protocol deviation	3.8%	4.7%
Lost to Follow-up	6.6%	3.6%
Other	4.3%	2.1%
Total withdrawn	30.6%	26.1%

Not unexpectedly, adverse experiences were more frequently the reason for discontinuation among paroxetine subjects, while lack of efficacy was more often a reason for dropping out from placebo treatment.

Deaths: There were no deaths in these clinical trials.

Serious adverse events: In their analysis, GSK included serious adverse events occurring up to 30 days after the end of the study, but omitted surgical procedures that were elective if they were unrelated to an adverse event.

Serious adverse events in OCD and MDD trials: The following shows the number of patients who experienced specific serious adverse events, out of the total sample of all patients (n=943), for adverse events that occurred in more than one patient.

Serious adverse event	Number (%) of 943 paroxetine patients
Emotional lability	28 (3.0)
Hostility	13 (1.4)
Depression	12 (1.3)
Agitation	8 (0.8)
Neurosis	5 (0.5)
Anxiety	3 (0.3)
Nausea	3 (0.3)
Trauma	3 (0.3)
Hallucinations	2 (0.2)
Insomnia	2 (0.2)
Manic reaction	2 (0.2)
Tremor	2 (0.2)

In addition to the events listed, the following serious adverse events occurred in one paroxetine patient: abnormal laboratory value, abnormal vision, abscess, accidental overdose, asthenia, asthma, convulsion, decreased appetite,

delusions, dizziness, drug dependence, dry mouth, euphoria, extrasystoles, gastrointestinal disorder, hypertension, hysteria, infection, kidney pain, myoclonus, nervousness, paralysis, paranoid reaction, peptic ulcer hemorrhage, postural hypotension, psychosis, skin hypertrophy, somnolence, vomiting, withdrawal syndrome, alcohol abuse, amnesia, angioedema, unintended pregnancy.

For adolescents, emotional lability was the most frequent serious adverse event, occurring in 3.9% of subjects; GSK coded suicide attempts and other self injurious behaviors under the WHOART term emotional lability. For children, hostility was the most frequent serious adverse event, occurring in 2.0% of subjects, followed by depression (1.7%), emotional lability (1.4%) and neurosis (1.1%). I was unable to find a corresponding table for placebo patients in the submission.

Serious adverse events in other trials: There were 2 serious adverse events in the pharmacokinetic study (715): A ten year old boy had a manic episode, and a 16 year old girl took an intentional overdose of paroxetine 50 mg, allegedly to make up for several days of missed dosages. In study 676, the recently completed pediatric social phobia study (for which there is no study report yet), four patients suffered serious adverse events during treatment. The treatment assignments for these patients were still blinded at the time of submission. Briefly, the events were depression, fractured arm, accidental overdose, and anemia. Details regarding these events were lacking in the submission, although further information will likely become available.

By my count, there were 11 instances of suicide attempt or self-injurious behavior among the paroxetine-treated patients in the acute trials 329, 377, 701 and 704, compared to 4 such cases among the placebo-treated patients (table 7.8 in the ISS). In these studies there were 387 placebo patients with a total of 73.1 patient-years of exposure, and 470 paroxetine patients with a total of 87.4 patient years of exposure. Thus, the rate of self injurious behavior was higher with paroxetine, although this was not statistically significant (relative risk = 2.3, p-value = 0.15, STATA software).

For completeness, GSK also surveyed their data from paroxetine clinical trials that were primarily adult studies but included some adolescent subjects. In such trials, there were a total of 30 serious adverse events in subjects younger than 18 years (see table 50.1 in the ISS); by far the greatest number of these (20) were suicide attempts.

Adverse Dropouts: For the total sample of 932 paroxetine treated subjects, the following adverse events resulted in discontinuation of at least 2% of the subjects in either the child or adolescent age group. For comparison, the numbers of patients dropping out for these events from the acute studies alone are shown in the two columns at the right.

Adverse event	% of children dropping out (n=345)	% of adolescents dropping out (n=587)	% of all paroxetine subjects dropping out (n=932)
Hostility	4.3	1.7	2.7
Emotional Lability	0.9	2.7	2.0
Hyperkinesia	3.8	0.5	1.7
Agitation	2.0	1.0	1.4

Neurosis	2.6	0.7	1.4
Depression	2.0	0.9	1.3
Concentration impaired	2.0	0	0.8

All adverse events commonly resulting in discontinuation were psychiatric in nature. As shown, these adverse events requiring discontinuation were generally more frequent in the younger subgroup, with the exception of "emotional lability," a term that included self-injurious behaviors in the sponsor's classification.

For the acute studies, the sponsor determined that the following adverse event discontinuations were both common (incidence of at least 1%) and possibly drug related (dropout incidence at least twice as great with paroxetine as with placebo):

Total age group—nausea, depression
Children—hyperkinesia, depression, hostility, nervousness
Adolescents—nausea, depression, headache, somnolence

The sponsor notes that this list of adverse events differs somewhat from that in the current Paxil labeling.

Common adverse event profile: For the acute treatment OCD and MDD studies combined, the following table from the submission presents the incidence of adverse events for those adverse events with an incidence of at least 5% with paroxetine in either age subgroup. Applying the customary definition of a common, potentially drug-related adverse event (i.e., those events having a relative risk of at least 2 and an absolute incidence of at least 5%), it will be seen that there are some differences by age group. For the combined sample, decreased appetite is the only adverse event meeting the criteria. For the subgroup of children, not only decreased appetite, but also insomnia, diarrhea, vomiting, hostility and hyperkinesia meet the criteria, while for the adolescent group, somnolence, decreased appetite, and tremor meet the criteria.

The sponsor provided a line listing (ISS table 6.14) of selected behavioral adverse events, of which there were 45 for paroxetine treated subjects. Sixteen of these events lead to premature discontinuation. These events were coded under the terms hostility, agitation, or emotional lability. However, the sponsor did not provide a similar listing for placebo treated patients, which would have provided comparative data.

	Age Group: Total		Age Group: Children		Age Group: Adolescents	
AE Preferred Term*	**Paroxetine (N = 470)**	**Placebo (N = 387)**	**Paroxetine (N = 108)**	**Placebo (N = 104)**	**Paroxetine (N = 362)**	**Placebo (N = 283)**
Patients with AEs	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total with ≥1 gender-non-specific AE	356 (75.7)	261 (67.4)	84 (77.8)	72 (69.2)	272 (75.1)	189 (66.8)
Headache	105 (22.3)	95 (24.5)	23 (21.3)	18 (17.3)	82 (22.7)	77 (27.2)
Nausea	90 (19.1)	50 (12.9)	12 (11.1)	12 (11.5)	78 (21.5)	38 (13.4)
Somnolence	55 (11.7)	23 (5.9)	5 (4.6)	5 (4.8)	50 (13.8)	18 (6.4)
Dizziness	51 (10.9)	31 (8.0)	3 (2.8)	5 (4.8)	48 (13.3)	26 (9.2)
Insomnia	42 (8.9)	19 (4.9)	10 (9.3)	2 (1.9)	32 (8.8)	17 (6.0)
Respiratory disorder	38 (8.1)	40 (10.3)	12 (11.1)	14 (13.5)	26 (7.2)	26 (9.2)
Abdominal pain	37 (7.9)	34 (8.8)	17 (15.7)	11 (10.6)	20 (5.5)	23 (8.1)
Asthenia	37 (7.9)	29 (7.5)	6 (5.6)	5 (4.8)	31 (8.6)	24 (8.5)
Infection	35 (7.4)	32 (8.3)	8 (7.4)	14 (13.5)	27 (7.5)	18 (6.4)
Decreased appetite	34 (7.2)	11 (2.8)	8 (7.4)	3 (2.9)	26 (7.2)	8 (2.8)
Dry mouth	30 (6.4)	18 (4.7)	3 (2.8)	3 (2.9)	27 (7.5)	15 (5.3)
Trauma	30 (6.4)	15 (3.9)	12 (11.1)	6 (5.8)	18 (5.0)	9 (3.2)
Diarrhea	23 (4.9)	14 (3.6)	7 (6.5)	3 (2.9)	16 (4.4)	11 (3.9)
Pharyngitis	23 (4.9)	25 (6.5)	5 (4.6)	8 (7.7)	18 (5.0)	17 (6.0)
Vomiting	22 (4.7)	13 (3.4)	8 (7.4)	3 (2.9)	14 (3.9)	10 (3.5)
Sinusitis	21 (4.5)	16 (4.1)	7 (6.5)	4 (3.8)	14 (3.9)	12 (4.2)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Tremor	21 (4.5)	3 (0.8)	3 (2.8)	0	18 (5.0)	3 (1.1)
Nervousness	20 (4.3)	18 (4.7)	6 (5.6)	3 (2.9)	14 (3.9)	15 (5.3)
Hostility	16 (3.4)	1 (0.3)	8 (7.4)	1 (1.0)	8 (2.2)	0
Hyperkinesia	16 (3.4)	8 (2.1)	11 (10.2)	4 (3.8)	5 (1.4)	4 (1.4)
Fever	12 (2.6)	15 (3.9)	7 (6.5)	7 (6.7)	5 (1.4)	8 (2.8)

For the OCD trial by itself, the common and potentially drug related adverse events were as follows, for both age groups combined: hyperkinesia, trauma, decreased appetite, hostility, diarrhea, asthenia, vomiting, agitation, neurosis.

Demographic subgroups: The sponsor used the Breslow-Day test to assess the homogeneity of odds ratios for adverse events with an incidence $\geq$ 2% and a relative risk $\geq$ 2. For the adverse event data from all acute trials combined there were no adverse events associated with a particular age group or race, and only one (tremor) that was associated with gender (more frequent in females).

Dose relatedness of adverse events: Because all the controlled trials employed a flexible dose design, no useful information regarding the relationship between dose and the incidence of adverse reactions is available.

Withdrawal associated adverse events: All clinical trials in this submission included a downward taper at the end of treatment, as either a required procedure or a recommendation. The sponsor reports in the ISS that no adverse events during the taper phase or 2 week post treatment follow up phase met the criteria of having an incidence of at least 2% with paroxetine and at least twice the incidence for placebo.

Clinical laboratories: The sponsor provided an analysis of clinical laboratory data from the acute treatment trials. The sponsor defined threshold laboratory values (for hematology and clinical chemistry, but not urinalysis) that were considered of potential clinical concern (please see table 10.3 in the ISS). The most common laboratory abnormality was low hematocrit, occurring in 12.2% of paroxetine patients and 6.8 % of placebo patients; this was the only laboratory abnormality with an incidence over 1% that did not occur in a roughly comparable proportion of placebo patients. There was no corresponding finding for hemoglobin. For urinalysis abnormalities, “urine bacteria many” and “many WBC” met the customary criteria for common and potentially drug-related. With respect to mean changes from baseline in laboratory values, by inspection, the paroxetine and placebo groups differed only slightly, if at all, although the sponsor did not perform statistical testing on these data.

Vital signs: In the acute trials, most subjects had vital signs measured before and during treatment; approximately ¾ of subjects were weighed and less than half had height measurements. The sponsor established criteria for clinically significant vital sign abnormalities (see table 11.10 in the ISS). Although the sponsor did not perform statistical comparisons between treatment groups, by inspection there did not appear to be significant discrepancies between paroxetine and placebo subjects with respect to the incidence of specific vital sign abnormalities. It appears that GSK did not exclude subjects who had abnormalities at baseline from the analysis, however (table 11.11). Certain abnormalities were very common in both treatment groups (e.g., low systolic blood pressure was observed in roughly 30% of subjects regardless of treatment), suggesting a problem with the criterion values. For mean changes from baseline in vital sign parameters, GSK performed no statistical comparisons, but by inspection there were no substantial differences between treatment groups on any specific parameter.

Growth parameters: The sponsor calculated mean weight velocity (defined as change in weigh divided by elapsed time between measurements, in units of kg/day) for subjects in study 329, according to treatment group and age group. There did not appear to be any consistent difference between paroxetine and placebo; however, the sponsor did not present an overall comparison of all paroxetine versus all placebo subjects.

ECGs: On July 15, 2002, the Division made the following request for ECG data (via email):

Although the supplement does include an analysis of ECG interval data for the open label pharmacokinetic study (715), GSK did not provide any analysis of ECG interval data for the controlled studies. The results provided for studies 701 and 704 consisted of a count of the numbers of patients with ECG abnormalities. In study 329, ECG abnormalities were considered adverse events but were not otherwise analyzed.

In order to complete our review of this application, we are requesting that GSK submit the typical kind of analyses conducted for these type of data; i.e., an analysis of mean change from baseline for measured ECG intervals, and a count of the numbers of patients on drug or placebo exceeding potentially clinically significant thresholds. We request that you use the ECG data from the placebo-controlled, parallel group trials that included pre-treatment and on-treatment ECGs (studies 329, 701 and 715).

At this time, the sponsor's response to this request is still pending. The ECG data from the clinical pharmacology trial did not suggest any effect of paroxetine, but of course this trial had no comparison group.

With respect to ECG abnormalities considered adverse events, one adolescent patient discontinued paroxetine because of AV block (patient 329.012.00226). Another patient was withdrawn from the open label run-in phase of study 453 due to extrasystoles.

Literature review: The sponsor conducted a literature search on the topic of pediatric use of paroxetine for OCD and MDD, and found 7 open-label studies, 4 case series, and 23 case reports. Behavioral adverse events (e.g., hypomania, hyperactivity) were mentioned in several publications. In addition, one article (by Myers and Krenzelok) reported a case series of 35 pediatric overdoses of paroxetine; no unusual toxicities were noted.

Postmarketing reports: GSK searched their postmarketing surveillance database (which also includes serious adverse events from clinical trials) for reports involving patients under age 18 years. This search yielded 926 case reports as of 12-12-01. Six were deaths (3 suicides, one fatal overdose in an infant, one homicide, and one allergic reaction). One of the suicides was a fatal overdose of paroxetine plus moclobemide, the other two were by firearm. The allergic reaction case (2000001200-1) deserves further description. This was an 11 year old male with obesity, ADHD, depression and an allergy to antihistamines (unspecified). Methylphenidate was a concomitant medication. After receiving his first dose of 20 mg, he developed skin erythema and altered mental status, and received emergency medical treatment but died in the hospital from an apparent allergic reaction.

The sponsor summarized the serious adverse event reports, of which there were 265. The most commonly reported serious event was suicide attempt (45 cases), followed by convulsions (35 cases), aggressive reaction (24 cases), and manic reaction (23 cases). There were 7 reports of

homicides committed by male adolescents receiving paroxetine. Other spontaneous adverse events of interest include serotonin syndrome (10 cases), withdrawal syndrome (9 cases), hepatic enzymes increased (8 cases), and hepatitis (5 cases).

D. Adequacy of Safety Testing

The sponsor's approach to coding psychiatric adverse events rendered the data on psychiatric events almost impossible to interpret. For example, GSK coded suicide attempts as emotional lability, physical aggression as hostility, and various psychiatric symptoms as neurosis. For this reason, I have proposed that we ask the sponsor to provide further information regarding all behavioral adverse events (see below).

Although the ISS did include an analysis of the incidence of abnormal vital signs, it did not provide an analysis of mean change from baseline in vital sign parameters.

With respect to growth parameters there were some deficiencies in the submission. The sponsor failed to measure height in the trials of longer duration. Also, GSK's approach to analyzing weight data in terms of clinically significant increases or decreases from baseline is more suited to adults whose weight is stable. On the other hand, their analysis of weight gain velocity may be useful once the data are pooled across age groups (see request below).

E. Summary of Critical Safety Findings and Limitations of Data

The most prominent adverse reactions (b) (4) appear to involve behavioral effects; these events were coded with terms such as hostility and emotional lability. As previously noted, the sponsor's method of coding these events was potentially confusing, and thus additional information will be helpful for the purpose of definitively assessing the potential behavioral toxicity of paroxetine treatment in pediatric patients.

There was one postmarketing spontaneous report that described a fatal allergic reaction in an 11 year old boy following a single dose of paroxetine (see above). The Paxil labeling contraindicates paroxetine in patients that are sensitive to it, although in this case there was apparently no way to know that the patient had this vulnerability.

VIII. (b) (4)

(b) (4)

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

In the positive pivotal OCD study (704), there was no significant gender-by-treatment interaction for the primary outcome measure. With respect to adverse events, the incidence of tremor was increased in females, but the significance of this is questionable.

Weight corrected clearance was shown to be significantly higher in male children than in female children (please refer to the OCPB review for details). GSK did not explore the effect of gender on adverse event incidences within the subgroup of children alone, however.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

As with gender, there was no age group by treatment interaction in the pivotal study. There were no adverse events that were associated with a particular age group or ethnic group. In my view, the sponsor's exploration of ethnicity and age effects was adequate.

C. Evaluation of Pediatric Program

This supplement is limited to pediatric trials.

D. Comments on Data Available or Needed in Other Populations

There is nothing to report.

X. Conclusions and Recommendations

A. Conclusions

(b) (4)

B. Recommendations

1. (b) (4)
2. The sponsor should be asked to supply the following information, in addition to the usual request for a safety update and world literature update:

1. Please provide the exposure (total number of patients and person-years) for placebo in all studies combined.
2. Please prepare a table showing the duration of exposure and mean daily dose for all paroxetine patients. In this table, the columns should represent mean daily dose and the rows should represent duration of exposure. Patients should be enumerated within each cell, and each patient should be counted in only one cell, according to the patient's duration of exposure and mean daily dose. We can provide an example of such a table if it would be helpful.
3. ISS tables 18.43 through 18.47 provide a listing of paroxetine patients with serious adverse events. Please provide a similar listing for placebo patients. It would also be helpful to provide a summary tabulation of these serious adverse events, similar to ISS table 4.1.2.
4. Please provide further information on the serious adverse events that occurred in study 676; at the time of this submission, the treatment assignments were still blinded.
5. Table 6.14 in the ISS listed paroxetine treated patients who experienced adverse events coded under the terms hostility, emotional lability or agitation. However, the table did not include placebo patients, nor did it include psychiatric adverse events that were coded under other terms. Please prepare an expanded version of this table, including all psychiatric and behavioral adverse events, and also those that occurred among placebo patients. In addition, it would be helpful if you could attach the narrative case summaries for those events that were either serious or resulted in premature discontinuation.
6. Please provide your rationale for coding suicide attempts and other forms of self-injurious behavior under the WHOART term "emotional lability."
7. ISS table 4.2.6 provides a comparison of weight gain velocity between paroxetine and placebo in study 329; however, the comparison is shown only by age subgroups. Please provide a comparison pooling all paroxetine and placebo patients across ages.
8. Weight corrected clearance was shown to be significantly higher in male children than in female children. Although section 16 of the ISS described analyses of adverse events according to age and gender subgroups, you did not explore the effect of gender on adverse event incidences within age subgroups. Please conduct an appropriate analysis to address this issue.
9. Please respond to the 7-15-02 email request for additional ECG data analyses.

3. [redacted] (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Andy Mosholder
10/7/02 11:56:19 AM
MEDICAL OFFICER

Thomas Laughren
10/8/02 08:00:49 AM
MEDICAL OFFICER

(b) (4) see memo to file for more detailed comments.--TPL