Report Synopsis

Study Title: A 38-Week, Two Phase, Multicenter Study to Investigate the Safety and Effectiveness of Paroxetine (10-60 mg/day) in the Treatment of Children and Adolescent Outpatients with Obsessive-Compulsive Disorder.

Investigators and Centers: Psychiatrist investigators from 26 study centers in the U.S. participated. All were appropriately experienced in the treatment of child and adolescent patients.

Publication: None at the time of study report preparation.

Study Dates: The study was initiated at the first study center on Jan. 13, 1997. The first patient was enrolled (Phase I, open-label paroxetine) on Jan. 23, 1997. The last study visit for the last patient to complete participation occurred on Dec. 28, 1998.

Objective(s): The primary objective was to evaluate the efficacy of paroxetine in children and adolescent outpatients with OCD by assessing the potential for relapse in patients previously responsive to paroxetine (during Phase I), after discontinuation of paroxetine during a 16-week, double-blind, placebo-controlled, randomized phase (Phase II).

The secondary objectives were to establish the clinical effectiveness of paroxetine (10-60 mg/day) in this population during a 16 week, open-label phase of the study (Phase I), and to evaluate the safety and tolerability of paroxetine in this population throughout the duration of the study.

Study Design: Multicenter, two-phase study. During Phase I, eligible subjects received open-label paroxetine for 16 weeks. There were six post-baseline (> Day 0) Phase I visits, which occurred at Weeks 2, 4, 6, 8, 12 and 16. At the end of Phase I, patients who achieved a therapeutic response (defined as $\geq$ 25% improvement in baseline CY-BOCS Total Score and a CGI Global Improvement Item Score of 1 or 2 at Week 16) were eligible to participate in Phase II.

Phase II was a 16-week, double-blind, placebo-controlled phase designed to establish the efficacy of paroxetine in this population by assessing the potential for relapse in previous responders when paroxetine was discontinued. Patients must have completed Phase I and met the response criteria to have been eligible to participate in Phase II. During Phase II, visits were scheduled every two weeks (except week 14) during this phase.

Study Population: Children and adolescent outpatients (8-17 years old) who met DSM-IV criteria for OCD (DSM-IV, 300.30) as their predominant psychiatric diagnosis.

Treatment and Administration: Paroxetine was supplied as white film-coated oval tablets containing 10 mg paroxetine (Batch no. U96157/Lot no. X10-6B10). The placebo tablets

were identical in appearance (Batch no. U96161/Lot no. X9-6B10PL). The tablets were packaged in bottles of 100 for Phase I and were packaged in foil-backed blister packs (60/pack) for Phase II. During Phase I, dosing followed a flexible-dose regimen (paroxetine 10-60mg/day, administered as a single daily dose). Dosing was titrated upward as necessary in 10mg increments no more frequently than once a week. Dose escalation was based on therapeutic response and tolerability. Double-blind dosing (Phase II) was based on the final dosage level reached during Phase I. Patients were randomly assigned (1:1) to paroxetine or placebo. Dose adjustments were not permitted during Phase II.

Evaluation Criteria

The primary efficacy outcome variable was the proportion of patients relapsing during the randomization phase (Phase II), and was defined as any one of the following:

1) Worsening of CGI Global Improvement Score by 1 point for 2 consecutive visits
2) Worsening of CGI Global Improvement Score by ≥ 2 points at any single visit
3) A CGI Global Improvement Score of 5 or greater

The secondary efficacy variables (in Phases I & II) included mean change from Baseline in CY-BOCS Total Score, mean change from Baseline in CY-BOCS obsessive and compulsive subscales, proportion of patients achieving ≥25% improvement in baseline CY-BOCS Total Score, proportion of patients achieving a CGI Global Improvement Score of 1 or 2, time to relapse (Phase II only), change from Baseline in CGI Severity of Illness item, mean change from Baseline in HAMD Score, mean change from Baseline in HAMA Score, the Yale Global Tic Scale - Total Tic Scores, and mean change from Baseline in GAF score.

Safety was assessed through routine adverse experience (AE) monitoring, vital sign (including body weight) determinations, and clinical laboratory evaluations. In addition, a physical examination and a 12-lead ECG were performed at periodic visits.

Statistical Methods: The primary population for the analyses of efficacy was the Phase II intention to treat (ITT) population. This included all patients who received at least one dose of randomized treatment and for whom at least one post-randomization baseline evaluation was available. A Per Protocol Population was identified and analyzed for the primary efficacy variable only. The primary inferences concerning efficacy were made using the last observation carried forward dataset (LOCF) of the Phase II ITT population, defined as the last on-drug assessment during the randomized phase. Two additional datasets were considered to ensure the robustness of the results: 1) an LOCF dataset at the latest time point (Visit) where at least 70% of the patients in each treatment group remained in the study (defined as the 70% endpoint), and 2) an Observed case (OC) dataset at 8 and 16 weeks.

The differences between paroxetine and placebo at study endpoint were estimated from the analysis as paroxetine minus placebo, and 95% confidence intervals were constructed around the estimated differences. All hypothesis tests were two-sided. The effect of interactions (e.g., treatment by center) were assessed at the 10% level of significance. All other statistical tests were performed at the 5% level of significance.

Summary statistics were generated for all efficacy parameters. In addition, statistical analyses were performed for the following efficacy parameters at specified timepoints: proportion of patients relapsing, time to relapse, change from baseline in CY-BOCS total score, and proportion of patients achieving ≥ 25% improvement in baseline CY-BOCS total score. The proportion of patients relapsing and the proportion of patients achieving ≥ 25% improvement in baseline CY-BOCS total score were analyzed using logistic regression, time to relapse was analyzed using the Log Rank test, and change from baseline in CY-BOCS total score was analyzed using ANCOVA. No formal hypothesis testing was conducted on the safety data. Summary tables of adverse experiences, vital signs, and laboratory data were produced.

Patient Disposition and Key Demographic Data: A total of 339 patients entered Phase I and were dispensed open-label paroxetine. Four patients did not return for any post-baseline efficacy evaluations, therefore the ITT population consisted of 335 patients. Of these 335 patients, 194 (57.9%) completed Phase I and were enrolled in Phase II. Of the 141 (42.1%) patients not entering Phase II, 40 (11.9%) were withdrawn due to an AE and 39 (11.6%) were either withdrawn due to lack of efficacy (n=19) or they were not eligible to enter Phase II because they did not meet the efficacy response criteria (n=20). One patient (paroxetine group) in Phase II was excluded from the ITT population because he/she did not return for any post-randomization baseline evaluations, therefore the Phase II ITT consisted of 193 patients. Of these patients, 42 (44.2%) in the paroxetine group and 33 (33.7%) in the placebo group completed Phase II. Lack of efficacy was the primary reason for withdrawal in both treatment groups.

Patient Disposition: Number (%) of Patient Withdrawals by Reason and Study Phase (ITT)

Reasons For Withdrawal	Open-Label Paroxetine N = 335		Double-Blind Paroxetine N = 95		Double-Blind Placebo N = 98	
	N	%	N	%	N	%
Adverse Experience	40	11.9	8	8.4	11	11.2
Lack of Efficacy	39*	11.6	33	34.7	45	45.9
Deviation from Protocol	22	6.6	5	5.3	3	3.1
Lost to Follow-up	8	2.4	3	3.2	0	0.0
Other Reason	32+	9.6	4	4.2	6	6.1
Totals Withdrawn	141*+	42.1	53	55.8	65	66.3

* includes patients who did not meet the protocol-defined response criteria (n = 20)

\+ includes patients eligible for entry into the Double-Blind Phase but who chose not to participate (n = 7).

The mean patient age was approximately 12 years old, with the open-label ITT population evenly split between children (age < 12, n=167/335, 49.9%) and adolescents (age ≥ 12, n=168/335, 50.1%). Most patients were male (198/335, 59.1%), and the majority were caucasian (308/335, 92%). In Phase II, the two treatment groups were generally similar with respect to all demographic characteristics. The mean age at onset of OCD was 10.1 years, with a range of 2 – 18 years. The severity of the illness was rated as moderate or severe at baseline in greater than 95% of the participants.

Efficacy Results

Primary Efficacy Variable

Approximately one-third (33/95, 34.7%) of the paroxetine patients met the relapse criteria, compared to 43.9% (43/98) of the patients randomized to placebo, although this difference was not statistically significant (p=0.136, odds ratio=0.62, C.I. of 0.34,1.16). Similar results were observed for the Per Protocol Population.

Secondary Efficacy Variables

The time to relapse was shorter in the placebo group, however this difference was not statistically significant. In Phase II, the proportion of patients with a decrease in CY-BOCS Total Score ≥ 25% from double-blind baseline was significantly greater for paroxetine than for placebo, both in the Week 16 LOCF dataset and at the 70% endpoint, and the mean increase in CY-BOCS Total Score (indicating an increase in symptoms) from double-blind baseline to Week 16 endpoint was significantly greater in patients switched to placebo than for those maintained on paroxetine, again in both the Week 16 LOCF dataset and at the 70% endpoint.

Furthermore, the data from all of the other secondary efficacy endpoints which were not statistically analyzed numerically favored paroxetine over placebo (i.e., CGI Global Improvement Item Responders, change from randomization baseline in the CY-BOCS subscale scores, CGI Severity of Illness Item rating, HAM-A and HAM-D scores, Yale Global Tic Score and GAF Scale) in the Week 16 LOCF dataset and at the 70% endpoint. However, the Observed Case (OC) datasets generally did not distinguish paroxetine from placebo.

Proportion (%) of Patients With a >= 25% Reduction in CY-BOCS Total Score From Randomization Baseline Double Blind Phase (ITT)

	Paroxetine			Placebo			Pairwise Comparisons*
	n	%	N	n	%	N	Odds Ratio/p-value/(95% CI)
Week 16	17	45.9	37	7	26.9	26	2.31/ 0.130 / (0.78, 6.80)
70% Endpoint**	22	26.5	83	8	8.9	90	3.70/ 0.003 / (1.54,8.86)
Week 16 Endpoint	24	28.9	83	13	14.4	90	2.41/ 0.023 / (1.13. 5.13)

*Unadjusted due to low numbers of patients per treatment/center group combination
**The 70% Endpoint visit is Week 4

CY-BOCS Total Score Mean Change from Randomization Baseline – ITT

	Paroxetine			Placebo			Pairwise Comparisons+
	n	Mean*	SE	n	Mean*	SE	Diff / p-value / (95% CI)
Baseline**	92	9.9	0.67	98	9.6	0.61	-
Week 16	41	- 0.4	1.07	30	1.3	0.93	-0.81 / 0.583 / (-3.73, 2.12)
70% Endpoint ++	92	2.3	0.82	98	6.3	0.82	-4.01 / 0.001/ (-6.30, -.72)
Week 16 Endpoint	92	3.6	0.92	98	6.9	0.86	-3.38 / 0.008 / (-5.88, -.88)

+Adjusted for terms retained in the final model (i.e., center group)
* Mean score at Randomization Baseline; Weeks scores are the mean changes from Baseline
** Baseline is the last open-label value prior to entering the double-blind phase
++ Note: The 70% Endpoint Visit is Week 4

The open-label efficacy data provide further support for the usefulness of paroxetine in treating this patient population. Almost three-quarters of the patients (68.7%) met both of the response criteria at Week 16 Endpoint (LOCF), with 86.2% of the patients who reached Week 16 meeting both response criteria.

Percentage (%) of Patients Meeting the Response Criteria - Open Label Phase (ITT)

	N	n	%
CGI Responders[1]			
Week 16	239	209	87.4
Week 16 Endpoint	315	231	73.3
CY-BOCS Responders[2]			
Week 16	239	217	90.8
Week 16 Endpoint	329	258	78.4
Meets Both Response Criteria[3]			
Week 16	239	206	86.2
Week 16 Endpoint	329	226	68.7

1 Includes patients with score of 1 (Very Much Improved) and 2 (Much Improved) on the CGI Global Improvement Item
2 Reduction of ≥ 25% from Open-Label Baseline
3 Meets both of the above criteria

The overall responsiveness to open-label paroxetine was also demonstrated based on the CGI Severity of Illness Item Score. At Open-Label Baseline, 98% of the patients had a CGI severity of illness rating ≥ 4 (moderately ill or worse [more than half were rated markedly or severely ill]). However, at Open-Label (OL) Week 16, only 28.5% of the patients were rated at least moderately ill.

Safety Results: The safety and tolerability of paroxetine in the age group studied in this trial (8-17 yr olds) were demonstrated. There were no deaths or unexpected safety findings, and in general the nature and incidence of AEs reported were similar to those reported for adult OCD patients who had received paroxetine in controlled trials. Headache (82/335, 24.5%) was the most commonly reported AE in the open-label phase, followed by asthenia (72/335, 21.5%), and insomnia (71/335, 21.2%). Respiratory disorder (54/335, 16.1%), somnolence (49/335, 14.6%), nausea (48/335, 14.3%), nervousness (45/335, 13.4%), trauma (45/335, 13.4%), abdominal pain (40/335, 11.9%), hyperkinesia (38/335, 11.3%), diarrhea (37/335, 11.0%) and weight gain (36/335, 10.7%) were also all reported in at least 10% of the open-label population. Headache was also the most common AE reported in both treatment groups in the double-blind phase (18/95 [18.9%] and 26/98 [26.5%] in the paroxetine and placebo groups, respectively).

Seventeen patients reported a total of 22 SAEs during the study (17/335, 5.1%). Thirteen patients in the open-label phase (3.9%) reported a total of 17 SAEs and four patients in the double-blind phase (2.1%) reported a total of 5 SAEs. Almost all of the SAEs reported (19/22, 86.4%) were CNS-related. Emotional lability (n=5) and hostility (n=4) were the two most common SAEs reported during open-label treatment, and were the only SAEs reported in more than one patient during the open-label phase.

Suicide attempt/ideation was reported in several patients, but could not be reasonably attributed to paroxetine. Some behavioral activation/hyperactivity type AEs (e.g., agitation, hostility, hyperkinesia, manic reaction and concentration impaired) occurred on open-label therapy with greater frequency than have been reported in adults, and summaries by age group suggest these events were more likely to occur in the younger age group (< 12 years). As noted above, some of these particular events were considered serious in a number of patients. One SAE of manic reaction was reported, in a patient who had comorbid ADHD as well as another SAE of hostility. Younger children may be more sensitive to the behavioral activation/disinhibition side effects of SSRIs and therefore should be closely monitored because of the reported risk with antidepressants for hypomanic/manic switch.

A total of 59 patients were withdrawn from the study due to AEs (59/335, 17.6%), 40 patients during the open-label phase (11.9%) and 19 patients during the double-blind phase (9.8%). The majority of the AEs leading to withdrawal were CNS-related. The AEs leading to withdrawal of more than 1% of the open-label phase population included hostility (9/335, 2.7%), hyperkinesia (7/335, 2.1%), agitation (6/335, 1.8%), concentration impaired (5/335, 1.5%), nervousness (4/335,

1.2%) and neurosis (4/335, 1.2%). The most common AEs leading to withdrawal in the DB phase were hostility (3.2% in the paroxetine group, 0.0% in the placebo group), neurosis (3.2% in the paroxetine group, 5.1% in the placebo group), and nervousness (1.1% in the paroxetine group and 2.0% in the placebo group).

Laboratory and vital sign abnormalities of significant clinical concern were few in number and not inconsistent with data generated in adults. Clinically significant weight gain was reported by the investigators in a number of patients, however, in the absence of pre- and post- dose body mass index data, the true clinical relevance of such findings is difficult to establish in an actively growing and maturing population such as this.

In summary, these safety findings suggest that paroxetine is safe and generally well-tolerated in pediatric patients with OCD when administered over the dosage range studied (10-60mg/day).

Conclusion(s): The results of this two-phase, multicenter, relapse-prevention design study provide supportive evidence that paroxetine is beneficial in the treatment of children and adolescents with OCD. Although there was no statistically significant difference between paroxetine and placebo with respect to the protocol-defined primary measurement of efficacy (the proportion of patients meeting relapse criteria during the double-blind phase), almost three-quarters (69%) of all patients enrolled met the response criteria during the OL phase and the proportion of responders in the double-blind phase (based on CY-BOCS Total Score) was statistically significantly greater in the paroxetine group than in the placebo group. The safety data generated in children and adolescents with OCD in this study did not reveal any adverse findings that were unique to this population nor any that would preclude its use in this population.