Report Synopsis

Study Title: A Randomized, Multicenter, 10-Week, Double-Blind, Placebo-Controlled, Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Obsessive-Compulsive Disorder (OCD) (29060/704).

Investigators and Centers: The study was carried out in 37 centers in the United States and 2 centers in Canada. All investigators were appropriately experienced in the treatment of child and adolescent patients. The study was terminated prematurely at the study center (Center 055) of Dr. xxxxxxxxxxxxxxxxxxxx, due to significant compliance violations.

Publication: No publications as of 14 November 2001.

Study Dates: The first dose of randomized study medication was administered on 20 January 2000 and the last dose of study medication (including Taper) was administered on 3 July 2001.

Objectives: To assess the efficacy of paroxetine versus placebo in the treatment of children and adolescents with OCD as measured by the change from Baseline in Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) total score at Week 10 last observation carried forward (LOCF) endpoint.

To assess the safety and tolerability of paroxetine vs. placebo in children and adolescents with OCD.

Study Design: This was a 10-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose trial in children (ages 7 through 11 years) and adolescents (ages 12 through 17 years). The randomization scheme was stratified by age subgroup.

Study Population: Male and female outpatients, 7 to 17 years of age, who met Diagnostic and Statistical Manual Version IV (DSM-IV) criteria for Obsessive-Compulsive Disorder (300.30), had a CY-BOCS total score ≥16, had a history of OCD symptoms for at least two months prior to the Screening visit, and met all other inclusion and exclusion criteria were eligible to enter the study. Each age subgroup was to account for at least 40% of the total number randomized.

Treatment and Administration: Both double-blind medications, i.e., paroxetine and placebo, were in the form of white, oval, film-coated tablets for oral

administration once daily. They were identical in size, shape and color. All active tablets contained 10 mg paroxetine. Batch numbers were U99074 and U00001 for paroxetine 10 mg and U96161 [X9-6B10PL] for placebo.

Following a 1-week Screening Phase, eligible patients were randomly assigned (1:1) to paroxetine or placebo. All randomized patients initiated therapy at Dose Level (DL) 1 (paroxetine 10 mg/day or matching placebo) for the first week of therapy. The dose could be titrated up in 10 mg weekly increments after the initial dose, up to a maximum of 50 mg per day (DL 5), according to the investigator's judgment based on efficacy and tolerability of the study medication. Dose reductions were allowed for an adverse event (AE); such a reduction was permitted only once. A Taper Phase with a gradual reduction of study medication was required for all patients on DL 2 or higher at the end of the study. Total study duration per patient, including Screening, Taper, and Follow-up Phases, was a maximum of 17 weeks.

Evaluation Criteria

Efficacy Parameters: The primary efficacy variable was the change from Baseline in the CY-BOCS total score.

Secondary efficacy variables were the proportion of responders in the CY-BOCS total score (where response was defined as a 25% [or greater] reduction from Baseline); the proportion of responders based on the Clinical Global Impressions (CGI) Global Improvement item (where response was defined as a score of 1 [very much improved] or 2 [much improved]); change from Baseline in the CGI Severity of Illness item score; change from Baseline in the Global Assessment of Functioning (GAF); and change from Baseline in the CY-BOCS Obsessions and Compulsions subscale scores.

Safety Parameters: Safety was assessed via AE monitoring, vital signs, laboratory evaluations, serum pregnancy tests, electrocardiograms (ECGs) and by physical examination.

Pharmacokinetic Parameters: Pharmacokinetic (PK) blood samples were drawn from consenting patients at Weeks 4 and 10 (or at early withdrawal from the study, if applicable) for paroxetine assay. These results will be reported separately, combined with similar data from studies 701 (Major Depressive Disorder) and 676 (Social Anxiety Disorder) to examine the effects of dose and selected demographic characteristics on paroxetine steady-state plasma concentrations in the pediatric population.

Statistical Methods: All patients who received at least one dose of randomized medication and had at least one post-baseline safety (including AEs) or efficacy assessment were included in the intention-to-treat (ITT) population. Statistical conclusions concerning the efficacy of paroxetine were made using the last observation carried forward (LOCF) and the observed cases (OC) datasets, based on the ITT population. All hypothesis tests were two-sided. The effect of interactions was assessed at the 10% level of significance. All other statistical tests were performed at the 5% level of significance. Continuous efficacy variables were analyzed by analysis of variance techniques with results presented as point estimates, 95% confidence intervals for the differences, and associated p-values. Binary data were analyzed using logistic regression with results presented as odds ratios, 95% confidence intervals around the odds ratios, and associated p-values. The change from Baseline in CGI Severity of Illness was analyzed using the Wilcoxon rank sum test with results presented as the median difference and p-value for the difference.

Analysis of the primary efficacy variable was performed with and without data from patients at Center 055 in both the ITT and Per-Protocol (PP) populations. Removal of these data did not change the findings or conclusions from the study. Results presented in this Report include the data from this center.

Patient Disposition and Key Demographic Data

A total of 265 patients were screened and 207 patients randomized, 100 (48.3%) to paroxetine and 107 (51.7%) to placebo. Of these, 203 patients were included in the ITT population. Four randomized patients were not included in the ITT population: One paroxetine patient and 2 placebo patients had no post-baseline assessments, and 1 paroxetine patient did not receive study medication. The all-randomized population comprised 57.0% children and 43.0% adolescents.

The percentage of randomized patients withdrawn prematurely from the study was slightly higher for the paroxetine group (35.0%, 35/100) than for the placebo group (25.2%, 27/107). The primary reasons for withdrawal in the ITT population were AE (10.2%, 10/98) in the paroxetine group and lack of efficacy (13.3%, 14/105) in the placebo group.

Patient Disposition

Study Stage/Population	Paroxetine	Placebo	Total
Screened	–	–	265
Randomized	100 (100.0%)	107 (100.0%)	207 (100.0%)
Withdrawn	35 (35.0%)	27 (25.2%)	62 (30.0%)
Completed Study	65 (65.0%)	80 (74.8%)	145 (70.0%)
Intention-to-Treat *	98 (98.0%)	105 (98.1%)	203 (98.1%)
Per Protocol **	73 (73.0%)	82 (76.6%)	155 (74.9%)
Entered Study 29060/716†	46 (46.0%)	62 (57.9%)	108 (52.2%)

* Randomized patients with at least one on-therapy safety or efficacy assessment. The Safety Population was the same as the ITT Population.
**Patients in the ITT population not identified as protocol violators during blind review.
†Information available at time of this Report.

There was no marked imbalance between the treatment groups in any of the patient characteristics, although there was a greater proportion of patients with comorbid psychiatric illnesses in the placebo group than in the paroxetine group. The percentage of males was also slightly higher in the placebo group than in the paroxetine group.

Demography and Baseline Characteristics (ITT Population)

	Paroxetine	Placebo	Total
Age Group: Total			
Females: Males	45:53	41:64	86:117
Mean age (SD): years	11.1 (3.03)	11.6 (2.97)	11.3 (3.00)
White: n (%)	85 (86.7)	94 (89.5)	179 (88.2)
Baseline CY-BOCS Total Score: Mean (SD)	24.4 (4.95)	25.3 (5.05)	24.8 (5.01)
Psychiatric Comorbidity: n (%)	30 (30.6)	42 (40.0)	72 (35.5)
Age Group: Children			
Females:Males	27:31	22:35	49:66
Mean age (SD): years	8.9 (1.47)	9.2 (1.51)	9.1 (1.49)
White: n (%)	49 (84.5)	51 (89.5)	100 (87.0)
Baseline CY-BOCS Total Score: Mean (SD)	23.8 (5.00)	25.3 (5.31)	24.4 (5.19)
Age Group: Adolescents			
Females: Males	18:22	19:29	37:51
Mean age (SD): years	14.2 (1.67)	14.3 (1.59)	14.3 (1.62)
White: n (%)	36 (90.0)	43 (89.6)	79 (89.8)
Baseline CY-BOCS Total Score: Mean (SD)	25.2 (4.82)	25.3 (4.79)	25.3 (4.77)

Efficacy Results

Datasets: Primary inferences from efficacy analyses were based on the ITT population at Week 10 LOCF. In addition, the primary efficacy variable was

analyzed using the PP population. The Week 10 OC and the 70% LOCF datasets were used to assess the robustness of the conclusions.

Primary Efficacy Variable: Analysis of the primary endpoint provided statistically significant evidence that paroxetine was more efficacious than placebo in the treatment of OCD in the pediatric population. The adjusted mean difference between the paroxetine and placebo groups in change from Baseline in CY-BOCS total score at Week 10 LOCF for the ITT population was -3.45 points in favor of paroxetine (95% confidence interval [-5.60, -1.29], p = 0.002). This result was supported by the Week 10 LOCF analysis in the PP population (-4.27 points in favor of paroxetine, 95% confidence interval [-6.50,-2.04], p<0.001) and by the Week 10 OC and 70% LOCF analyses in both populations. There was no evidence of any statistically significant treatment by covariate interactions.

Secondary Efficacy Variables: Analysis of 3 of the 6 secondary efficacy endpoints also provided statistically significant evidence that paroxetine was more efficacious than placebo in treating children and adolescents with OCD. The odds of being a CY-BOCS responder on paroxetine vs. placebo at Week 10 LOCF were 2.66 (95% confidence interval [1.45, 4.87], p=0.002). For the CY-BOCS Obsession and Compulsion Subscale scores, the adjusted mean differences between paroxetine and placebo at Week 10 LOCF were -1.80 points in favor of paroxetine (95% confidence interval [-2.94, -0.67], p=0.002) and -1.72 points in favor of paroxetine (95% confidence interval [-2.85, -0.60], p=0.003), respectively. The analysis of results for CGI Global Improvement, CGI Severity of Illness, and GAF did not detect a statistically significant difference between the effects of paroxetine and placebo. However, each of these secondary endpoints showed numerical superiority in favor of paroxetine.

Safety Results

Adverse Events: In the ITT population, 83 patients (84.7%) in the paroxetine group and 77 patients (73.3%) in the placebo group reported gender-non-specific, Treatment Phase-emergent AEs. The most common (>10%) gender-non-specific AEs on paroxetine were headache, abdominal pain, nausea, respiratory disorder, somnolence, hyperkinesia, and trauma; the most common (>10%) AEs on placebo were headache, abdominal pain, respiratory disorder, infection, nausea, and rhinitis. The only gender-specific AE reported was dysmenorrhea in 3 female patients on paroxetine and 1 female patient on placebo. Hyperkinesia, trauma, decreased appetite, hostility, diarrhea, asthenia, vomiting, agitation, and neurosis

occurred at an incidence ≥5% and at least twice as frequently in patients receiving paroxetine than in those receiving placebo.

In the paroxetine group, the overall incidence of AEs was approximately the same in children and adolescents (84.5% vs. 85.0%, respectively). However, among the most common AEs, nausea (25.0% vs. 10.3%), somnolence (17.5% vs. 8.6%), asthenia (12.5% vs. 5.2%), and dizziness (10.0% vs. 1.7%) were each reported more frequently in the adolescent subgroup. Abdominal pain (22.4% vs. 10.0%), hyperkinesia (17.2% vs. 5.0%), and insomnia and hostility (each 12.1% vs. 5.0%) were reported more frequently in children than in adolescent patients.

Most AEs were mild to moderate in intensity. The most frequent (>10%) AEs reported as related or possibly related to study medication in the paroxetine group were headache, somnolence, hyperkinesia, abdominal pain, and nausea. These AEs, with the exception of headache, had a related or possibly related incidence in the paroxetine group that approached or exceeded twice that in the placebo group. During the Treatment Phase, 20/98 patients in the paroxetine group (20.4%) and 8/105 patients in the placebo group (7.6%) had AEs that led to dose reductions.

Serious Adverse Events: There were no deaths during the study or within 30 days of the last dose of study medication.

No serious AEs (SAEs) were reported during the screening phase. Three patients in the paroxetine group and 1 patient in the placebo group had SAEs after the first dose of randomized medication, including the 30-day period following the last dose of study medication. Hostility (aggressive behavior) was experienced by 1 patient (2 occurrences) in the paroxetine group and 1 patient in the placebo group during the Treatment Phase and in 1 patient in the paroxetine group 1 day after stopping taper medication. Emotional lability (suicidal thoughts), which also led to withdrawal from the Treatment Phase, occurred in 1 patient in the paroxetine group. All of the SAEs were considered unrelated or probably unrelated to study medication, and all, except hostility in the placebo patient, were considered severe.

Withdrawals Due to Adverse Events: In total, 10.2% of patients (10/98 including 8 children) receiving paroxetine and 2.9% of patients (3/105 including 1 child) receiving placebo were withdrawn during the Treatment Phase due to an AE. The only AE leading to withdrawal that occurred in more than 1 patient in the same treatment group was hyperkinesia, experienced by 3 patients (all

children 7 to 8 years old) in the paroxetine group. Neurosis leading to withdrawal was experienced by 1 patient in each treatment group.

Vital Signs: Changes in vital signs values from Baseline to Week 10 and endpoint were small for both treatment groups and of no clinical concern. Only a small number of patients were identified as having a vital signs value meeting predefined potential clinical concern criteria (9 patients in the paroxetine group and 11 in the placebo group). The most common concern values were for diastolic blood pressure <50 mmHg and decrease from Baseline ≥ 20 mmHg.

Laboratory Data: In total, 14/98 patients (14.3%) in the paroxetine group and 11/105 patients (10.5%) in the placebo group had laboratory values that met predefined potential clinical concern criteria at any time during study treatment. The majority of these patients, 11 in the paroxetine group and 7 in the placebo group, had low hematocrit values of potential concern. No remarkable mean changes in laboratory parameters were observed in either treatment group.

Electrocardiograms: During the study, the only abnormal ECG (as assessed by the investigator) in either treatment group was noted in a patient in the placebo group at the end of the Treatment Phase; the patient's ECG was normal at the end of the Taper Phase.

Conclusions

Assessment of the primary efficacy variable, change from Baseline in the CY-BOCS total score at the Week 10 LOCF endpoint, provided statistically significant evidence that paroxetine was more efficacious than placebo in treating children and adolescents with OCD. This conclusion was supported by statistically significant results from analysis of 3 of the 6 secondary efficacy variables and numerical results indicating a benefit of paroxetine over placebo for the other secondary variables.

Data from this study demonstrated that paroxetine was safe and generally well tolerated when used in children and adolescents with OCD over a period of up to 10 weeks. There was some indication that the AE profile in children may differ slightly from that in adolescents.