Report Synopsis

Study Title: A Multicenter, Open-label, Six-Month Extension Study to Assess the Long-Term Safety of Paroxetine in Children and Adolescents with Major Depressive Disorder (MDD) or Obsessive-Compulsive Disorder (OCD) (29060/716).

Investigators and Centers: This interim report includes data from 43 centers in the United States and 2 centers in Canada. All investigators were experienced in the treatment of child and adolescent patients. The study center of Dr. xxxxxxxxxxxxxxxxxxx (center 055) was terminated because of significant compliance violations.

Publication: No publications as of January 2002.

Study Dates: The first dose of open-label study medication was administered on May 13, 2000. This interim report includes data for all patients who entered the open-label extension study from acute studies 701 (patients with MDD) and 704 (patients with OCD) and had a completed 716 week 4 CRF or a 716 CRF study conclusion page received in-house by GlaxoSmithKline by October 1, 2001. Data from patients who entered this extension study after completing study 715 (open-label, forced-titration, steady state pharmacokinetic evaluation in patients with MDD or OCD) are not included in this interim report as the database for 715 was finalized after the study 716 database. These data will be included in the 716 final clinical study report.

Objectives: The objectives were to:

Assess the long-term (6-month) safety of paroxetine in the treatment of children and adolescents with MDD or OCD who completed paroxetine study 701, 704, or 715, and chose to enter this study.

Monitor the long-term (6-month) efficacy of paroxetine in the treatment of children and adolescents with MDD or OCD who completed paroxetine study 701, 704, or 715, and chose to enter this study.

Study Design: This was a multicenter, open-label, 6-month extension study in children (aged 7 to 11 years inclusive) and adolescents (aged 12 to 17 years inclusive) who completed acute paroxetine study 701, 704 or 715, and who chose to enter this study.

Study Population: Children and adolescents who completed paroxetine study 701, 704, or 715, and who met all other inclusion and none of the exclusion criteria were eligible to enter this study. Data from patients who entered this extension study after completing study 715 are not included in this interim report.

Treatment and Administration: Paroxetine was supplied in the form of white, oval, film-coated tablets for oral administration once daily. Each tablet contained 10 mg of paroxetine (batch number U00001).

Patients were to receive paroxetine (10 to 50 mg/day) for a period of 24 weeks during the treatment phase of study 716. Patients entering study 716 from acute study 701 or 704 were to be started on therapy at 10 mg/day. Patients entering study 716 from study 715 could, at the investigator's discretion, be initiated at a higher dosage level (e.g., the dosage level achieved at 715 endpoint). Starting at week 2, the dose of paroxetine could be increased by 10 mg/day up to a maximum dose of 50 mg/day, according to clinical response and tolerability. Dose reductions of 10 mg/day at weekly intervals were permitted at the discretion of the investigator. During the taper phase, patients who completed the treatment phase or were prematurely withdrawn at a dosage of $\geq$ 20 mg/day were down-titrated at a rate of 10 mg/day/week for a period of up to 4 weeks until they finished one week of taper phase dosing at 10 mg/day.

Evaluation Criteria

Safety Parameters: Safety, of primary interest in this study, was assessed via AE monitoring, vital sign measurements, laboratory evaluations, serum pregnancy tests, electrocardiograms (ECGs) and physical examinations.

Efficacy Parameters: There was no primary efficacy variable in this study.

Secondary efficacy variables were change from baseline in the Children's Depression Rating Scale-Revised (CDRS-R) total score, assessed only in patients with a primary diagnosis of MDD; change from baseline in the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) total score, assessed only in patients with a primary diagnosis of OCD; 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]), assessed in patients with a primary diagnosis of either MDD or OCD; and change from baseline in the CGI Severity of Illness item score, assessed in patients with a primary diagnosis of either MDD or OCD.

Statistical Methods: This is an open label study and no hypothesis testing was performed. Efficacy data were summarized descriptively, both overall and by acute study treatment group at each visit, with inferences based on the week 24 observed cases (OC) and last observation carried forward (LOCF) datasets. Categorical data were summarized by counts and percentages. Continuous data were summarized by the mean, median, standard deviation and range (minimum, maximum). Two patient populations were evaluated. The intention-to-treat (ITT) population consisted of all patients who received at least one dose of open-label medication and for whom at least one valid post-baseline (study 716, visit 1) open-label evaluation (including any adverse event) was available. The pure paroxetine (PPX) population consisted of all patients who received paroxetine in their acute study, received at least one dose of open-label medication, and for whom at least one valid post-baseline (study 716, visit 1) open-label evaluation (including any adverse event) was available.

Patient Disposition and Key Demographic Data

A total of 261 patients were entered into this open-label study. Of these, 223 patients met the criteria for inclusion in this interim analysis (117 patients from acute study 701 and 106 patients from acute study 704). Of these, 221 patients were included in the ITT population [94 patients who received paroxetine in their acute study (referred to as acute study paroxetine patients) and 127 patients who received placebo in their acute study (referred to as acute study placebo patients)]. Two patients were not included in the ITT population as they had no post 716 baseline assessments.

Patient Disposition (All Patients)

Study Stage/Population	Acute Study Treatment Group					
	Paroxetine		Placebo		Total	
	n	%	n	%	n	%
716 Baseline Only	0	-	0	-	0	-
Entered	96	(100.0)	127	(100.0)	223	(100.0)
Completed *	40	(41.7)	33	(26.0)	73	(32.7)
Ongoing**	11	(11.5)	15	(11.8)	26	(11.7)
Early Withdrawal	45	(46.9)	79	(62.2)	124	(55.6)
Intention-to-Treat	94	(97.9)	127	(100.0)	221	(99.1)
Pure Paroxetine	94	(97.9)	-	-	94	(42.2)

*A patient was considered to have completed the study if they completed a week 24 visit CRF.

** Ongoing patients were patients who did not have a study conclusion page, but had a completed week 4 CRF in-house by October 1, 2001

The acute study paroxetine group includes two patients who entered study 716, but had no post-baseline assessments

As of the clinical cut-off date of October 1, 2001, a total of 73 patients had completed the study, 124 had withdrawn early and 26 were continuing to receive open-label paroxetine having already completed a week 4 CRF. Overall, of all patients entered into study 716, more patients from the acute study placebo group withdrew early (62.2%, 79/127) compared to patients from the acute study paroxetine group (46.9%, 45/96). The primary reasons for withdrawal in the overall population were 'adverse event' (14.9%), 'other' reason (13.6%), and 'lack of efficacy' (11.8%). In patients who had received paroxetine in the acute study, 'other' was the primary reason leading to withdrawal (13.8%), whereas in patients who had received placebo in the acute study 'adverse event' was the primary reason leading to withdrawal (18.9%). The withdrawal rate was slightly higher for children than adolescents, but independent of primary diagnosis.

Baseline demographic and efficacy parameters are presented below. Demographic data were collected at acute study baseline; efficacy parameters, CDRS-R and CY-BOCS, are presented for study 716 baseline. Mean age, height, weight and BMI were similar between acute study treatment groups for the ITT population. There were more male patients (57.0%, 126/221) than female patients (43.0%, 95/221). The proportion of females in patients from the acute study paroxetine group (47.9%, 45/94) was higher than in patients from the acute study placebo group (39.4%, 50/127). The proportion of males from the acute study paroxetine group (52.1%, 49/94) was lower than in patients who had received placebo in the acute study (60.6%, 77/127).

There were slightly more children than adolescents in the ITT population, 53.8% (119/221) compared to 46.2% (102/221), respectively. This imbalance was most prominent in the patients who received placebo in their acute study.

Demography and Baseline Characteristics (ITT Population)

	Acute Study Treatment Group		
	Paroxetine	**Placebo**	**Total**
Total Patients Age Group: Total			
Females: Males	45:49	50:77	95:126
Mean age (SD): years	11.5 (3.00)	11.6 (2.83)	11.5 (2.90)
White: n (%)	77 (81.9)	109 (85.8)	186 (84.2)
Total Patients Age Group: Children			
Females: Males	27:22	26:44	53:66
Mean age (SD): years	9.0 (1.42)	9.4 (1.32)	9.3 (1.37)
White: n (%)	40 (81.6)	61 (87.1)	101 (84.9)
Total Patients Age Group: Adolescents			
Females: Males	18:27	24:33	42:60
Mean age (SD): years	14.2 (1.49)	14.2 (1.73)	14.2 (1.62)
White: n (%)	37 (82.2)	48 (84.2)	85 (83.3)
Patients with MDD Age Group: Total			
Females: Males	23:27	29:37	52:64
Mean age (SD): years	11.6 (2.82)	11.6 (2.94)	11.6 (2.88)
White: n (%)	39 (78.0)	54 (81.8)	93 (80.2)
716 Baseline CDRS-R Total Score: Mean	36.7 (13.26)	37.3 (13.93)	37.1(13.60)
Patients with MDD Age Group: Children			
Females: Males	14:11	14:22	28:33
Mean age (SD): years	9.2 (1.34)	9.4 (1.29)	9.3 (1.31)
White: n (%)	9 (76.0)	30 (83.3)	49 (80.3)
716 Baseline CDRS-R Total Score: Mean	37.8 (15.12)	35.3 (12.92)	36.2 (13.72)
Patients with MDD Age Group: Adolescents			
Females: Males	9:16	15:15	24:31
Mean age (SD): years	14.0 (1.50)	14.3 (1.86)	14.2 (1.70)
White: n (%)	20 (80.0)	24 (80.0)	44 (80.0)
716 Baseline CDRS-R Total Score: Mean	35.8 (11.55)	39.9 (14.92)	38.1 (13.54)
Patients with OCD Age Group: Total			
Females: Males	22:22	21:40	43:62
Mean age (SD): years	11.5 (3.22)	11.5 (2.73)	11.5 (2.93)
White: n (%)	38 (86.4)	55 (90.2)	93 (88.6)
716 Baseline CY-BOCS Total Score: Mean	16.5 (8.86)	19.9 (7.59)	18.5 (8.27)
Patients with OCD Age Group: Children			
Females: Males	13:11	12:22	25:33
Mean age (SD): years	8.9 (1.51)	9.5 (1.38)	9.2 (1.45)
White: n (%)	21 (87.5)	31 (91.2)	52 (89.7)
716 Baseline CY-BOCS Total Score: Mean	15.0 (9.65)	19.0 (8.38)	17.3 (9.06)
Patients with OCD Age Group: Adolescents			
Females: Males	9:11	9:18	18:29
Mean age (SD): years	14.6 (1.47)	14.1 (1.59)	14.3 (1.54)
White: n (%)	17 (85.0)	24 (88.9)	41 (87.2)
716 Baseline CY-BOCS Total Score: Mean	18.4 (7.65)	20.9 (6.50)	19.1 (7.03)

Safety Results

Adverse Events: Overall, 72.9% (161/221) of patients reported a gender-non-specific adverse event during the open-label treatment phase: 75.5% (71/94) of patients who had received paroxetine in the acute study and 70.9% (90/127) of patients who had received placebo in the acute study. The most common (>10%) gender-non-specific adverse events for patients in the acute study paroxetine group were headache (25.5%), respiratory disorder (16.0%), infection (13.8%), trauma (12.8%), and nausea (10.6%), while the most common adverse events for patients in the acute study placebo group were respiratory disorder (19.7%), headache (18.9%), infection (11.8%), and nervousness (10.2%). Six female patients reported a female-specific emergent adverse event during the open label treatment phase. There were no male specific adverse events during the open label treatment phase.

The overall frequency of gender-non-specific adverse events was slightly higher among children compared to adolescents. A total of 77.3% (92/119) of children reported gender-non-specific adverse events during the open-label treatment phase; 79.6% (39/49) of patients from the acute study paroxetine group and 75.7% (53/70) of patients from the acute study placebo group. A total of 67.6% (69/102) of adolescents reported gender-non-specific adverse events during the open-label treatment phase; 71.1% (32/45) of patients from the acute study paroxetine group and 64.9% (37/57) of patients from the acute study placebo group.

The overall frequency of gender-non-specific adverse events in patients with a primary diagnosis of MDD was 70.7% (82/116). A total of 76.0% (38/50) of patients with a primary diagnosis of MDD from the acute study paroxetine group and 66.7% (44/66) of patients from the acute study placebo group reported at least one gender-non-specific adverse event during the open label treatment phase. The overall frequency of gender-non-specific adverse events in patients with a primary diagnosis of OCD was 75.2% (79/105). A total of 75.0% (33/44) of patients with a primary diagnosis of OCD from the acute study paroxetine group and 75.4% (46/61) of patients from the acute study placebo group reported at least one gender-non-specific adverse event during the open label treatment phase. The nature of the adverse events were similar among patients with a primary diagnosis of MDD and patients with a primary diagnosis of OCD.

Overall, 11.3% (25/221) patients reported a severe gender-non-specific adverse event during the open-label treatment phase. The proportion of patients reporting at least one severe gender-non-specific adverse event during the open-label treatment phase was 9.6% (9/94) of patients from the acute study paroxetine group and 12.6% (16/127) of patients from the acute study placebo group. The only severe adverse events occurring in more than one patient in either acute study treatment group were hostility (4 patients), emotional lability (3 patients) and infection (3 patients). There were no severe gender-specific adverse events. The majority of open-label treatment phase-emergent severe adverse events were considered unrelated to study medication. One patient from the acute study paroxetine group and 6 patients from the acute study placebo group had severe adverse events during the open-label treatment phase that were considered by the investigator to be related or possibly related to open-label study medication.

Overall, 47.1% (104/221) of patients reported a gender-non-specific adverse event judged by the investigator to be related or possibly related to open-label study medication during the open-label treatment phase: 47.9% (45/94) of patients from the acute study paroxetine group and 46.5% (59/127) of patients from the acute study placebo group. The most common (>5% in patients from either acute study treatment group) gender-non-specific adverse events judged to be related or possibly related to open-label study medication were headache, nervousness, hyperkinesia, weight gain, nausea, insomnia and decreased appetite. The only gender-specific adverse event judged to be related or possibly related to open-label study medication was female genital disorders, which occurred in 1 patient from the acute study placebo group.

Serious Adverse Events: No deaths were reported prior to the clinical cut-off for this interim report (October 1, 2001).

Overall, 5.4% (12/223) of all patients enrolled experienced at least one serious adverse event during the open-label treatment phase, taper phase, or within 30 days of the last dose of open-label study medication. The proportion of patients with at least one serious adverse event was similar between patients from the two acute study treatment groups: 5.2% (5/96) of patients from the acute study paroxetine group and 5.5% (7/127) of patients from the acute study placebo group. (Note: the total number of patients includes two patients who had no post-716 baseline assessments). Of the 14 serious adverse events reported, 12 were reported during the open-label treatment phase. The majority of serious adverse events were judged as moderate or severe in intensity and unrelated to open-label study medication. No gender-specific serious adverse events were reported for either acute study treatment group.

Withdrawals Due to Adverse Events:
Overall, 14.9% (33/221) of patients were withdrawn from the study during the open-label treatment phase because of an adverse event (31 patients during the open-label treatment phase and 2 patients during the taper phase). Of the 33 patients withdrawn from the study because of an adverse event 15.1% (18/119) were children and 14.7% (15/102) were adolescents. The proportion of patients withdrawn because of an adverse event was lower in patients who received paroxetine in their acute study (9.6%, 9/94) compared to patients who received placebo in their acute study (18.9%, 24/127). The majority of the adverse events leading to withdrawal were judged moderate or severe in intensity by the investigator.

Adverse events leading to withdrawal during the open-label treatment phase (excluding taper) occurring in more than 1% of the total population were hostility (3.6%, 8/221), emotional lability (1.8%, 4/221), hyperkinesia (1.8%, 4/221) and nervousness (1.4%, 3/221). Two patients in the acute study placebo group reported a gender specific adverse event leading to withdrawal (libido decreased and abnormal ejaculation).

Vital Signs: Overall, 40 patients (20 patients from the acute study paroxetine group and 20 patients from the acute study placebo group) had vital sign values that met the sponsor's definition of potential clinical concern during the open-label treatment phase of the study. The majority of these patients, 12 from the acute study paroxetine group and 9 from the acute study placebo group, had an increase in body weight, which was ≥ 7% and were above the normal weight range for their age. Changes in vital signs values from acute study baseline to week 24 and endpoint were small for both acute study treatment groups and age groups and of no clinical concern.

Laboratory Data : In total, 53 patients had laboratory values that met the sponsor's definition of potential clinical concern during the course of the study (27 patients from the acute study paroxetine group and 26 patients from the acute study placebo group). The majority of these patients had low hematocrit values of potential clinical concern. No remarkable mean changes in laboratory parameters were observed in patients from either acute study treatment group or age group.

Electrocardiograms : No patients had abnormal ECG findings at the study 716 baseline visit or the week 24/early withdrawal visit. One patient who had received paroxetine in the acute study had an abnormal ECG assessment (as assessed by the investigator) during the taper phase, and one patient who had received placebo in the acute had an abnormal ECG assessment (as assessed by the investigator) during the follow-up phase. One patient who had received paroxetine in the acute had an abnormal ECG assessment (as assessed by the investigator) during the follow-up phase that was associated with an adverse event. In addition, one patient who had received placebo in the acute study had an ECG during the open-label treatment phase of the study that was associated with an adverse event.

Efficacy Results

Datasets : Two datasets were used to summarize the results: an observed case (OC) dataset and a last observation carried forward (LOCF) dataset. For both the ITT population and PPX population, descriptive summaries were produced based on the OC data set at each visit and the LOCF data set, with primary inferences based on the protocol defined week 24 endpoint.

Primary Efficacy Variable : There was no primary efficacy variable defined in this study as this study was not formally designed to assess efficacy.

Secondary Efficacy Variables: Results of the secondary endpoints suggest that MDD and OCD patients who respond to paroxetine during acute treatment generally will continue to respond during long term (i.e, 6 month) treatment. The mean CDRS-R total score remained substantially decreased from acute study baseline to the week 24 OC and week 24 LOCF endpoints in patients with a primary diagnosis of MDD. Similarly, the mean CY-BOCS total score remained substantially decreased from acute study baseline to the week 24 OC and week 24 LOCF endpoints for patients with a primary diagnosis of OCD. The majority of patients with a primary diagnosis of MDD or OCD met the CGI-Global Improvement item responder criteria at the week 24 OC and week 24 LOCF endpoints.

Conclusions

Data from this study demonstrate that paroxetine (10-50 mg/day) is safe and generally well-tolerated when used to treat children and adolescents with MDD or OCD for a period of up to 24 weeks. The adverse event profile with longer term dosing was comparable to that observed during acute (short term) dosing in earlier studies. As was the case in the prior acute studies, the long term safety data suggest that the common adverse event profile may differ somewhat between children and adolescents.

The efficacy results suggest that patients who responded to paroxetine in the acute study are likely to continue to respond to paroxetine during long term administration, however this study was not designed to evaluate this.