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: 49 centers in the US and 2 centers in Canada. All investigators were experienced in the treatment of child and adolescent patients. The study center of Dr. x. xxxxxxxxxxxxxxxxxxxxxxx(Center 055) was terminated because of significant compliance violations during acute Study 704.

Publication: Gallagher D, Gardiner C, Carpenter D, Bailey A. Interim Results of a 6-month Extension Study to Assess the Long Term Safety and Tolerability of Paroxetine in Children and Adolescents. Poster presented at American Psychiatric Association 155th Annual Meeting, Philadelphia, PA. 22 May 2002.

Study Dates: The first dose of open-label study medication was administered on 13 May 2000. This report includes data for all patients who entered the open-label extension study from acute Studies 701 (patients with MDD), first double-blind dose date 20 March 2000; 704 (patients with OCD), first double-blind dose date 20 January 2000; and 715 (open-label, forced-titration, steady-state pharmacokinetic [PK] evaluation in patients with MDD or OCD), first dose date 15 August 2000. The last dose of Study 716 study medication (including taper) was administered on 06 January 2002.

Objectives: 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.

To 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 at acute study entry) and adolescents (aged 12 to 17 years inclusive at acute study entry) who completed acute Study 701 or 704 or PK Study 715, and who chose to enter this study.

Study Population: Children and adolescents who completed Study 701, 704, or 715 and who met all other inclusion and none of the exclusion criteria were eligible to enter this study.

Treatment and Administration: Paroxetine was supplied as 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 PK Study 715 could, at the investigator's discretion, be initiated at a higher dose level (e.g., the dose level achieved at Study 715 endpoint, or 10 mg/day higher or lower).

Starting at Week 2, the dose of paroxetine for any patient could be increased by one dose level (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. Patients who completed the Treatment Phase or were prematurely withdrawn at a dose of ≥20 mg/day were to be down-titrated at a rate of 10 mg/day per 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 (patients from Study 701 or from Study 715 with MDD as clinically predominant Axis I disorder); 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 (patients from Study 704 or from Study 715 with OCD as clinically predominant Axis I disorder); 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 (all patients); and change from baseline in the CGI Severity of Illness item score, assessed in patients with a primary diagnosis of either MDD or OCD (all patients).

Statistical Methods: This was 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. A pure paroxetine (PPX) population was identified for purposes of describing the maintenance effect of paroxetine. It consisted of all ITT patients who received paroxetine in their acute study and were evaluated for key disorder efficacy (i.e., CDRS–R or CY–BOCS) at the conclusion of the acute study. Patients from Study 715 were not part of the PPX population as they had no key disorder efficacy assessments collected at the conclusion of the study.

Patient Disposition and Key Demographic Data:

A total of 265 patients were entered into this open-label study. Of these, 263 patients were included in the ITT population: 133 patients who received paroxetine in their acute or PK study (referred to as acute-study paroxetine patients) and 130 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-baseline assessments in this study.

Patient Disposition (All Patients)

Study Stage/ Population	Acute-study Treatment Group: Paroxetine n	Paroxetine %	Placebo n	Placebo %	Total n	Total %
Entered **	135	(100.0)	130	(100.0)	265	(100.0)
Completed *	68	(50.4)	46	(35.4)	114	(43.0)
Early Withdrawal	67	(49.6)	84	(64.6)	151	(57.0)
Intention-to-Treat	133	(98.5)	130	(100.0)	263	(99.2)
Pure Paroxetine	96	(71.1)	–	–	96	(36.2)

* Patients were considered to have completed the study if they completed a Week 24 visit CRF.
** The acute-study paroxetine group includes two patients who entered Study 716 but had no post-baseline assessments and are therefore not included in the ITT population.

In the ITT population, 43.3% (114/263) of patients completed the study and 56.7% (149/263) withdrew early. The primary reasons for withdrawal were "other" (includes unknown and non-study related personal reasons) (13.7%, 36/263), adverse event (13.3%, 35/263), and lack of efficacy (12.2%, 32/263). More patients from the acute-study placebo group withdrew early (64.6%, 84/130) than patients from the acute-study paroxetine group (48.9%, 65/133). The primary reason for withdrawal in patients receiving paroxetine in their acute study was "other" (includes unknown and non-study related personal reasons) (13.5%, 18/133), similar to the number withdrawn for "other" in the placebo group (13.8%, 18/130). Among patients who had received placebo in their acute study, the primary reason for withdrawal was adverse event (18.5%, 24/130), compared to 8.3% (11/133) of patients who had received paroxetine in their acute study. The withdrawal rate was slightly higher for children than adolescents, but was independent of primary diagnosis.

Demographic data were collected at baseline for Studies 701 and 704 and screening for Study 715; 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. Overall, there were more male patients (57.4%, 151/263) than female patients (42.6%, 112/263). The proportion of males in the acute-study paroxetine group (54.1%, 72/133) was slightly lower than in the acute-study placebo group (60.8%, 79/130).

There were slightly more children than adolescents in the ITT population, 52.9% (139/263) compared to 47.1% (124/263), respectively. This difference occurred only among 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 (%)	45.9:54.1	39.2:60.8	42.6:57.4
Mean age (SD): years	11.7 (2.93)	11.6 (2.82)	11.6 (2.87)
White: n (%)	111 (83.5)	112 (86.2)	223 (84.8)
Total Patients–Age Group: Children			
Females: Males (%)	52.2:47.8	37.5:62.5	44.6:55.4
Mean age (SD): years	9.0 (1.36)	9.4 (1.32)	9.3 (1.34)
White: n (%)	56 (83.6)	63 (87.5)	119 (85.6)
Total Patients–Age Group: Adolescents			
Females: Males (%)	39.4:60.6	41.4:58.6	40.3:59.7
Mean age (SD): years	14.3 (1.54)	14.2 (1.72)	14.2 (1.62)

White: n (%)	55 (83.3)	49 (84.5)	104 (83.9)

Demography and Baseline Characteristics (ITT Population) (continued)

	Acute-study Treatment Group		
	Paroxetine	**Placebo**	**Total**
Patients with MDD–Age Group: Total			
Females: Males (%)	40.7:59.3	43.9:56.1	42.2:57.8
Mean age (SD): years	11.8 (2.85)	11.6 (2.94)	11.7 (2.88)
White: n (%)	65 (80.2)	54 (81.8)	119 (81.0)
716 Baseline CDRS–R Total Score: Mean (SD)	35.5 (13.14)	37.4 (13.93)	36.4 (13.50)
Patients with MDD–Age Group: Children			
Females: Males (%)	48.7:51.3	38.9:61.1	44.0:56.0
Mean age (SD): years	9.3 (1.28)	9.4 (1.29)	9.3 (1.28)
White: n (%)	31 (79.5)	30 (83.3)	61 (81.3)
716 Baseline CDRS–R Total Score: Mean (SD)	33.9 (14.02)	35.3 (12.92)	34.6 (13.39)
Patients with MDD–Age Group: Adolescents			
Females: Males (%)	33.3:66.7	50.0:50.0	40.3:59.7
Mean age (SD): years	14.2 (1.55)	14.3 (1.86)	14.3 (1.68)
White: n (%)	34 (81.0)	24 (80.0)	58 (80.6)
716 Baseline CDRS–R Total Score: Mean (SD)	36.9 (12.36)	39.9 (14.92)	38.1 (13.46)
Patients with OCD–Age Group: Total			
Females: Males (%)	53.8:46.2	34.4:65.5	43.1:56.9
Mean age (SD): years	11.5 (3.22)	11.5 (2.73)	11.5 (2.93)
White: n (%)	46 (88.5)	58 (90.6)	104 (89.7)
716 Baseline CY–BOCS Total Score: Mean (SD)	14.7 (9.21)	19.0 (8.20)	17.1 (8.84)
Patients with OCD–Age Group: Children			
Females: Males (%)	57.1:42.9	36.1:63.9	45.3:54.7
Mean age (SD): years	9.0 (1.48)	9.5 (1.36)	9.3 (1.42)
White: n (%)	25 (89.3)	33 (91.7)	58 (90.6)
716 Baseline CY–BOCS Total Score: Mean (SD)	17.9 (8.10)	21.1 (6.48)	19.7 (7.34)
Patients with OCD–Age Group: Adolescents			
Females: Males (%)	50.0:50.0	32.1:67.9	40.4:59.6
Mean age (SD): years	14.4 (1.56)	14.1 (1.57)	14.2 (1.55)
White: n (%)	21 (87.5)	25 (89.3)	46 (88.5)
716 Baseline CY–BOCS Total Score: Mean (SD)	16.2 (8.78)	20.0 (7.51)	18.3 (8.27)

Safety Results:

Adverse Events: Overall, 75.7% (199/263) of patients reported a gender-non-specific adverse event during the open-label Treatment Phase: 79.7% (106/133) of patients in the acute-study paroxetine group and 71.5% (93/130) of patients in the acute-study placebo group. The most common (≥10%) gender-non-specific adverse events were headache (25.1%), respiratory disorder (18.3%), trauma (13.7%), infection (12.5%), pharyngitis (10.6%), and abdominal pain (10.3%).

In the acute-study paroxetine group, the most common (≥10%) adverse events were headache (29.3%), respiratory disorder and trauma (each 16.5%), pharyngitis (13.5%), infection (12.0%), abdominal pain (11.3%), and nausea (10.5%); the most common adverse events for patients in the acute-study placebo group were headache (20.8%), respiratory disorder (20.0%), infection (13.1%), trauma (10.8%), and nervousness (10.0%). Ten female patients reported a female-specific adverse event during the open-label Treatment Phase. There were no male-specific adverse events emergent during the open-label Treatment Phase.

The overall frequency of gender-non-specific adverse events was slightly higher among children than adolescents. A total of 78.4% (109/139) of children reported gender-non-specific adverse events during the open-label Treatment Phase: 80.6% (54/67) of patients in the acute-study paroxetine group and 76.4% (55/72) of patients in the acute-study placebo group. A total of 72.6% (90/124) of adolescents reported gender-non-specific adverse events during the open-label Treatment Phase: 78.8% (52/66) of patients in the acute-study paroxetine group and 65.5% (38/58) of patients in the acute-study placebo group. Adverse events that occurred in children with an incidence of ≥5% and with an incidence of at least twice that in adolescents were pharyngitis, hyperkinesia, vomiting, otitis media, cough increased, and pain. Adverse events that occurred in adolescents with an incidence of ≥5% and with an incidence of at least twice that in children were allergic reaction, emotional lability, asthenia, somnolence, asthma, and albuminuria.

The overall frequency of gender-non-specific adverse events in patients with a primary diagnosis of MDD was 74.8% (110/147): 81.5% (66/81) of patients in the acute-study paroxetine group and 66.7% (44/66) of patients in the acute-study placebo group. The overall frequency of gender-non-specific adverse events in patients with a primary diagnosis of OCD was 76.7% (89/116): 76.9% (40/52) of patients in the acute-study paroxetine group and 76.6% (49/64) of patients in the acute-study placebo group. Adverse events that occurred in patients with a primary diagnosis of MDD with an incidence of ≥5% and with an incidence of at least twice that in patients with a primary diagnosis of OCD were vomiting (10.9% compared to 0.9%), and emotional lability (6.8% compared to 3.4%). Adverse events that occurred in patients with a primary diagnosis of OCD with an incidence of ≥5% and with an incidence of at least twice that in patients with a primary diagnosis of MDD were hyperkinesia (10.3% compared to 2.0%) and anxiety (5.2% compared to 2.0%).

Overall, 11.8% (31/263) of patients reported a severe gender-non-specific adverse event during the open-label Treatment Phase: 9.8% (13/133) of patients in the acute-study paroxetine group and 13.8% (18/130) of patients in the acute-study placebo group. The only severe adverse events occurring in more than one patient in either acute-study treatment group were emotional lability (4 and 1), hostility (2 and 3), infection (2 and 1), trauma (1 and 2) and urinary incontinence (0 and 2) for patients in the acute-study paroxetine group and acute-study placebo group, respectively. There were no severe gender-specific adverse events. The majority of severe adverse events were considered unrelated to study medication. Two patients from the acute-study paroxetine group and 7 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; the only such event occurring in more than one patient was hostility (1 patient in the acute-study paroxetine group and 2 patients in the acute-study placebo group).

Overall, 49.4% (130/263) 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: 49.6% (66/133) of patients in the acute-study paroxetine group and 49.2% (64/130) of patients in the acute-study placebo group. The most common (≥5% of 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, insomnia, weight gain, nausea, 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 (inorgasmia), which occurred in one adolescent patient in the acute-study placebo group with a primary diagnosis of MDD.

During the Taper Phase or Follow-up Phase, 34.6% (54/156) of patients reported a gender-non-specific emergent adverse event. The most common (≥5%) gender-non-specific adverse events were headache and respiratory disorder.

Serious Adverse Events: There were no deaths during the study, and no deaths have been reported since the completion of the study.

Overall, 5.7% (15/265) of all patients enrolled in Study 716 reported at least one serious adverse event (SAE) during the open-label Treatment Phase or Taper Phase, or within 30 days of the last dose of open-label study medication (including taper). The proportion of patients reporting at least one SAE was similar between the two acute-study treatment groups: 5.9% (8/135) of patients in the acute-study paroxetine group and 5.4% (7/130) of patients in the acute-study placebo group. Of the 18 SAEs reported, 14 occurred during the open-label Treatment Phase. The majority of SAEs were judged moderate or severe in intensity and unrelated to open-label study medication.

The most common SAE was emotional lability, occurring in 2.3% of patients (6/265), 5 of whom were in the acute-study paroxetine group. Verbatim terms for the preferred term of emotional lability were suicidal ideation (2 patients), attempted suicide (2 patients) and suicidal (1 patient) in the acute-study paroxetine group, and hospitalization for suicide attempt in the acute-study placebo group. The only other SAEs occurring in more than one patient were depression and hostility, each occurring in one patient in each acute-study treatment group. No gender-specific SAEs were reported for either acute-study treatment group.

Withdrawals Due to Adverse Events: Overall, 11.8% (31/263) of patients were withdrawn from the study because of an adverse event emergent during the Treatment Phase. The proportion of patients withdrawn because of an adverse event was lower in the acute-study paroxetine group (7.5%, 10/133) than in the acute-study placebo group (16.2%, 21/130). Additionally, 3 patients withdrew during the Treatment Phase for an adverse event that started during the Acute Phase of the prior study, and 2 patients withdrew during the Taper or Follow-up Phase due to an adverse event. Of the 36 patients (12 in the acute-study paroxetine group and 24 in the acute-study placebo group) withdrawn from the study because of an adverse event, 58.3% (21/36) were children and 41.7% (15/36) were adolescents; 52.8% (19/36) had a primary diagnosis of MDD and 47.2% (17/36) had a primary diagnosis of OCD. 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 (3.4%, 9/263), emotional lability (1.9%, 5/263), hyperkinesia (1.5%, 4/263) and nervousness (1.1%, 3/263). One male and one female, both in the acute-study placebo group, reported a gender-specific adverse event leading to withdrawal, one of which started in a placebo patient during the acute study.

Vital Signs: Overall, 55 patients (29 patients from the acute-study paroxetine group and 26 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, Taper or Follow-up Phase of the study. The majority of these patients, 19 from the acute-study paroxetine group and 15 from the acute-study placebo group, had an increase in body weight ≥7% from acute-study baseline and above the normal weight range for their age. Eight patients had adverse events associated with the vital sign of concern, 7 for weight gain and one for weight loss. With the exception of weight gain, mean changes in vital sign values from acute-study baseline to Week 24 were generally small for both acute-study treatment groups and age groups and of no clinical concern.

Laboratory Data: In total, 71 patients had laboratory values that met the sponsor's definition of potential clinical concern during the study (36 patients from the acute-study paroxetine group and 35 patients from the acute-study placebo group). The majority of these patients had low hematocrit values of potential clinical concern. Twelve of the 71 patients had adverse events associated with the laboratory value of 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 assessments at the Study 716 Baseline Visit or Week 24. One acute-study paroxetine patient had an abnormal ECG assessment at Taper End, which was normal on repeat; one acute-study placebo patient had an abnormal ECG assessment at Early Withdrawal that was associated with an adverse event (bundle branch block); and one acute-study paroxetine patient had an abnormal ECG assessment during the Follow-up Phase reported as an adverse event (electrocardiogram abnormal). Both events were considered by the investigator to be of mild intensity and unrelated to study medication.

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 dataset at each visit and the Week 24 LOCF dataset, 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 responded 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.

Among patients with a primary diagnosis of MDD, the majority met the CGI Global Improvement item responder criteria: 93.7% (59/63) of patients in the Week 24 OC dataset and 70.4% (100/142) of patients in the Week 24 LOCF dataset. Among patients with a primary diagnosis of OCD, the majority also met the CGI Global Improvement item responder criteria: 87.8% (43/49) of patients in the Week 24 OC dataset and 67.5% (77/114) of patients in the Week 24 LOCF dataset.

Among patients with a primary diagnosis of MDD, 76.6% (49/64) of patients in the Week 24 OC dataset and 58.0% (83/143) of patients in the Week 24 LOCF dataset were rated as normal or borderline mentally ill according to the CGI–Severity of Illness scale, compared to no patients at acute-study baseline. Among patients with a primary diagnosis of OCD, 53.1% (26/49) of patients in the Week 24 OC dataset and 33.3% (38/114) of patients in the Week 24 LOCF dataset were rated as normal or borderline mentally ill, compared to no patients at acute-study baseline.

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 long-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.

Although this study was designed primarily to assess safety, the efficacy results suggest that patients who responded in the acute study are likely to continue to respond to paroxetine during long-term administration.