Report Synopsis

Study Title: A Randomized, Multicenter, 8-Week, Double-blind, Placebo-Controlled Flexible-Dose Study to Evaluate the Efficacy and Safety of Paroxetine in Children and Adolescents with Major Depressive Disorder (29060/701)

Investigators and Centers: The study was conducted in 40 centers in the US and 1 in Canada.

Publication: No publication as of 20 July 2001.

Study Dates: The first dose of randomized study medication was administered on 20 March 2000 and the last dose of study medication (excluding Taper) was administered on 24 January 2001.

Objectives: To compare the efficacy of paroxetine versus placebo in the treatment of children and adolescents with Major Depressive Disorder (MDD), as measured by the change from Baseline in the Children's Depression Rating Scale–Revised (CDRS–R) Total Score at Week 8 last observation carried forward (LOCF) endpoint.

To compare the safety and tolerability of paroxetine versus placebo in the treatment of children and adolescents with MDD.

Study Design: This was an 8-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose trial in children (ages 7 through 11) and adolescents (ages 12 through 17). 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 Major Depressive Disorder (single episode [296.2] or recurrent [296.3]) and who satisfied all other entrance criteria were eligible for 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 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 (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 level, up to a maximum of 50 mg per day (DL 5), according to the judgment of the investigator 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 Taper Phase, was a maximum of 15 weeks.

Evaluation Criteria

Efficacy Parameters: The primary efficacy variable was the change from Baseline in the CDRS–R total score.

The secondary efficacy variables were the change from Baseline in the Clinical Global Impression (CGI) Severity of Illness item score; the proportion of responders based on the CGI Global Improvement item (where response was defined as a score of 1 [very much improved] or 2 [much improved]); and the change from Baseline on the Global Assessment of Functioning (GAF) Scale. An additional efficacy variable was the change from Baseline in the Kutcher Adolescent Depression Rating Scale (KADS) total score in the 12- to 17-year-old patients. The KADS is a non-validated self-report instrument under development.

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

Pharmacokinetics: Pharmacokinetic (PK) blood samples were drawn from consenting patients at Weeks 4 and 8 (or early withdrawal from the study, if applicable) for paroxetine assay. These results will be combined with similar data from studies 704 (Obsessive-Compulsive Disorder) and 676 (Social Anxiety Disorder) at a later date 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 one post-dose safety (including AEs) or efficacy assessments were included in the ITT population. Statistical conclusions concerning the efficacy of paroxetine were made using data obtained from the last assessment of the ITT population and the observed cases (OC) dataset. 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.

Patient Disposition and Key Demographic Data

A total of 305 patients were screened and 206 patients randomized, 104 (50.5%) to paroxetine and 102 (49.5%) to placebo. Of these, 203 patients were included in the intention-to-treat (ITT) population, defined as all patients who were randomized into the study, who received at least one dose of double-blind medication, and who had at least one safety or efficacy post-Baseline assessment. The all-randomized population comprised 47.1% children and 52.9% adolescents.

Study Stage/Population	Paroxetine	Placebo	Total
Screened	—	—	305
Randomized	104 (100.0%)	102 (100.0%)	206 (100.0%)
Withdrawn	34 (32.7%)	23 (22.5%)	57 (27.7%)
Completed Study	70 (67.3%)	79 (77.5%)	149 (72.3%)
Intention-to-Treat *	101 (97.1%)	102 (100.0%)	203 (98.5%)
Per Protocol **	74 (71.2%)	83 (81.4%)	157 (76.2%)
Entered Long-term Study 29060/716	50 (48.1%)	63 (61.8%)	113 (54.9%)

* Randomized patients with at least one on-therapy safety or efficacy assessment. The Safety Population was the same as the ITT population.
** Per protocol (PP) patients were those patients in the ITT population not identified as protocol violators during blind review.

The percentage of randomized patients who were withdrawn prematurely from the study was slightly higher for the paroxetine group (32.7%) than the placebo group (22.5%). The primary reason for withdrawal in the ITT population was AE (9/101, 8.9%) in the paroxetine group and lack of efficacy (11/102, 10.8%) in the placebo group.

The two treatment groups showed no marked imbalances in any of the patient characteristics, although there was a slightly higher proportion of patients with comorbid psychiatric illnesses in the paroxetine group than in the placebo group.

Demography and Baseline Characteristics (ITT Population)

	Paroxetine	**Placebo**	**Total**
Age Group: Total	101	102	203
Females:Males	48:53	47:55	95:108
Mean age (SD): years	11.9 (3.00)	12.1 (2.95)	12.0 (2.97)
White: n (%)	76.2%	82.4%	79.3%
Baseline CDRS–R Total Score: Mean (SD)	60.7 (9.37)	62.6 (8.96)	61.7 (9.19)
Psychiatric Comorbidity Yes:No	28:73	18:84	46:157
Age Group: Children	49	47	96
Females:Males	23:26	18:29	41:55
Mean age (SD): years	9.2 (1.28)	9.4 (1.28)	9.3 (1.28)
White: n (%)	69.4%	83.0%	76.0%
Age Group: Adolescents	52	55	107
Females:Males	25:27	29:26	54:53
Mean age (SD): years	14.4 (1.60)	14.5 (1.72)	14.4 (1.66)
White: n (%)	82.7%	81.8%	82.2%

Efficacy Results

Datasets: Primary inferences from efficacy analyses were based on the ITT population at Week 8 LOCF. In addition, the primary efficacy variable was analyzed using the Per Protocol (PP) population.

Primary Efficacy Variable: Analysis of the primary endpoint provided no evidence that paroxetine was more efficacious than placebo in the treatment of MDD in the pediatric population. Although there was a large mean change from Baseline in CDRS–R total score in paroxetine-treated patients, there was also a large placebo effect. The adjusted mean difference between paroxetine and placebo in change from Baseline in CDRS–R total score at Week 8 LOCF for the ITT population was 0.8 points in favor of placebo (95% confidence interval [-3.09, 4.69], p = 0.684). This result was supported by the analysis of the PP population and the analysis of the Week 8 OC dataset in each population.

There was evidence of a statistically significant treatment by age group interaction (p = 0.049), indicating varying treatment effect across the age groups; therefore the analysis was carried out separately for each age group. Children (ages 7 through 11) exhibited a 5.3-point difference in favor of placebo in the CDRS–R total score change from Baseline, although this difference was not statistically significant (p = 0.054). Adolescents (ages 12 through 17) exhibited a 2.6-point difference in favor of paroxetine in the CDRS–R total score change from Baseline; again this difference was not statistically significant (p = 0.375).

Secondary Efficacy Variables: None of the secondary efficacy variables (CGI Severity of Illness, CGI Global Improvement, GAF) provided evidence that paroxetine is more efficacious than placebo in the treatment of children and adolescents with MDD.

Other Efficacy Variable: Analysis of the additional variable of interest (KADS, adolescents only) provided no evidence of a statistically significant benefit of paroxetine over placebo.

Safety Results

Adverse Events: In the ITT population, 71 patients (70.3%) in the paroxetine group and 62 patients (60.8%) in the placebo group reported non-gender-specific Treatment Phase-emergent AEs. The five most common non-gender-specific AEs on paroxetine were headache, nausea, trauma, respiratory disorder and insomnia; the five most common AEs on placebo were headache, respiratory disorder, nausea, asthenia and trauma. Only 3 patients reported gender-specific AEs, 1 male (impotence) and 1 female (menstrual disorder) on paroxetine and 1 female (dysmenorrhea) on placebo.

In the paroxetine group, the overall incidence of AEs was comparable between children and adolescents (69.4% vs. 71.2%, respectively). However, somnolence (19.2% vs. 0%), insomnia (15.4% vs. 6.1%) and pharyngitis (13.5% vs. 2.0%) were each reported more frequently in the adolescents subgroup. Abdominal pain (8.2% vs. 0%) and infection (10.2% vs. 3.8%) were the only AEs reported more frequently in the younger (7- to 11-year-old) patients than in adolescent (12- to 17-year-old) patients in the paroxetine group.

Most AEs were mild to moderate in intensity. The most frequent AEs reported to be related or possibly related to study medication in the paroxetine group were headache, nausea, somnolence, and insomnia. Of these, only insomnia had an incidence in the paroxetine group (10/101, 9.9%) that approached twice that in the placebo group (6/102, 5.9%). Nine of 101 patients in the paroxetine group (8.9%) and 5/102 patients in the placebo group (4.9%) had AEs that led to dose reductions during the Treatment Phase.

Serious Adverse Events: No deaths were reported to the sponsor during the course of the study or at any time since the last dose of study medication

A total of 6 patients in the paroxetine group and 1 patient in the placebo group were reported to have serious adverse events (SAEs) during this trial, including the 30-day period following the last dose of study medication. Emotional lability and depression were experienced by more than one patient (3 patients each in the paroxetine group, and emotional lability 1 patient in the placebo group). Emotional lability and hypertension in one patient in the paroxetine group were considered severe and related to study medication.

Withdrawals Due to Adverse Events: In total, 8.9% (9/101) of paroxetine patients and 2.0% (2/102) of placebo patients in the ITT population were withdrawn during the treatment phase due to an AE. The only AEs leading to withdrawal that occurred in more than 1 patient in the same treatment group were depression, experienced by 4 patients in the paroxetine group, and emotional lability, experienced by 2 patients in the placebo group and 1 patient in the paroxetine group. Nervousness leading to withdrawal was experienced by 1 patient in each treatment group.

Vital Signs: Changes in vital signs values from Baseline to Week 8 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 sponsor-defined clinical concern criteria (9 patients in the paroxetine group and 6 in the placebo group). The most common concern values were decreased pulse rate and increased weight (3 patients in the paroxetine group and 2 patients in the placebo group for each parameter).

Laboratory Data: In total, 10/101 patients in the paroxetine group (9.9%) and 12/102 patients in the placebo group (11.8%) had laboratory values that met the sponsor's definition of potential clinical concern at any time during the study. For the majority of cases, the values were consistent with values obtained at the Screening or Baseline Visits. No remarkable mean changes in laboratory parameters were observed in either treatment group.

Electrocardiograms: No abnormal ECGs (as assessed by the investigator) were seen at Week 8 or Early Withdrawal in either treatment group.

Conclusions

The results of this study failed to provide evidence for the primary and secondary endpoints that paroxetine is more efficacious than placebo in treating children and adolescents with MDD.

Paroxetine was generally well tolerated in this pediatric population compared to placebo, with no unexpected adverse events or findings in laboratory tests, vital signs, or ECGs. More paroxetine patients than placebo patients withdrew due to adverse events, and more children than adolescents withdrew due to AEs in the paroxetine group. The safety profile appeared similar to that previously reported for adults except that there were few gender-specific adverse events.