# Report Synopsis

**Study Title:** A 16 Week Double-Blind, Placebo Controlled Study to Investigate the Efficacy and Tolerability of Paroxetine in the Treatment of Children and Adolescents with Social Anxiety Disorder/Social Phobia (29060/676)

**Investigators and Centers:** Psychiatrist investigators from 22 centers in the US, 10 in South Africa, 4 in Canada and 2 in Belgium participated.

**Publication:** None published as of the date of this report.

**Study Dates:** The first dose of randomized study medication was administered on 30 November 1999 and the last dose of study medication (including taper) was taken on 19 October 2001.

**Objectives:** The primary objective was to investigate the efficacy of paroxetine compared to placebo in the treatment of children and adolescents with Social Anxiety Disorder / Social Phobia as measured by the proportion of responders based on the Clinical Global Impression Global Improvement item at the Week 16 last observation carried forward (LOCF) endpoint.

The secondary objective was to investigate the safety and tolerability of paroxetine in the treatment of children and adolescents with Social Anxiety Disorder/Social Phobia.

**Study Design:** This was a 16-week, multicenter, randomized double-blind placebo-controlled parallel-group, flexible-dose trial in children (8–11 years) and adolescents (12–17 years).

After screening, eligible patients entered the Treatment Phase and received paroxetine or placebo for 16 weeks. There were 9 post-baseline visits, which occurred at Weeks 1, 2, 3, 4, 6, 8, 10, 12 and 16. Upon completion of the Treatment Phase or upon early withdrawal, study medication was gradually reduced over a maximum of four weeks during the Taper Phase. A safety follow-up visit was performed 14 days ± 3 days after the last dose of taper medication.

**Study Population:** Male and female outpatients, 8-17 years of age, who met Diagnostic and Statistical Manual Version IV (DSM-IV) criteria for Social Anxiety Disorder (300.23) and also met all other entrance criteria.

**Treatment and Administration:** Paroxetine was supplied as blue, size 1, hard gelatin capsules. Batch numbers for paroxetine were N99194 (5 mg); N98187 (10 mg); N98080 (15 mg); N98189 (20 mg); or N98058 (25 mg). The placebo capsules (Batch no. N99102) were identical in appearance. All bottles contained sufficient medication for one week of treatment plus an overage of 3 days medication (20 capsules/bottle). Therefore, one bottle was dispensed for Weeks 1, 2, 3 and 4, two bottles for Weeks 5-6, 7-8, 9-10 and 11-12 and four bottles for Weeks 13-16. The Taper Phase medication (Weeks 17, 18, 19 and 20) was also supplied as single bottles, each bottle containing sufficient medication for one week.

Eligible patients were randomly assigned (1:1) to paroxetine or placebo and were instructed to take 2 capsules each morning, with food. For the first week, all patients received dose level (DL) 1 (10 mg/day) of paroxetine or matching placebo. The dose could then be up-titrated in single dose level (10 mg/day) increments no more frequently than every seven days, up to a maximum of DL 5 (50 mg/day on paroxetine), according to clinical response and tolerability. Dose escalation was permitted only at the clinic visit. One dose reduction to the next lower dose level consequent to an AE was permitted. Patients who were unable to tolerate DL 1 or who required more than one dose reduction were withdrawn from the study. A gradual reduction of study medication was required for all patients on DL 2 or higher at the end of the study.

**Evaluation Criteria**

**Efficacy Parameters:** The primary efficacy parameter was the proportion of responders based on a Clinical Global Impression (CGI) Global Improvement score of 1 or 2 at the Week 16 LOCF endpoint. All other efficacy parameters were assessed as the change from baseline at the Week 16 LOCF endpoint.

The secondary efficacy parameters included change from baseline on the CGI Severity of Illness, the Liebowitz Social Anxiety Scale for Children and Adolescents (LSAS–CA), the Dalhousie Generalized Social Anxiety Disorder Scale for Adolescents (D–GSADS–A: ages 11 to 18 only); the Social Phobia Anxiety Inventory (SPAI–C: ages 8 years to 13 years 11 months; SPAI: ages 14 years to 17 years 11 months); and the Global Assessment of Functioning Scale (GAF).

An additional variable of interest was the Children's Depression Rating Scale–Revised (CDRS–R).

**Safety Parameters:** Safety was assessed through routine adverse event (AE) monitoring, vital sign (including body weight) determinations, and clinical laboratory evaluations. In addition, physical examinations were performed at Screening and Week 16/Early Withdrawal.

**Pharmacokinetic Parameters:** Pharmacokinetic (PK) blood samples were drawn from consenting patients at Weeks 4 and 16 (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 704 (Obsessive Compulsive 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 were randomized to double-blind medication, received at least one dose of randomized study 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), the observed cases (OC) and the 70% LOCF 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. 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. 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.

Analysis of the primary efficacy variable was performed in the ITT population with and without data from patients at Center 001 because the investigator broke the blind at the end of the study. 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 425 patients were screened and 322 were randomized, 165 (51.2%) to paroxetine and 157 (48.8%) placebo. Of these, 319 patients were included in the ITT population. Three randomized patients were not included in the ITT population: one paroxetine patient and one placebo patient had no post-baseline assessment or AE; one paroxetine patient who was randomized in error at the Screening Visit had no baseline assessment and the post-baseline assessment was after the last dose of medication. The percentage of randomized patients withdrawn from the study was slightly higher for the placebo group (34.4%, 54/157) than for the paroxetine group (25.5%, 42/165). The primary reasons for withdrawal in the ITT population were protocol deviation (6.7%, 11/163) in the paroxetine group and lack of efficacy (14.1%, 22/156) in the placebo group.

**Patient Disposition**

| Study Stage/Population | Treatment Group | | Total |
|---|---|---|---|
| | **Paroxetine n (%)** | **Placebo n (%)** | **n (%)** |
| Screened | – | – | 425 |
| Randomized | 165 (100.0) | 157 (100.0) | 322 (100.0) |
| Withdrawn | 42 (25.5) | 54 (34.4) | 96 (29.8) |
| Completed the study | 123 (74.5) | 103 (65.6) | 226 (70.2) |
| Intention-to-Treat* | 163 (98.8) | 156 (99.4) | 319 (99.1) |
| Per-Protocol** | 124 (75.2) | 110 (70.1) | 234 (72.7) |

* Randomized patients who received at least one dose of double-blind medication and who had at least one post-baseline efficacy or safety assessment

** Patients in the ITT population not identified as protocol violators during blind review

The ITT population comprised 28.5% children and 71.5% adolescents. There were no marked imbalances between the treatment groups in any of the patient characteristics, although there was a greater proportion of females in the paroxetine group and a greater proportion of males in the placebo group. The percentage of patients with comorbid psychiatric illness was slightly greater in the paroxetine group (56.4%, 92/163) than in the placebo group (48.7%, 76/156).

The proportion of patients in each severity rating for Social Anxiety Disorder based on the ADIS for DSM-IV:C was similar between the two treatment groups at Screening. Baseline severity scores for CGI–S and LSAS were also similar between the two treatment groups.

**Demography and Baseline Characteristics (ITT Population)**

| | Treatment Group | | |
|---|---|---|---|
| | **Paroxetine** | **Placebo** | **Total** |
| **Age Group: Total** | | | |
| Males: Females | 71:92 | 89:67 | 160:159 |
| Mean age (SD): years | 13.0 (2.81) | 13.3 (2.73) | 13.1 (2.77) |
| Caucasian: n (%) | 139 (85.3) | 131 (84.0) | 270 (84.6) |
| Baseline LSAS mean (SD) | 77.6 (28.72) | 77.7 (7.05) | 77.6 (27.87) |
| Baseline CGI-S: Mildly ill, n (%) | 4 (2.5) | 6 (3.8) | 10 (3.1) |
| Moderately ill, n (%) | 74 (45.4) | 69 (44.2) | 143 (44.8) |
| Markedly ill, n (%) | 61 (37.4) | 61 (39.1) | 122 (38.2) |
| Severely/among the most extremely ill, n (%) | 23 (14.1) | 19 (12.2) | 42 (13.2) |
| **Age Group: Children** | | | |
| Males: Females | 25:21 | 23:22 | 48:43 |
| Mean age (SD): years | 9.3 (1.26) | 9.8 (1.15) | 9.5 (1.22) |
| Caucasian: n (%) | 38 (82.6) | 41 (91.1) | 79 (86.8) |
| Baseline LSAS | 70.7 (31.00) | 71.2 (28.65) | 70.9 (29.66) |
| Baseline CGI-S: Mildly ill, n (%) | 1 (2.2) | 3 (6.7) | 4 (4.4) |
| Moderately ill, n (%) | 25 (54.3) | 20 (44.4) | 45 (49.5) |
| Markedly ill, n (%) | 16 (34.8) | 20 (44.4) | 36 (39.6) |
| Severely/among the most extremely ill, n (%) | 3 (6.5) | 2 (4.4) | 5 (5.5) |
| **Age Group: Adolescents** | | | |
| Males: Females | 46:71 | 66:45 | 112:116 |
| Mean age (SD): years | 14.5 (1.67) | 14.7 (1.71) | 14.6 (1.69) |
| Caucasian: n (%) | 101 (86.3) | 90 (81.1) | 191 (83.8) |
| Baseline LSAS | 80.3 (27.49) | 80.3 (26.04) | 80.3 (26.74) |
| Baseline CGI-S: Mildly ill, n (%) | 3 (2.6) | 3 (2.7) | 6 (2.6) |
| Moderately ill, n (%) | 49 (41.9) | 49 (44.1) | 98 (43.0) |
| Markedly ill, n (%) | 45 (38.5) | 41 (36.9) | 86 (37.7) |
| Severely/among the most extremely ill, n (%) | 20 (17.1) | 17 (15.3) | 37 (16.2) |

**Efficacy Results**

**Datasets:** Primary inferences from efficacy analyses were based on the ITT population at Week 16 LOCF. In addition, the primary efficacy variable was analyzed using the per-protocol (PP) population. The Week 16 OC and the 70% LOCF datasets were used to assess the robustness of the conclusions from the primary analysis.

**Primary Efficacy Variable:** Analysis of the primary endpoint provided statistically significant evidence that paroxetine was more efficacious than placebo in the treatment of Social Anxiety Disorder in the population under study. The proportion of patients treated with paroxetine who were CGI Global Improvement responders at Week 16 LOCF endpoint was 77.6% (125/161) and the proportion of placebo-treated patients was 38.3% (59/154). The odds of being a CGI Global Improvement responder on paroxetine compared to placebo at Week 16 LOCF for the intention-to-treat population were 7.02 (95% CI: [4.07, 12.11], $p < 0.001$), showing a statistically significant benefit of paroxetine over placebo. This conclusion was supported by the Week 16 LOCF analysis in the PP population (odds ratio 8.41, 95% CI: [4.36, 16.21], $p < 0.001$) and by the Week 16 OC and 70% LOCF analyses in both populations. There was no evidence of any statistically significant treatment by covariate interactions for age group, gender, CGI Severity of Illness baseline scores, or country grouping.

**Secondary Efficacy Parameters:** Statistically significant differences favoring paroxetine over placebo were achieved in all secondary parameters in both the LOCF and OC datasets.

**Safety Results**

**Adverse Events:** In the ITT population, 144 (88.3%) patients in the paroxetine group and 125 (80.1%) in the placebo group reported gender-non-specific, Treatment Phase-emergent AEs. The most common (>10%) gender-non-specific AEs on paroxetine were headache, infection, respiratory disorder, abdominal pain, asthenia, insomnia, somnolence, rhinitis, and nausea, while the most common AEs on placebo were headache, infection, respiratory disorder, and rhinitis

The only gender-specific AEs reported were dysmenorrhea in 5 female patients on paroxetine and 4 female patients on placebo, amenorrhea in one female patient on paroxetine, and abnormal ejaculation in one male patient on paroxetine. Insomnia, decreased appetite, and vomiting 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 (84.6% vs. 83.5%, respectively).

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, asthenia, insomnia, and somnolence. 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, 17.2% of patients in the paroxetine group (28/163) and 38.0% of patients in the placebo group (6/156) had AEs that led to dose reductions.

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

Three patients in the paroxetine group and one in the placebo group reported a serious adverse event after the first dose of randomized medication, including the 30-day period following the last dose of study medication. All of the SAEs were considered unrelated to study medication, except for unintentional overdose in the one placebo patient. Anemia, which also led to withdrawal from the Treatment Phase, occurred in the paroxetine group. Serious adverse events for the other 2 patients in the paroxetine group occurred post-treatment: fear and depression related to Social Anxiety Disorder (14 days post-treatment) and injury (broken arm) (20 days post-treatment).

**Withdrawals Due to Adverse Events:** In total, 5.5% (9/163 of patients receiving paroxetine, including 2 children) and 1.3% (2/156, both children) of patients 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 manic reaction, experienced by 2 patients in the paroxetine group. One adolescent in each treatment group withdrew due to an AE during the Taper Phase.

**Vital Signs:** Twenty-two patients on paroxetine and 17 patients on placebo had an on-therapy absolute value and change in value in one or more of the vital signs that met the criteria for potential clinical concern. Three paroxetine patients and one placebo patient had vital sign values of concern that were reported as AEs by the investigator, all for increased body weight. Mean changes in all vital sign parameters were very small and generally comparable between groups.

**Laboratory Tests:** Twenty-five patients on paroxetine and 15 patients on placebo had an on-therapy value in one or more of the laboratory parameters that met the criteria for potential clinical concern. The most common value of concern was low hematocrit (13 paroxetine patients and 6 placebo patients). One patient had a laboratory value of concern that was reported as an AE by the investigator, a patient in the paroxetine group with high neutrophils and AEs of leukocytosis and leukopenia, considered probably unrelated to study medication. There were no substantial differences between the paroxetine and the placebo groups in any mean laboratory values at Week 16, at endpoint, or in the change from Baseline at endpoint.

**Conclusions:** Assessment of the primary efficacy variable, the proportion of responders based on the Clinical Global Impression–Global Improvement item at the Week 16 last observation carried forward (LOCF) endpoint, provided statistically significant and clinically relevant evidence that paroxetine was more efficacious than placebo in treating children and adolescents with Social Anxiety Disorder. This conclusion was supported by statistically significant results favoring paroxetine over placebo for all secondary efficacy variables. This conclusion was further supported by statistically significant results from analysis of all efficacy variables using the Week 16 Observed Cases (OC) dataset and the 70% LOCF dataset.

Data from this study demonstrated that paroxetine was safe and generally well tolerated compared to placebo when used in children and adolescents with Social Anxiety Disorder over a period of up to 16 weeks over the dosage range of 10-50 mg/day. There were no serious unexpected adverse events or findings in laboratory tests or vital signs. There was some indication that the AE profile in children may differ slightly from that in adolescents.