# Report Synopsis

## Title

A Multicenter Study to Assess the Pharmacokinetics of Paroxetine Following Repeat Dose Administration in Children and Adolescents with Obsessive-Compulsive Disorder (OCD) and/or Depression

## Investigator(s) and Center(s)

Twelve (12) Centers in the United States.

## Publication

None as of February 2002.

## Study Dates

15 August 2000 to 27 September 2001.

## Objective(s)

BRL 29060 (paroxetine hydrochloride; Paxil®) is used in the treatment of OCD and depression, conditions which occur in the pediatric, as well as in the adult, population. Since current information about the disposition of paroxetine in the pediatric population is limited, this study descriptively assessed the pharmacokinetics of paroxetine under steady state conditions in children and adolescents administered repeat oral doses of paroxetine hydrochloride. The specific study objectives were: 1) to determine the steady state pharmacokinetic profile of paroxetine following repeat oral doses of paroxetine hydrochloride to children and adolescents and 2) to assess the safety and tolerability of paroxetine following repeat oral doses of paroxetine hydrochloride to children and adolescents.

## Study Design

This was a multicenter, open-label, repeat dose, dose-rising study in children and adolescents with OCD and/or depression. Each patient received paroxetine hydrochloride orally according to the following schedule:

| | |
|---|---|
| Days 1-14 (-2/+3): | 10 mg once daily |
| Days 15-28 (-2/+3): | 20 mg once daily |
| Days 29-42 (-2/+3): | 30 mg once daily |
| Days 43-49 (-2/+3): | Dose-tapering (20 mg once daily) |
| Days 50-56 (+3): | Dose tapering (10 mg once daily) |

Pharmacokinetic sampling for measurement of plasma paroxetine concentrations was conducted over an approximately 24 hour period following the final dose at each dosing level in the dose rising stage. There were follow-up visits at the end of the taper dosing period and at 14 (± three) days following the final dose of paroxetine hydrochloride. Patients completing this study were allowed to enroll in a six month, open-label extension study administrated under a separate protocol at the investigator's discretion. The taper dosing period was optional and the 14 day follow-up visit was not required for patients entering the open-label extension dosing study.

## Study Population

Approximately 30 children ages seven to 11 years, inclusive, and approximately 30 adolescents ages 12 to 17 years, inclusive, who currently met DSM-IV criteria for OCD and/or depression (MDD) were enrolled in this study. Each age group was to be enrolled such that a ratio no greater than 2:1 was achieved based upon gender if possible.

## Treatment and Administration

BRL 29060 (paroxetine hydrochloride, Paxil®) oral tablets, 10 mg (Batch number U00001) were taken once daily in doses of 10 mg, 20 mg or 30 mg, depending upon the phase of the study.

## Evaluation Criteria

### Safety Parameters

The safety and tolerability of protocol-specified treatments were assessed by vital signs, 12-lead ECGs, clinical laboratory tests and clinical monitoring.

### Pharmacokinetic Parameters

Serial blood samples were collected over a 24 hour dosing interval after the final dose at each dose level. Plasma concentrations of paroxetine were quantitated using a method based on LC/MS/MS with on-line solid-phase extraction. Paroxetine Cmax, Tmax, AUC(0-24), CL/F and C(24) were derived using non-compartmental pharmacokinetic analysis, and their relationships with dose, age, weight, gender and CYP2D6 genotype were explored.

## Subject Disposition and Key Demographic Data

Sixty-two (62) children (7-11 years) and adolescents (12-17 years) with either OCD and/or MDD were enrolled and dosed with paroxetine during this study. There were a total of twenty-one (21) withdrawals, which were either due to adverse events (6), lost to follow-up (4), protocol deviations (7) or other reasons (4). Demographic data for all enrolled patients are summarized below:

| | | Age (years) | Height (cm) | Weight (kg) |
|---|---|---|---|---|
| **Children** | **Mean** | 10 | 142.9 | 42.1 |
| n = 27 | **SD** | 1.1 | 9.63 | 13.62 |
| 74% Male, 26% Female | **Range** | 8-11 | 125.5-164.0 | 25.9-76.5 |
| **Adolescents** | **Mean** | 14 | 164.5 | 68.2 |
| n = 35 | **SD** | 1.8 | 12.41 | 22.96 |
| 57% Male, 43% Female | **Range** | 12-17 | 129.0-190.5 | 30.1-141.0 |
| **Pooled** | **Mean** | 12 | 155.1 | 56.8 |
| n = 62 | **SD** | 2.8 | 15.53 | 23.31 |
| 65% Male, 35% Female | **Range** | 8-17 | 125.5-190.5 | 25.9-141.0 |

**Children**: 85% White; 7% Black; 7% Other; **Adolescents**: 83% White; 11% Black; 6% Other; **Pooled**: 84% White; 10% Black; 6% Other

## Safety Results

There were no deaths during this study. There were two (2) serious adverse events [manic reaction (1) and drug level increased (1)] and six (6) withdrawals due to adverse events (AEs) [manic reaction –1, drug level increased (overdose) – 1, asthma (exacerbation) - 1, rash - 1, manic reaction and hyperkinesia – 1 and dizziness and hyperkinesia], which included the two (2) serious AEs. Summary details for the treatment-emergent AEs reported during this study are listed by patient and treatment group in the table below:

| | **Children** | | | | | **Adolescents** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Paroxetine Dose (mg UID)** | | | | | **Paroxetine Dose (mg UID)** | | | | |
| | 10 | 20 | 30 | 20T | 10T | 10 | 20 | 30 | 20T | 10T |
| **Total Number of AEs** | 53 | 41 | 25 | 11 | 2 | 72 | 41 | 29 | 6 | 3 |
| **Most frequent AE = Headache** | 8 | 4 | 2 | 0 | 0 | 11 | 10 | 4 | 0 | 1 |
| **Number of Patients with AEs** | 18 | 12 | 11 | 5 | 2 | 25 | 20 | 15 | 4 | 2 |
| **Number of Patients Exposed** | 27 | 25 | 25 | 13 | 7 | 35 | 33 | 30 | 16 | 5 |

T = Taper.

There were no clinically significant changes in vital signs (height, weight, heart rate, blood pressure) or ECG intervals. Only one (1) safety laboratory value of potential clinical concern was considered clinically significant during this study. This increased AST (97 IU/L) was considered an AE by the investigator, but was asymptomatic, considered probably unrelated to paroxetine and resolved in approximately two weeks.

## Pharmacokinetics

Of the 62 pediatric patients (27 children and 35 adolescents) entered into the study, a total of 59 (25 children and 34 adolescents) completed the first period of dosing (10 mg/day) and provided plasma samples for pharmacokinetic analysis. Most of these patients (23 children and 28 adolescents) went on to complete the dose-rising phase and provided samples at all three dose levels (10, 20 and 30 mg/day). However, pharmacokinetic data at 20 mg/day from one patient were excluded from further analysis due to a dosing error, and data from three others were deemed uninterpretable due to internal data inconsistencies. The most important steady state pharmacokinetic parameters - Cmax, AUC(0-24) and CL/F (before and after normalization for weight) - are summarized by dose and age-group below.

| **Paroxetine steady state pharmacokinetic parameter** [units] | | **Children** | | | **Adolescents** | | |
|---|---|---|---|---|---|---|---|
| | | **10 mg** [n=23] | **20 mg** [n=23] | **30 mg** [n=21] | **10 mg** [n=33] | **20 mg** [n=29] | **30 mg** [n=27] |
| **Cmax** | Mean | 19.5 | 58.6 | 129.0 | 12.0 | 42.7 | 94.0 |
| [ng/mL] | SD | 18.2 | 34.5 | 106.9 | 13.0 | 30.0 | 51.4 |
| | Minimum | 1.3 | 19.4 | 28.3 | 0.3 | 10.7 | 28.5 |
| | Maximum | 90.9 | 142.4 | 552.6 | 62.8 | 129.9 | 262.9 |
| | **Geom. mean** | **14.0** | **50.0** | **105.5** | **6.6** | **35.0** | **82.4** |
| | **CVb** | **109%** | **63%** | **68%** | **191%** | **70%** | **56%** |
| **AUC(0-24)** | Mean | 285 | 899 | 2081 | 189 | 733 | 1631 |
| [ng.h/mL] | SD | 291 | 552 | 1737 | 227 | 581 | 1040 |
| | Minimum | 14 | 295 | 529 | 4 | 150 | 501 |
| | Maximum | 1424 | 2633 | 9018 | 1134 | 2628 | 5485 |
| | **Geom. mean** | **188** | **772** | **1711** | **94** | **570** | **1395** |
| | **CVb** | **131%** | **60%** | **66%** | **227%** | **82%** | **60%** |
| **CL/F** | Mean | 93.3 | 29.8 | 20.6 | 273.3 | 44.4 | 24.8 |
| [L/h] | SD | 144.1 | 15.9 | 12.4 | 495.8 | 32.3 | 13.2 |
| | Minimum | 7.0 | 7.6 | 3.3 | 8.8 | 7.6 | 5.5 |
| | Maximum | 708.7 | 67.9 | 56.7 | 2597.4 | 133.8 | 59.8 |
| | **Geom. mean** | **53.2** | **25.9** | **17.5** | **106.6** | **35.1** | **21.5** |
| | **CVb** | **131%** | **60%** | **66%** | **227%** | **82%** | **60%** |
| **CL/F** | Mean | 2.22 | 0.73 | 0.50 | 3.63 | 0.65 | 0.36 |
| **(weight-** | SD | 3.66 | 0.37 | 0.33 | 5.79 | 0.38 | 0.16 |
| **normalized)** | Minimum | 0.26 | 0.20 | 0.12 | 0.16 | 0.09 | 0.12 |
| [(L/h)/kg] | Maximum | 18.36 | 1.76 | 1.47 | 29.58 | 1.52 | 0.78 |
| | **Geom. mean** | **1.31** | **0.64** | **0.42** | **1.64** | **0.54** | **0.33** |
| | **CVb** | **117%** | **58%** | **66%** | **202%** | **76%** | **53%** |

At corresponding doses, median Tmax values in the two age-groups were similar (3-5 hours), suggesting comparable rates of absorption. No pharmacokinetic differences due to gender were evident in the Cmax, AUC(0-24) or CL/F data in either age-group at any of the three dose levels.

The Cmax and AUC(0-24) data confirm that, at each dose level, paroxetine steady state systemic exposure was higher in children (8-11 years) than in adolescents (12-17 years). However, for both parameters, the differences diminished with increasing dose; geometric mean values in children were approximately 100% higher at 10 mg but less than 30% higher at 30 mg. Mean Cmax and AUC(0-24) values increased disproportionately with dose in both groups, but this was accompanied by a marked reduction in variability (CVb), most notably between the 10 and 20 mg dose levels. Expressed in terms of clearance, geometric mean CL/F (un-normalized) at 10 mg in children was approximately 50% lower than in adolescents, but only 25% lower at 20 mg and 20% lower at 30 mg. Within each group, geometric mean CL/F fell more than two-fold between 10 and 20 mg, but by less than 40% between 20 and 30 mg.

As suggested by the groupwise (mean) data, Cmax and AUC(0-24) tended to fall with increasing age, while CL/F tended to rise. Variability was, however, considerable. Mirroring the effect of age, AUC(0-24) and Cmax also tended to fall with increasing weight, while CL/F again tended to rise. However, weight-normalized CL/F values at each dose level appeared to remain relatively constant across the age range studied.

Because the combined effects of age, weight and dose on the pharmacokinetics of paroxetine in the pediatric population are evidently rather complex, a covariate analysis was performed. Strong associations ($P \leq 0.001$) were observed between weight and Cmax, AUC(0-24) and un-normalized

CL/F, but no statistically significant association was observed between weight and weight-normalized CL/F. After adjusting for weight, no significant effect was found for any of these parameters when age was added to the model. However, significant interactions ($P<0.05$) between weight and dose were observed for Cmax, AUC(0-24) and un-normalized CL/F, due to small differences between the 10 mg dose level and the two higher doses in the degree of change with increasing weight.

CYP2D6 genotyping was performed for 53 of the 59 patients providing pharmacokinetic data, enabling their baseline phenotypes to be predicted. As expected, the EM phenotype predominated. No PMs were identified among the younger group, but three of the adolescents were predicted to possess this phenotype. Although one of these had the highest Cmax and AUC(0-24) and the lowest clearance in this age-group, parameter values in the other two putative PM patients were less readily distinguishable from the EM patients.

## Conclusion

In both pediatric age-groups, paroxetine steady state systemic exposure (Cmax and AUC(0-24)) increased disproportionately with dose, but also became less variable, mirroring the behavior of paroxetine in the adult population. Cmax and AUC(0-24) were higher and clearance lower in children than in adolescents. The association of paroxetine plasma concentrations with dose and weight (age) in this study may at first appear to support a weight-based dosing recommendation in pediatric patients. However, normalization of clearance for weight did not significantly reduce the very broad between-subject pharmacokinetic variability at any dose level. Moreover, noting the similarities between the adolescent and adult exposure data, and the absence of a clear relationship of exposure to effectiveness in adult patients treated with paroxetine, the results do not warrant a weight-based dosing regimen in the pediatric patient population. Paroxetine was generally safe and well-tolerated by pediatric patients ages 8 to 17 years.