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# An International, Multicenter, Placebo-Controlled Trial of Paroxetine in Adolescents with Major Depressive Disorder

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## ABSTRACT

***Objective:*** **The aim of this study was to examine the efficacy, safety, and tolerability of paroxetine in adolescents with unipolar major depression.**

***Method:*** **Two hundred eighty-six (286) adolescents with unipolar major depression were randomly assigned to receive either paroxetine or placebo for 12 weeks.**

***Results:*** **The proportion of Montgomery-Åsberg Depression Rating Scale (MADRS) responders (at least 50% reduction from baseline) for paroxetine and placebo were similar and not statistically different at endpoint ($p$ = 0.702). A similar result was obtained for change from baseline on the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-L) depression subscale. Among secondary endpoints, only a significantly higher Clinical Global Impression—Improvement (CGI-I) response rate was reported in paroxetine-treated patients versus placebo (69.2% versus 57.3%; $p$ = 0.045). In general, results differed by age, with patients older than 16 years demonstrating a greater response to active treatment. This age group also reported more adverse experiences (AEs) relative to placebo than younger adolescents. Overall, paroxetine was generally well tolerated (11% discontinued owing to an AE versus 7% of placebo-treated patients). A post hoc analysis of AEs related to suicidal behavior suggested a greater incidence of these events for paroxetine than for placebo (4.4% versus 2.1%); however, this difference was not statistically significant (odds ratio, 2.15, 95% Confidence Interval 0.45, 10.33; $p$ = 0.502).**

***Conclusions:*** **No statistically significant differences were observed for paroxetine compared with placebo on the two prospectively defined primary efficacy variables. Paroxetine at 20–40 mg/day administered over a period of up to 12 weeks was generally well tolerated.**

## INTRODUCTION

Depression in adolescents can be a chronic, debilitating condition with major impact on family, social, and school life. Epidemiological research suggests an estimated prevalence rate for major depressive disorder (MDD) in adolescents of between 0.4% and 8.3%, with a lifetime prevalence rate of 15%–20% (Birmaher et al. 1996). A substantial risk of recurrence

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exists with estimates of 26% within 1 year and 40% by 2 years (Birmaher et al. 1996; Kovacs et al. 1984). Estimates of recurrence at 3 years have ranged from 23 to 54% and are as high as 70% by 5 years (Birmaher et al. 1996; Goodyer et al. 1997; Lewinsohn et al. 1994).

Suicide is the third-leading cause of death in adolescents, and depression is a major risk factor for suicide. Each year 5%–8% of adolescents pass into the high suicide risk group by attempting suicide and 20% experience suicidal ideation (Grunbaum et al. 2002). Between 2% and 8% will actually commit suicide over the course of a decade (ACNP 2004).

Selective serotonin reuptake inhibitors (SSRIs) are widely used in the treatment of depression in adults and whereas extensive data exist to support their use in adults with MDD, few adequately powered, well-controlled clinical trials have produced evidence of efficacy in depressed children and adolescents. Among a number of antidepressants that have now been studied in pediatric MDD, only fluoxetine has reproducibly demonstrated sufficient efficacy to be granted approval for the treatment of depression in patients less than 18 years of age in the United States. The existing data for all other antidepressants in pediatric MDD, including three paroxetine trials (GlaxoSmithKline 2004), are far more equivocal (Whittington et al. 2004; Jureidini et al. 2004).

Whereas the efficacy of these agents in pediatric MDD has been a subject of debate for some time, the safety of these agents in this population has recently come under increased scrutiny. Responding to data submitted by the manufacturer concerning a greater incidence of potentially suicidal acts and thoughts in paroxetine-treated patients versus placebo-treated patients in pediatric clinical trials, the U.K. regulatory authority, the "MHRA," responded by advising:

> "Seroxat [paroxetine] must not be used for treatment of children . . . there is an increase in the rate of self-harm and potentially suicidal behavior in this age group, when Seroxat is used for depressive illness. It has become clear that the benefits of Seroxat in children, for the treatment of depressive illness, do not outweigh these risks"(U.K. Department of Health Advisory 2004).

In the United States, the U.S. Food and Drug Administration (FDA) responded by issuing a Talk Paper and requesting supplemental trial data from nine manufacturers of SSRIs and other frequently used antidepressants (Laughren 2004), launched a case-by-case expert review of this data, mandated cautionary language in the labeling of these nine antidepressants, and recommended that paroxetine not be used in pediatric MDD. Review of these data by the FDA Advisory Committee concluded that the aggregated data suggested that antidepressants were causally associated with a risk of suicidal behavior and/or ideation that was twice the rate of placebo (4% drug versus 2% placebo) and requested antidepressant manufacturers to warn of this in a "black box" in their product's information (FDA 2004).

Results of a previously completed North American study examining paroxetine therapy in depressed adolescents have already been published (Keller et al. 2001). Whereas that initial study provided evidence suggestive of efficacy (based on secondary endpoints), questions still remained regarding the usefulness of paroxetine in this population. We report in this paper the results of a second multicenter, placebo-controlled study conducted to examine paroxetine therapy in adolescents with unipolar major depression, this time in an international setting. Additionally, given concerns regarding suicidality in adolescents using SSRIs, a post hoc review of adverse events (AEs) in this trial possibly relating to suicidality was conducted and is summarized.

## METHOD

### *Participants*

Male and female adolescent outpatients (13–18 years of age) with a current Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (APA, 1994) diagnosis of unipolar major depression were eligible to participate. Diagnosis was confirmed by the Kiddie-Schedule for Affective Disorders and Schizophrenia For School-Age Children-Lifetime (K-SADS-L) at baseline (Kaufman et al. 1996). Patients also had to have a symptom se-

verity rating of at least 16 on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg 1979) at screening and baseline and a Children's Global Assessment Score (C-GAS) of less than 69 (Shaffer et al. 1983) at screening. A total of 324 patients entered the study at 33 centers in Belgium ($n$ = 64; 9 centers), Italy ($n$ = 28; 6 centers), Spain ($n$ = 1; 1 center), United Kingdom ($n$ = 1; 1 center), The Netherlands ($n$ = 9; 3 centers), Canada ($n$ = 15; 2 centers), South Africa ($n$ = 111; 3 centers), United Arab Emirates ($n$ = 24; 1 center), Argentina ($n$ = 37; 5 centers), and Mexico ($n$ = 34; 2 centers). Centers in Belgium and South Africa enrolled the majority of patients, 61 (22.7%) and 100 (30.8%), respectively. Most centers were in university hospital settings. Patients were recruited for participation through a combination of clinic referral and advertisement.

The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki (amended in Somerset West, Republic of South Africa, October 1996), with the protocol and statement of informed consent approved by institutional review boards/ethics committees prior to each center's initiation. Written, informed consent/assent was obtained from all patients and their parents or guardians prior to study entry.

*Eligibility criteria*

Patients were evaluated at the screening and baseline visits and were excluded if they had primary conduct disorder in childhood, autism or pervasive mental disorder, or had obsessive-compulsive disorder, panic disorder, social phobia, or posttraumatic stress disorder that preceded the diagnosis of depression. Other grounds for exclusion were: Current psychiatric disorder, including schizophrenia, epilepsy, previous response to psychotherapy as a treatment for depression or previous use of paroxetine, anticipated long-term formal psychotherapy (routine short-term supportive psychotherapy or family supportive therapy was permitted), substance abuse/dependence, concurrent psychoactive medication use, known sensitivity to SSRIs, pregnancy/lactation, recent electroconvulsive therapy, or clinically significant abnormal laboratory or electrocardiogram findings. Although a history of suicide attempt(s) was not exclusionary, patients with current serious suicidal ideation were excluded.

*Design and procedures*

This was a prospective, multicenter, randomized, double-blind, placebo-controlled, flexible-dose, parallel-group, outpatient study. Patients meeting eligibility criteria were enrolled into a 2-week, single-blind, placebo run-in period. Patients still meeting entry criteria at the end of the run-in period were randomly assigned 2:1 to receive either paroxetine (20–40 mg daily, flexible dose) or placebo for a period of 12 weeks. Study assessments were scheduled at the end of weeks 1, 2, 3, 4, 6, 8, and 12, with depression rating scales administered at each visit. Adverse events and vital signs were also monitored at each visit. At the end of the study treatment period, patients were tapered off of study medication with a 2-week pack of "run-out" medication. A follow-up visit was then conducted for a final assessment of safety.

*Study medication and dosing regimen*

A centralized, computer-generated randomization list was used to assign patients to each treatment group. Centers were allocated study medication in blocks of six consecutively numbered patient packs. Placebo and paroxetine capsules were centrally prepared and packaged and were identical in appearance, so that all study personnel and patients were blinded to treatment.

All patients received a 2-week, single-blind period of placebo medication during the run-in phase of the study. After the placebo run-in period, patients who were randomly allocated to receive placebo continued to receive placebo during the entire study. Patients who were randomly allocated to the paroxetine group started at 20 mg/day. Patients were instructed to take study medication in the morning with food. Dosing was flexible, between 20 mg and 40 mg/day, according to clinical response and tolerability with up-titration or down-titration allowed at weekly intervals (10 mg per week maximum). At the end of the study treatment

period or in the case of early withdrawal, patients were down-titrated off study medication in a double-blind fashion over a period of 2 weeks (10 mg/week down to 20 mg/day). If further treatment was needed, alternative antidepressant medication was prescribed at the discretion of the investigator.

### *Outcome measures*

*Efficacy endpoints.* There were two primary efficacy parameters for this study: (1) the proportion of responders (defined as patients with a 50% or greater reduction between baseline and last observation carried forward [LOCF] endpoint in the MADRS total score); and (2) the change from baseline at LOCF endpoint in the K-SADS-L depression subscale score. The MADRS is an observer-rated scale based on clinical interview that consists of 10 items assessing apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts, each of which is scored between 0 and 6 in defined steps. The K-SADS-L is also a clinical interview consisting of 56 questions in 30 subsections relating to various aspects of mood, self-image, attitude to life, psychomotor agitation/retardation, sleep problems, appetite/weight loss/weight gain, and suicidal ideation over the previous 2 weeks. The K-SADS-L Depression Subscale consists of nine of these questions. Most questions are scored between 0 and a maximum of 4 to 7 in defined steps.

Secondary efficacy parameters were change from baseline to endpoint in MADRS total score, Clinical Global Impression of Severity (CGI-S; Guy 1976) score, Beck Depression Inventory (BDI; Beck et al. 1979), Mood and Feelings Questionnaires (MFQ; Costello and Angold 1988), and Clinical Global Impression of Improvement score (CGI-I; Guy 1976). All efficacy variables (primary and secondary) were also analyzed at weeks 6, 8, and study endpoint (if withdrawn prematurely).

Post hoc analyses of the mean change from baseline to endpoint on the "reported sadness" item from the MADRS (Item 2) and CGI-I responder rate (based on an improvement score of either 1, "very much improved," or 2, "much improved) at week 12 LOCF were also completed.

*Safety endpoints.* Safety was assessed at every visit through AE monitoring and vital sign determination (e.g., blood pressure, pulse). Ascertainment of AEs was done by asking the patient a nonleading question, such as "Do you feel different in any way since starting the new treatment/since the last assessment?" A serious adverse event (SAE) was defined as any event that was fatal, life threatening, disabling/incapacitating or resulted in hospitalization, prolonged a hospital stay, or was associated with congenital abnormality, cancer, or overdose (either accidental or intentional). In addition, any experience that the investigator regarded as serious or that suggested any significant hazard, contraindication, side effect, or precaution that may have been associated with the use of the drug was documented as a serious event. Clinical laboratory evaluations (e.g., hematology, serum chemistry) and physical examinations (including weight) were performed at baseline and week 12 or upon early withdrawal.

Post hoc analyses were conducted on the incidence of on-therapy AEs related to suicidality that were identified by computerized searches of AE terms and an unblinded review of accidental injuries and SAE narratives. The on-therapy period was defined as the double-blind treatment phase, including 1 day after the last dose of study medication. Events classified as "suicide-related" (i.e., suicide threat, suicide gesture, suicide ideation, and suicide attempt) were combined for analyses comparing the paroxetine and placebo groups (Fong et al. 2004). The same analyses were also performed for events classified as suicide attempts only.

### *Statistical analyses*

It was estimated that 120 and 60 evaluable patients in the paroxetine and placebo treatment groups, respectively, would be sufficient to detect a 25% difference between response rates (i.e., based on at least 50% reduction in MADRS total score) for those randomly assigned to paroxetine compared to placebo. This

difference is detectable with a power of 90%, given a significance level of 5% and using a two-sided significance test.

All patients who were randomized into the treatment phase, received at least 1 dose of study medication, and had at least one postbaseline safety or efficacy assessment were included in a modified intention-to-treat (mITT) population, whereas all randomized patients who received at least 1 dose of study medication were included in the safety population.

The primary efficacy analysis population for the study was the mITT population using the LOCF datasets, with the LOCF week 12 time point being the primary time point of interest. In this dataset, the last available on-therapy observation for a patient was used to estimate missing data points.

Additional analyses of the mITT population were conducted on the observed cases (OC) dataset. In this dataset, efficacy data were evaluated only for the time point when collected.

The proportion of MADRS responders (at least 50% reduction in MADRS total score) was analyzed using logistic regression. The mean change from baseline in K-SADS-L depression subscale, item 2 ("reported sadness") on the MADRS and MADRS total scores, BDI, and MFQ scores, were analyzed using analysis of covariance. Least squares means (LSMs) were compared at the 5% level. Both sets of analyses included treatment group, country group, and covariates of age and baseline score in the model. The effect of adding treatment-by-country group interaction into the model was assessed, was not statistically significant ($p \geq 0.1$), and was dropped from the model. Treatment-by-covariate and covariate-by-covariate interactions were assessed in a similar way.

The changes from baseline in the CGI-S were analyzed using the Wilcoxon Rank Sum test. No adjustment was made for country grouping or covariates. The CGI-I scores were compared using Cochran-Mantel-Haenszel chi-square tests (stratifying by country group) at the 5% level. The proportion of CGI-I responders was analyzed using logistic regression.

The hypothesis of no association between treatment and the incidence of AEs related to suicidality was tested using Fisher's Exact test (two-tailed), with significance assessed at the 5% level. To account for differences in the duration of exposure to study medication, incidence rates relative to Person Years Exposure (PYE; the sum of the number of years that each patient in the population was treated) were also calculated. Poisson Regression (incidence density analysis) was used for the comparison of the number of patients with events relative to drug exposure.

## RESULTS

### *Patient characteristics*

A total of 324 patients were screened and 286 were randomly assigned to double-blind treatment. The mITT population consisted of 275 patients (182 randomly assigned to paroxetine and 93 to placebo). Baseline demographic and clinical characteristics were similar between treatment groups (Table 1). Nearly 67% of the study population was female. Mean age in the two treatment groups was 15–16 years. A relatively diverse ethnic population was enrolled, with Caucasians comprising 68% of the randomized subjects. Most patients (approximately 83%) were experiencing their first major depressive episode that was continuing at the time of study entry; 17% had previous episodes. The most common comorbid psychiatric condition in the overall population was generalized anxiety disorder (5%; 14 of 275).

The mean baseline MADRS scores for both the paroxetine and placebo groups was 25.9 (standard error = 0.5 and 0.6, respectively), indicating a moderately to severely ill population overall. At baseline, 33.7% of paroxetine patients and 39.3% of placebo patients were either markedly or severely ill, as measured by the CGI-S rating.

### *Patient disposition*

The progress of patients through the study and details of reasons for withdrawal are shown in Figure 1. A total of 71.3% (196 of 275) patients completed the 12-week, double-blind treatment phase (mITT population). Overall, the percentage of patients who withdrew was numerically higher in the paroxetine group

**Table 1. Demographic and Baseline Characteristics (mITT Population)[a]**

| *Demographic characteristics* | *Paroxetine* (n = *182*)[b] | *Placebo* (n = *93*) |
|---|---|---|
| Gender, *n* (%) | | |
| Male | 60 (33.0) | 32 (34.4) |
| Female | 122 (67.0) | 61 (65.6) |
| Age, years | | |
| Mean (SD) | 15.5 (1.6) | 15.8 (1.6) |
| Age range | 12–19 | 13–18 |
| Race, *n* (%) | | |
| Caucasian | 126 (69.2) | 61 (65.6) |
| African-American | 2 (1.1) | 4 (4.3) |
| Asian | 2 (1.1) | 0 (0.0) |
| Other[c] | 52 (28.6) | 28 (30.1) |
| Height, cm | | |
| Mean (SD) | 163.6 (9.1)[e] | 164.5 (8.5) |
| Range | 140–185 | 131–184 |
| Current comorbid conditions | | |
| Continuing major depressive episode | 152 (83.5) | 77 (82.8) |
| Anxiety disorder[d] | 30 (16.5) | 14 (15.1) |
| ADHD | 3 (1.6) | 0 (0.0) |
| Previous major depressive episode | | |
| No | 129 (70.9) | 64 (68.8) |
| Suspected | 14 (7.7) | 10 (10.8) |
| Yes | 39 (21.4) | 19 (20.4) |
| Baseline symptom severity | | |
| MADRS (mean [SE]) | 25.9 (0.5) | 25.9 (0.6) |
| CGI—Severity (mean [SE]) | 4.2 (0.1) | 4.2 (0.1) |
| BDI (mean [SE]) | 23.0 (0.8) | 22.4 (1.2) |

ADHD = attention-deficit/hyperactivity disorder; mITT = modified intention to treat; MADRS = Montgomery-Åsberg Depression Rating Scale; CGI = Clinical Global Impression; BDI = Beck Depression Inventory.

[a]Eleven (11) patients were not included in the mITT population, 5 from the paroxetine group (2 because of adverse events, 1 protocol violation, 1 lost to follow-up), and 6 from the placebo group (1 because of lack of efficacy, 1 protocol violation, 1 lost to follow-up, and 1 for another reason).

[b]One subject randomized to paroxetine was included in the mITT population in error. This subject did not take any active study medication.

[c]Other primarily comprised of Hispanic, Arab, and mixed racial descent.

[d]Includes specific phobia, separation anxiety disorder, panic disorder, social phobia, and generalized anxiety disorder.

[e]*n* = 180.

(30.2%; 55 of 182) than the placebo group (25.8%; 24 of 93). Rates of withdrawal owing to AEs were higher in the paroxetine group (11.0% paroxetine versus 7.5% placebo), whereas withdrawals owing to lack of efficacy were higher in the placebo group (6.5% placebo versus 4.9% paroxetine).

### *Dosage summary*

The mean maximum daily dose was 26.1 mg. More than half the patients (56%) assigned to paroxetine remained on the lowest dose of 20 mg/day throughout the study. Only 17% of the paroxetine group had dose increases to the maximum dose of 40 mg/day, compared to 24% in the placebo group. At endpoint (week 12 LOCF), the mean dose for paroxetine was 25.8 mg/day, with 59% of patients receiving the lowest dose of 20 mg/day.

### *Efficacy*

*Primary efficacy.* The proportion of MADRS responders for paroxetine (60.5%) and placebo (58.2%) was similarly high and did not differ statistically ($p = 0.702$) or clinically at week 12 LOCF (Table 2). There was a decrease of 9.3 points from baseline to study endpoint on the K-SADS-L depression subscale in paroxetine-treated patients and 8.9 points in the placebo group (Table 2), which did not differ statisti-

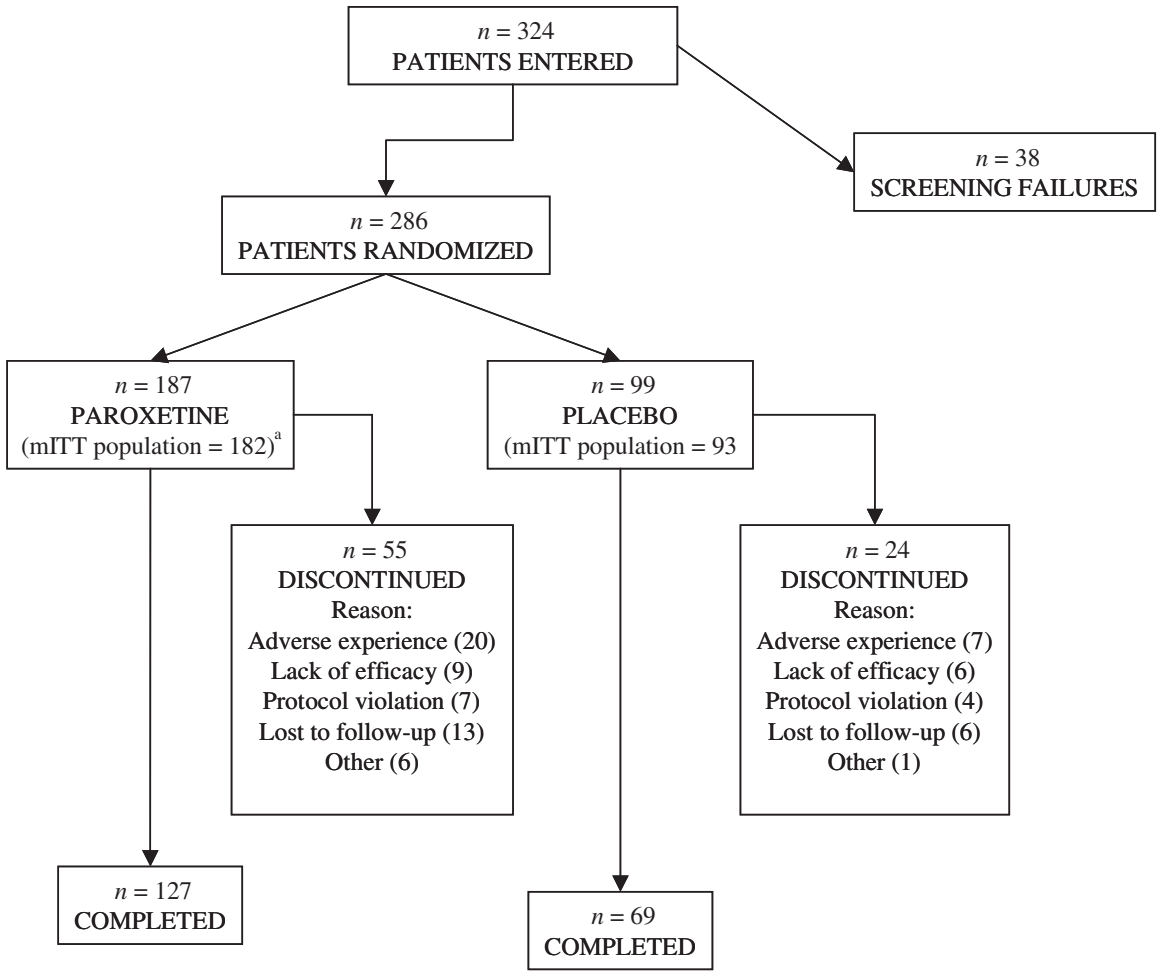


**FIG. 1.** Summary of patient disposition. mITT = modified intention to treat. [a]One subject randomized to paroxetine was included in the mITT population in error. This subject did not take any active study medication.

cally ($p$ = 0.616) or clinically. The results were similar in the week 12 observed case (OC) dataset for both primary efficacy parameters (data not shown).

*Secondary efficacy.* Neither the proportion of MADRS responders nor the change from baseline in K-SADS-L depression subscale was significantly greater for paroxetine versus placebo at any other time point of interest (weeks 6 or 8). Similarly, improvement from baseline in the total MADRS and Item 2 ("reported sadness") MADRS scores, symptom severity as measured by the CGI-S, and change from baseline in BDI and MFQ scores were not significantly different between treatment groups at any time point (Table 3). The only significant difference between treatments in the overall population was the post hoc analysis of CGI-I responders, which indicated a significantly higher response rate in paroxetine-treated patients compared to placebo (69.2%, 119 of 172 versus 57.3%, 51 of 89; odds ratio [OR] 1.74, 95% Confidence Interval [CI] 1.01, 2.99, $p$ = 0.045; Table 3). This latter finding was seen in the week 12 OC dataset as well (data not shown).

*Subgroup analysis by age.* A significant treatment-by-age interaction was observed for both coprimary variables. Further analyses of the primary efficacy dataset by prospectively defined age groups (less than or equal to 16 and greater than 16 years old) showed a pattern of greater response in older adolescents treated with paroxetine compared to younger adolescents. For example, in patients over 16 years of age, the proportion of MADRS responders was

**Table 2. Primary Efficacy Results—Proportions of Patients with at Least 50% Reduction from Baseline in Total MADRS Score and Change from Baseline in K-SADS-L Depression Subscale**

| | *Week* | *Paroxetine n/N* | *Placebo n/N* | *Adjusted odds ratio* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
|---|---|---|---|---|---|---|---|---|
| MADRS | 6 | 73/177 (41.2%) | 33/91 (36.3%) | 1.24 | (0.73, 2.12) | 1 | 0.63 | 0.427 |
| | 8 | 97/177 (54.8%) | 45/91 (49.5%) | 1.26 | (0.75, 2.12) | 1 | 0.76 | 0.382 |
| | 12 | 107/177 (60.5%) | 53/91 (58.2%) | 1.11 | (0.65, 1.88) | 1 | 0.15 | 0.702 |

| | | *Paroxetine* | | | *Placebo* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Week* | *N* | *LSM* | *SE* | *N* | *LSM* | *SE* | *Difference* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
| K-SADS-L | 6 | 171 | −7.66 | 0.50 | 88 | −7.46 | 0.65 | −0.20 | (−1.69, 1.30) | 1 | 0.07 | 0.793 |
| | 8 | 171 | −8.76 | 0.51 | 88 | −8.20 | 0.67 | −0.55 | (−2.07, 0.97) | 1 | 0.51 | 0.477 |
| | 12 | 171 | −9.33 | 0.54 | 88 | −8.92 | 0.70 | −0.41 | (−2.01, 1.19) | 1 | 0.25 | 0.616 |

MADRS = Montgomery-Åsberg Depression Rating Scale; K-SADS-L = Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children; n = Number of patients with at least 50% reduction in MADRS score at study endpoint; N = Total number of patients in the treatment group at that time; LSM = Least Squares Mean; SE = standard error.

**TABLE 3. SECONDARY EFFICACY RESULTS (CHANGE FROM BASELINE IN MADRS TOTAL SCORE AND OTHER SECONDARY ENDPOINTS)**

| | | *Paroxetine* | | | *Placebo* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Week* | *N* | *LSM* | *SE* | *N* | *LSM* | *SE* | *Difference* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
| MADRS (Total) | 6 | 177 | −10.47 | 0.73 | 91 | −9.93 | 0.95 | −0.54 | (−2.73, 1.65) | 1 | 0.24 | 0.627 |
| | 8 | 177 | −12.38 | 0.80 | 91 | −11.01 | 1.05 | −1.37 | (−3.77, 1.03) | 1 | 1.27 | 0.260 |
| | 12 | 177 | −13.60 | 0.82 | 91 | −12.80 | 1.08 | −0.80 | (−3.28, 1.67) | 1 | 0.42 | 0.520 |
| MADRS (Item 2) | 6 | 177 | −1.30 | 0.10 | 91 | −1.30 | 0.14 | −0.08 | (−0.39, 0.24) | 1 | 0.23 | 0.629 |
| | 8 | 177 | −1.60 | 0.11 | 91 | −1.40 | 0.15 | −0.23 | (−0.56, 0.11) | 1 | 1.79 | 0.182 |
| | 12 | 177 | −1.80 | 0.11 | 91 | −1.70 | 0.15 | −0.10 | (−0.44, 0.23) | 1 | 0.37 | 0.542 |
| BDI | 12 | 174 | −12.50 | 0.82 | 90 | −12.07 | 1.08 | −0.43 | (−2.92, 2.06) | 1 | 0.12 | 0.734 |
| MFQ | 12 | 169 | −16.42 | 1.18 | 88 | −15.68 | 1.54 | −0.74 | (−4.27, 2.80) | 1 | 0.17 | 0.681 |
| CGI-S | 12 | 172 | 2.0[a] | — | 89 | 2.0[a] | — | — | — | 1 | 0.04 | 0.847 |

| | | *Paroxetine n/N* | *Placebo n/N* | *Odds ratio* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
|---|---|---|---|---|---|---|---|---|
| CGI-I responders | 6 | 98/172 (57.0%) | 44/89 (49.4%) | 1.41 | (0.83, 2.39) | 1 | 1.66 | 0.198 |
| | 8 | 105/172 (61.0%) | 49/89 (55.1%) | 1.32 | (0.77, 2.25) | 1 | 1.04 | 0.307 |
| | 12 | 119/172 (69.2%) | 51/89 (57.3%) | 1.74 | (1.01, 2.99) | 1 | 4.01 | 0.045* |

MADRS = Montgomery-Åberg Depression Rating Scale; BDI = Beck Depression Inventory; MFQ = Mood and Feelings Questionnaires; CGI-S = Clinical Global Impression—Severity; LSM = Least Squares Mean; SE = standard error; n = Number of patients with at least 50% reduction in MADRS score at study endpoint; N = Total number of patients in the treatment group at that time.

*Significant at the 5% level.

[a]Median value.

higher in the paroxetine group than for placebo (at week 8, 69.5% versus 38.2%, $p = 0.003$; at week 12, 71.2% versus 47.1%, $p = 0.021$), although this analysis was unadjusted for covariates owing to lack of responders per treatment group (Table 4, Fig. 2). Conversely, in patients less than or equal to 16 years of age, the proportion of MADRS responders was higher for those taking placebo compared to paroxetine (64.9% versus 55.1%), although this difference was not statistically significant. Similarly, for the K-SADS-L depression subscale, the difference from placebo in mean change from baseline in older adolescents was numerically larger in the paroxetine group (Table 5). This pattern was evident at each visit and reached statistical significance at week 8 ($p = 0.019$), although not at week 12 ($p = 0.067$). In the younger adolescents, the mean change from baseline was numerically larger in the placebo group than in the paroxetine group at weeks 6, 8, and 12, although the observed differences were not statistically significant. These results were similar in the OC dataset (data not shown).

A similar pattern in treatment response distinguishing the older from younger adolescents was also observed in a number of secondary efficacy variables. Older adolescent patients treated with paroxetine showed significant improvement on the reported sadness item from the MADRS (adjusted difference from placebo $-0.61$ points, $p = 0.042$; Table 5) and a trend for greater improvement on the total score at week 12 LOCF ($p = 0.098$). In both instances, younger adolescents failed to show an advantage for paroxetine over placebo. Furthermore, although significant in the overall population, the treatment difference in CGI-I responder rate for paroxetine versus placebo in the two age subgroups was significant only in the older adolescent group (at weeks 8 [$p = 0.014$] and 12 [$p = 0.040$] and also nearly at week 6 [$p = 0.053$]; Table 4, Fig. 2).

*Safety and tolerability*

Similar proportions of patients in the paroxetine and placebo groups experienced AEs (65.9% of paroxetine patients versus 59.1% of placebo patients). Nausea (24.2%), headache (18.7%), dizziness (10.4%), somnolence (9.3%), decreased appetite (7.7%), infection (7.7%), and asthenia (6.6%) were the most commonly reported (at least 5%) AEs in the paroxetine group. However, for only one of these AEs was the incidence in the paroxetine group at least twice the incidence for placebo (decreased appetite, 7.7% versus 3.2%). The majority of AEs in both groups was reported within the first 2 weeks of active treatment and considered by investigators to be mild or moderate in severity. For all randomized patients, 11.8% in the paroxetine group withdrew because of AEs compared to 7.1% of patients in the placebo group. Adverse events leading to discontinuation of study medication in more than a single paroxetine patient and at a rate greater than that for placebo were headache (1.1% versus 0%), nausea (3.3% versus 1.1%), vomiting (1.1% versus 0%), agitation (1.6% versus 0%), anxiety (1.1% versus 0%), and somnolence (2.2% versus 1.1%). Four (4) patients on paroxetine and 1 on placebo required a dose reduction owing to an AE.

Few adverse experiences were reported in either group during the down-titration phase of treatment. Nineteen (19) patients in the paroxetine group (14.3%) and 6 patients in the placebo group (8.3%) reported adverse experiences during this phase. There were no specific adverse events emergent upon treatment discontinuation that occurred at an indicence of at least 5% in either treatment group.

Twenty-two (22; 12.1%) patients in the paroxetine group and 6 (6.5%) patients in the placebo group experienced SAEs during the treatment phase. None of the events was fatal. Serious AEs that occurred in more than 1 patient in the paroxetine group and at a greater incidence than in the placebo group were nausea (1.1% versus 0%), agitation (1.6% versus 0%), and depression (1.1% versus 0%).

Mean changes in vital-sign measurements (blood pressure and pulse rate) between baseline and week 12 were small for both treatment groups and of no clinical concern. Similar proportions of patients in the two treatment groups had one or more laboratory values meeting sponsor-defined clinical concern criteria (29.1% for paroxetine and 33.3% for placebo). The most common clinical chemistry parameter meeting these criteria was high alkaline phosphatase

**TABLE 4. PROPORTION OF RESPONDERS ON MADRS AND CGI-I BY AGE SUBGROUP AT WEEKS 6, 8, AND 12**

*Age group ≤16 years*

| *Rating instrument* | *Week* | *Paroxetine* | *Placebo* | *Adjusted odds ratio* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
|---|---|---|---|---|---|---|---|---|
| MADRS | 6 | 43/118 (36.4%) | 22/57 (38.6%) | 0.84 | (0.43, 1.66) | 1 | 0.24 | 0.622 |
| (*n* = 118, 57) | 8 | 56/118 (47.5%) | 32/57 (56.1%) | 0.65 | (0.34, 1.25) | 1 | 1.68 | 0.194 |
| | 12 | 68/118 (55.1%) | 37/57 (64.9%) | 0.61 | (0.31, 1.20) | 1 | 2.05 | 0.153 |
| | *Week* | *Paroxetine* | *Placebo* | *Adjusted odds ratio* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
| CGI-I | 6 | 57/114 (50.0%) | 27/56 (48.2%) | 1.02 | (0.53, 1.97) | 1 | 0.00 | 0.994 |
| (*n* = 114, 56) | 8 | 63/114 (55.3%) | 33/56 (58.9%) | 0.83 | (0.43, 1.60) | 1 | 0.31 | 0.577 |
| | 12 | 74/114 (64.9%) | 32/56 (57.6%) | 1.36 | (0.70, 2.65) | 1 | 0.82 | 0.364 |

*Age group >16 years*

| | *Week* | *Paroxetine* | *Placebo* | *Raw odds ratio*[a] | *95% CI*[a] | *Degrees of freedom* | *Test statistic* | *P value*[a] |
|---|---|---|---|---|---|---|---|---|
| MADRS | 6 | 30/59 (50.9%) | 11/34 (32.4%) | 2.16 | (0.90, 5.22) | 1 | 2.99 | 0.084 |
| (*n* = 59, 34) | 8 | 41/59 (69.5%) | 13/34 (38.2%) | 3.68 | (1.52, 8.93) | 1 | 8.81 | 0.003* |
| | 12 | 42/59 (71.2%) | 16/34 (47.1%) | 2.78 | (1.16, 6.69) | 1 | 5.33 | 0.021* |
| | *Week* | *Paroxetine* | *Placebo* | *Adjusted odds ratio* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
| CGI-I | 6 | 41/58 (70.7%) | 17/33 (51.5%) | 2.48 | (0.99, 6.24) | 1 | 3.74 | 0.053 |
| (*n* = 58, 33) | 8 | 42/58 (72.4%) | 16/33 (48.5%) | 3.49 | (1.29, 9.45) | 1 | 6.05 | 0.014* |
| | 12 | 45/58 (77.6%) | 19/33 (57.6%) | 2.70 | (1.04, 6.97) | 1 | 4.20 | 0.040* |

MADRS = Montgomery-Åsberg Depression Rating Scale; CGI-I = Clinical Global Impression—Improvement.
*Significant at the 5% level.
[a]Indicates that the full model could not be fitted owing to convergence problems caused by lack of responders per treatment group/country group combination. The analysis presented is unadjusted for covariates.

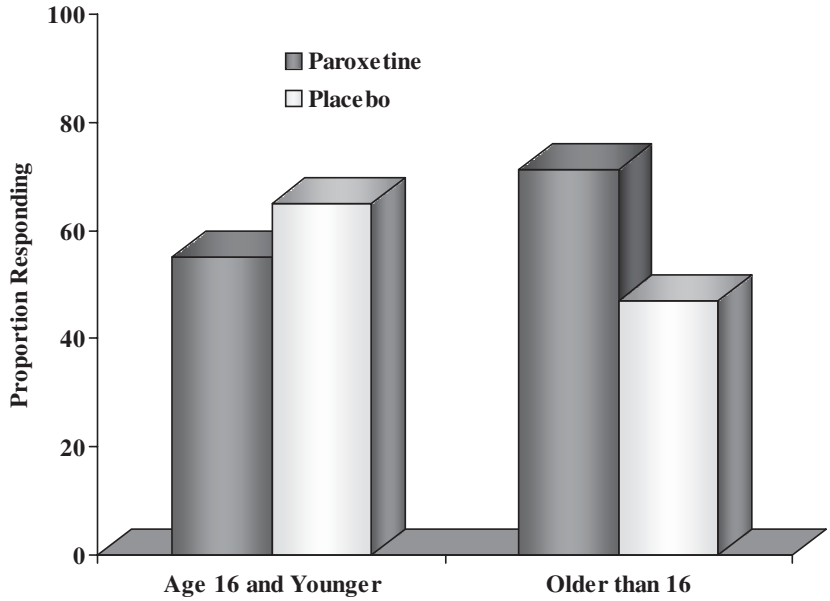


**FIG. 2.** Proportion of patients responding by age group (LOCF analysis). LOCF = last observation carried forward.

levels (at least 390 U/L), occurring in 11 (6.1%) paroxetine patients and 2 (2.2%) in the placebo group. A high eosinophil count (at least 10%) occurred in 9 (5%) and 4 (4.3%) patients in the paroxetine and placebo groups, respectively.

Examination of AEs by age subgroup suggested a pattern of greater differences between paroxetine and placebo-treated patients in older adolescents compared to younger adolescents. For example, although the overall AE incidence in younger adolescents was comparable between treatment groups (63.6% of paroxetine patients versus 59.6% of placebo patients), there was a higher incidence of AEs in paroxetine-treated patients (70.5%) compared to placebo (58.3%) in older adolescents. The incidence of AEs leading to withdrawal in older adolescents treated with paroxetine was also higher compared to placebo (11.5% versus 5.6% respectively), whereas in younger adolescents, the incidence rates were similar between treatment groups (9.9% paroxetine versus 8.8% placebo). As noted above, the overall incidence of SAEs was higher in the paroxetine group compared to placebo; the magnitude of this difference was found to be greater in older adolescents (8.2% paroxetine versus 2.8% placebo) than younger adolescents (8.3% paroxetine versus 5.3% placebo).

*Adverse events related to suicidality*

The incidence of AEs related to suicidality was not statistically different between patients treated with paroxetine compared to placebo when calculated as either incidence or incidence density (Table 6). There were 8 of 181 (4.4%) paroxetine patients (younger adolescents, $n = 4$; older adolescents, $n = 4$) and 2 of 95 (2.1%) placebo patients (younger adolescents, $n = 2$) who experienced a suicide-related AE (OR 2.15, 95% CI 0.45, 10.33; $p = 0.502$). Of the events that involved a suicide attempt, 3 of 181 (1.7%) occurred in paroxetine patients (younger adolescents, $n = 1$; older adolescents, $n = 2$), whereas 2 of 95 (2.1%) were reported in placebo patients (OR 0.78, 95% CI 0.13, 4.77; $p = 1.000$).

## DISCUSSION

No statistically significant differences were observed for paroxetine compared with placebo on either of the two prospectively defined primary efficacy variables in this study. Among the secondary efficacy variables, only the CGI-I responder rate suggested paroxetine to be significantly superior to placebo in the primary population of interest (i.e., total mITT popula-

**TABLE 5. CHANGE FROM BASELINE IN MADRS TOTAL AND K-SADS-L DEPRESSION SUBSCALE SCORES BY AGE GROUP AT WEEKS 6, 8, AND 12**

*Age group ≤16 years*

| | | *Paroxetine* | | | *Placebo* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Week* | *N* | *LSM* | *SE* | *N* | *LSM* | *SE* | *Difference* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
| MADRS (Total) | 6 | 118 | −9.40 | 0.86 | 57 | −10.25 | 1.19 | 0.86 | (−1.89, 3.61) | 1 | 0.38 | 0.539 |
| | 8 | 118 | −11.12 | 0.92 | 57 | −12.41 | 1.27 | 1.29 | (−1.65, 4.22) | 1 | 0.75 | 0.388 |
| | 12 | 118 | −12.58 | 0.95 | 57 | −13.50 | 1.30 | 0.91 | (−2.11, 3.93) | 1 | 0.35 | 0.552 |
| MADRS (Item 2 only) | 6 | 118 | −1.20 | 0.12 | 57 | −1.30 | 0.17 | 0.05 | (−0.35, 0.45) | 1 | 0.06 | 0.813 |
| | 8 | 118 | −1.40 | 0.13 | 57 | −1.50 | 0.18 | 0.13 | (−0.29, 0.54) | 1 | 0.37 | 0.545 |
| | 12 | 118 | −1.60 | 0.13 | 57 | −1.70 | 0.18 | 0.14 | (−0.27, 0.55) | 1 | 0.45 | 0.501 |

| | | *Paroxetine* | | | *Placebo* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Week* | *N* | *LSM* | *SE* | *N* | *LSM* | *SE* | *Difference* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
| K-SADS-L | 6 | 113 | −6.67 | 0.57 | 55 | −7.85 | 0.78 | 1.18 | (−0.62, 2.99) | 1 | 1.68 | 0.197 |
| | 8 | 113 | −7.83 | 0.57 | 55 | −8.88 | 0.78 | 1.05 | (−0.77, 2.87) | 1 | 1.30 | 0.256 |
| | 12 | 113 | −8.42 | 0.61 | 55 | −9.38 | 0.83 | 0.97 | (−0.95, 2.89) | 1 | 0.99 | 0.321 |

*Age group >16 years*

| | | *Paroxetine* | | | *Placebo* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Week* | *N* | *LSM* | *SE* | *N* | *LSM* | *SE* | *Difference* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
| MADRS (Total) | 6 | 59 | −12.50 | 1.60 | 34 | −9.76 | 1.90 | −2.75 | (−6.43, 0.94) | 1 | 2.20 | 0.142 |
| | 8 | 59 | −14.35 | 1.81 | 34 | −8.49 | 2.15 | −5.87 | (−10.05, −1.70) | 1 | 7.82 | 0.006* |
| | 12 | 59 | −15.52 | 1.93 | 34 | −11.79 | 2.28 | −3.73 | (−8.16, 0.71) | 1 | 2.79 | 0.098 |
| MADRS (Item 2) | 6 | 59 | −1.50 | 0.22 | 34 | −1.2 | 0.26 | −0.35 | (−0.86, 0.16) | 1 | 1.87 | 0.175 |
| | 8 | 59 | −1.90 | 0.24 | 34 | −1.0 | 0.28 | −0.91 | (−1.46, −0.36) | 1 | 10.86 | 0.001* |
| | 12 | 59 | −1.90 | 0.25 | 34 | -1.3 | 0.30 | -0.61 | (-1.20, -0.02) | 1 | 4.27 | 0.042* |

| | | *Paroxetine* | | | *Placebo* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Week* | *N* | *LSM* | *SE* | *N* | *LSM* | *SE* | *Difference* | *95% CI* | *Degrees of freedom* | *Test statistic* | *P value* |
| K-SADS-L | 6 | 58 | −9.45 | 1.15 | 33 | −6.86 | 1.35 | −2.59 | (−5.27, 0.09) | 1 | 3.69 | 0.058 |
| | 8 | 58 | −10.13 | 1.17 | 33 | −6.85 | 1.37 | −3.28 | (−6.00, −0.56) | 1 | 5.72 | 0.019* |
| | 12 | 58 | −11.16 | 1.25 | 33 | −8.44 | 1.47 | −2.73 | (−5.64, 0.19) | 1 | 3.44 | 0.067 |

*Significant at the 5% level.

MADRS = Montgomery-Åsberg Depression Rating Scale; K-SADS-L = Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children; LSM = Least Squares Mean; SE = standard error.

**Table 6. Incidence and Incidence Density Rates for Adverse Events Associated with Suicidality**

| *Suicide-related events*[a] | | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Paroxetine* | *Placebo* | *Odds ratio* | *(95% CI)* | *Degrees of freedom* | *Test statistic* | *P value* |
| n/N (%) | 8/181 (4.4%) | 2/95 (2.1%) | 2.15 | (0.45, 10.33) | 1 | 0.45 | 0.502 |
| n/PYE | 8/40 | 2/21 | — | — | 1 | 0.90 | 0.342 |
| *Suicide attempts* | | | | | | | |
| | *Paroxetine* | *Placebo* | *Odds ratio* | *(95% CI)* | *Degrees of freedom* | *Test statistic* | *P value* |
| n/N (%) | 3/181 (1.7%) | 2/95 (2.1%) | 0.78 | (0.13, 4.77) | 1 | 0.00 | 1.000 |
| n/PYE | 3/40 | 2/21 | — | — | 1 | 0.06 | 0.801 |

n = patients with suicidal event; N = overall patient sample; PYE = person year exposure.
[a]Includes suicide threats, suicide gestures, suicide ideation, and suicide attempts.

tion, week 12 LOCF). These findings, though less suggestive of an effect of paroxetine than those from a prior study also examining paroxetine in adolescent depression (Keller et al. 2001), are not inconsistent with the findings for most other antidepressants studied in this population. Moreover, a recent FDA review of efficacy results from 15 trials in pediatric MDD for nine different antidepressants reported an overall success rate of only 20% (3 of 15 trials positive based on primary outcome measures; Laughren 2004).

Although treatment with paroxetine in the present study yielded a 60% response rate on the MADRS, an equally high response rate (~58%) was observed in the placebo group. This pattern (high placebo response matching that seen for paroxetine) was observed for other efficacy parameters as well. Demonstrating statistically and clinically significant differences from placebo in the face of high placebo response rates has been one of the challenges researchers face when studying MDD, especially in pediatric populations. This study did not preclude subjects from receiving nondirective supportive therapy, which has been shown to reduce self-reported depression in 36% of adolescents with major depression (Brent et al. 1997). Therefore, it is possible that at least part of the strong placebo effect may have resulted from supportive psychotherapy.

A statistically significant treatment-by-age interaction was observed for both primary efficacy parameters and most of the secondary parameters, suggesting that depressed patients greater than 16 years did respond to treatment with paroxetine. This pattern of greater efficacy in the older adolescent age group has been observed in pediatric trials of other SSRIs (Wagner et al. 2003; Jonas 2004). It is unclear whether this reflects age-related differences in disease characteristics, response to medication, or a combination of both. These data do, however, argue against combining children and older adolescents in the same study population.

Paroxetine administered over a period of up to 12 weeks and within the dose range of 20–40 mg/day in this study was generally well tolerated. Approximately 11% of paroxetine-treated patients discontinued treatment owing to an AE, a figure that is comparable to that typically seen in adult paroxetine studies.

Interestingly, while the results were suggestive of greater efficacy in patients greater than 16 years of age, this age group also reported more AEs relative to placebo than younger adolescents. The safety of antidepressants in children and adolescents, particularly the issue of possible treatment-emergent suicidality, has been the focus of much attention from manufacturers of antidepressants, the FDA, and regulatory agencies in other countries. Review of the aggregated suicidality data by the FDA Advisory Committee led to the addition of new precautionary language to the label in April 2004 and a finding in September 2004 that 2%–3% more patients on medication may experience an increase in suicidality. As a result, the FDA has required antidepressants to carry "black box" warnings about increased suicidal tendencies (FDA 2004). Additionally, the European Committee for Medicinal Products for Human Use (CHMP) is currently finalizing its language for paroxetine and has also initiated a class referral for SSRIs. Although the results from this specific study do not demonstrate a statistically significant difference between treatments with respect to possibly suicide-related AEs, the incidence of such events by treatment in this study are generally consistent with that reported in the FDA's aggregated dataset (i.e., approximately 4% versus 2% for paroxetine versus placebo, respectively).

Paroxetine is not approved for use by children or adolescents. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior; families and caregivers should be advised of the need for close observation and communication with the prescriber.

### *Limitations*

As noted, this study did not preclude subjects from receiving nondirective supportive therapy, nor attempt to ensure that it was consistently or systematically applied between treatment groups or across study centers. The influence of this lack of standardization on the overall study results is unknown. In addition, although no country-by-treatment group interaction was detected, there was considerable variability in the response patterns observed

within different country groups. Conducting a relatively small study such as this in 10 different countries (on five continents) may have introduced a confounding level of variability. Lastly, the MADRS has not been validated in adolescent patients with MDD. Although it has been shown to be sensitive to assessing change over time in adults, its heavy reliance on cognitive features of major depression may impact the sensitivity with which it assesses depressive symptomatology in younger patients. In this study, the MADRS appeared to be more sensitive in the older adolescent population. Similarly, the K-SADS Depression subscale has not been shown to be sensitive to changes owing to pharmacotherapy.

## CONCLUSIONS

No clinical or statistically significant treatment differences between paroxetine and placebo were detected in either of the two primary efficacy variables in the total population. Among secondary efficacy measures, however, the CGI-I responder rate was found to be statistically greater for paroxetine-treated patients compared to those who had received placebo. Treatment differences were not noted on other secondary efficacy measures. There were treatment-by-age interactions for the primary efficacy variables and most of the secondary efficacy variables, suggesting that older adolescents (i.e., over the age of 16) may respond positively to paroxetine treatment. Paroxetine administered over a period of up to 12 weeks and within the dose range of 20–40 mg/day in this study was generally well tolerated. Further investigations of paroxetine should involve an examination of age and characteristics of major depressive disorder, including duration of depressive episode and treatment history, and how these variables impact treatment efficacy in adolescents with unipolar major depression.

## DISCLOSURES

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