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Paroxetine

29060

A Multi-center, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression–Continuation Phase

Final Clinical Report
329

Addendum to Study Report–Continuation Phase

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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

P. Clarke 31/10/2001
Date

GlaxoSmithKline

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Date 10/31/01

Report Synopsis

Title

A Multi-center, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression–Continuation Phase (29060/329) [Addendum to Acute Phase Report]

Study Dates

The final date on which the last patient took study medication during the continuation phase was 03 September 1997.

Objectives

The primary objective of the acute phase of this study was to compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression.

In this continuation phase, the objectives were as follows:

To provide information on the safety profile of paroxetine and imipramine when these agents are given to adolescents for an extended period of time.

To estimate the rate of relapse among paroxetine, imipramine, and placebo responders who were maintained on treatment.

Study Design

This was a multi-center, double-blind, placebo-controlled, parallel-group trial of the efficacy and safety of treatment with paroxetine or imipramine compared with placebo in adolescents with major depressive disorder. The study included two phases, an acute phase in which patients were treated for 8 weeks and a continuation phase in which responders had the option to continue to receive blinded study medication for an additional six months. At the completion of the 8-week study, patients who met specific criteria for a clinical response could be continued on the same medication in a double-blind manner for a six-month continuation treatment phase; clinic visits were made monthly.

The acute phase has been reported separately. This report on the continuation phase is an addendum to the Acute Phase Report.

Study Population

Patients eligible for the acute phase were adolescents (12 years 0 months through 18 years 11 months inclusive) who were currently in an episode of major depression (DSM-III-R criteria) for at least 8 weeks, and who had a total score ≥12 on the 17-item Hamilton Depression Scale (HAM-D). Patients eligible for the continuation phase were patients judged to be responders, defined as having a final (week 8) HAM-D score that was ≤8, or a decrease in HAM-D score at week 8 that was at least 50% of the baseline score.

Treatment and Administration

Patients took their study medication twice daily, once in the morning and once at night. Total daily doses of paroxetine were 20 mg for dose levels 1 to 4, 30 mg for level 5, and 40 mg for level 6. Total daily doses of imipramine were 50, 100, 150, 200, 250, and 300 mg for dose levels 1 to 6, respectively. At the beginning of the continuation phase, all patients started at the same level at which they completed the acute phase. Doses could be titrated up to dose level 6 at the discretion of the investigator. Titration up or down no more often than once per week was permitted

Evaluation Criteria

Safety Parameters: Adverse events, vital signs and body weight; clinical laboratory evaluations; and electrocardiograms (EKGs).

Efficacy Parameters: The efficacy assessment for estimation of rate of relapse in the trial was the Hamilton Rating Scale for Depression (HAM-D). The percent of patients withdrawing for lack of efficacy was evaluated once at the end of the continuation phase for each patient. Other assessments were the 9-item depression subscale of the Schedule for Affective Disorders and Schizophrenia for School-age Children–Lifetime Version (K-SADS-L), the Clinical Global Improvement (CGI), and the following functional and quality of life assessments: the Self Perception Profile (SPP), the Autonomous Functioning Checklist (AFC), and the Sickness Impact Profile (SIP).

Other Parameters: Blood samples for determination of serum imipramine and desipramine concentrations were taken at the completion of 20 and 32 weeks of treatment.

Patient Disposition and Key Demographic Data

Of the 190 patients who completed the acute phase of the study, 65 patients did not enter the continuation phase. Lack of efficacy was the predominant reason for patients not participating in the continuation phase.

Thirty-five percent of the patients (44/125) who entered the continuation phase completed six additional months of treatment as prescribed by the protocol. The proportions of patients completing the continuation phase were generally comparable in all three treatment groups. In the imipramine group, 20% of the patients withdrew due to adverse events, compared to 12% in the placebo group and 8% in the paroxetine group. The proportions of patients withdrawn for lack of efficacy or lost to follow-up were comparable across treatment groups.

Patient Disposition

	Treatment Group			
	Paroxetine n = 52	**Imipramine n = 40**	**Placebo n = 33**	**Total n = 125**
Withdrawn Before 6 Months	34 (65.4%)	27 (67.5%)	20 (60.6%)	81 (64.8%)
Adverse Events	4 (7.7%)	8 (20.0%)	4 (12.1%)	16 (12.8%)
Lack of Efficacy	7 (13.5%)	6 (15.0%)	6 (18.2%)	19 (15.2%)
Protocol Violation (including non-compliance)	12 (23.1%)	7 (17.5%)	4 (12.1%)	23 (18.4%)
Lost to Follow-up	3 (5.8%)	2 (5.0%)	3 (9.1%)	8 (6.4%)
Other	8 (15.4%)	4 (10.0%)	3 (9.1%)	15 (12.0%)
Completed 6 Months	18 (34.6%)	13 (32.5%)	13 (39.4%)	44 (35.2%)
Mean duration of exposure (days) ± SE	114.3 ± 9.32	110.2 ± 10.25	110.9 ± 13.30	

Safety Results

Extent of Exposure: The mean duration of exposure to study medication in the continuation phase was approximately four months in each of the three treatment groups. In the paroxetine group, 23/93 (24.7%) patients had long-term exposure (>168 days).

Adverse Events: There were no deaths during the trial. Serious adverse events during the continuation phase occurred in nine patients, six in the paroxetine group, two in the imipramine group, and one in the placebo group. One of the paroxetine patients experienced a peptic ulcer hemorrhage, which was considered unrelated to study medication by the investigator. For the remaining patients in the paroxetine group the serious events were psychiatric in nature and included intentional overdose (three patients) and manic reaction (one patient); one patient experienced agitation, fatigue, nausea, drowsiness, and tremor after missing some doses of taper medication. In the imipramine group, one patient developed tricyclic toxicity and another took an intentional overdose. In the placebo group, one patient had homicidal and suicidal ideation.

Four patients (7.7%) in the paroxetine group, eight patients (20.0%) in the imipramine group, and four patients (12.1%) in the placebo group were withdrawn due to an adverse event. Adverse events related to the nervous system and leading to withdrawal occurred in three patients in the paroxetine group (all for adverse events of emotional lability), three patients in the imipramine group (one for emotional lability, one for neurosis, and one for convulsion), and one patient in the placebo group (for emotional lability, hostility, and manic reaction). All other events leading to withdrawal occurred in no more than one patient in any group.

Five adverse events occurred in 5% or more of the patients in the paroxetine group and with a frequency at least twice that of placebo. Three of these events occurred in the Nervous System body system: emotional lability, tremor, and insomnia. In the imipramine group, there were 6 adverse events that occurred in 5% or more of the patients and at least twice that in the placebo group.

Adverse Events Occurring in ≥5% of Any Group and at Least 2X Placebo

Adverse Event	Paroxetine N = 52	Imipramine N = 40	Placebo N = 33
Abdominal Pain	6 (11.5%)	4 (10.0%)	1 (3.0%)
Weight Gain	4 (7.7%)	1 (2.5%)	0 (0.0%)
Emotional Lability	4 (7.7%)	1 (2.5%)	1 (3.0%)
Insomnia	4 (7.7%)	3 (7.5%)	1 (3.0%)
Tremor	3 (5.8%)	0 (0.0%)	0 (0.0%)
Tachycardia	1 (1.9%)	2 (5.0%)	0 (0.0%)
Dry Mouth	1 (1.9%)	3 (7.5%)	0 (0.0%)
Myalgia	1 (1.9%)	3 (7.5%)	0 (0.0%)
Dyspepsia	0 (0.0%)	2 (5.0%)	0 (0.0%)

Vital Signs: Changes in blood pressure and pulse rate were small in the paroxetine and placebo treatment groups. In the imipramine treatment group, however,

substantial increases were seen in the standing pulse rate (mean change of 15.2 bpm from acute baseline to endpoint), and seven patients had a standing pulse rate meeting potential clinical concern criteria (>120 bpm and increase ≥30 bpm from acute baseline). Weight gain of concern (increase ≥7% from acute baseline) was seen in 25% of patients in the paroxetine group, compared to 15% of patients in the imipramine group and 18% of patients in the placebo group.

Laboratory Tests: The number of patients identified with laboratory values meeting the potential clinical concern criteria was low in all treatment groups. None was considered to be clinically significant by the investigator except for one patient in the imipramine group with anemia (low hematocrit).

Other: Two patients in the imipramine group developed tricyclic toxicity during the continuation phase.

Adverse Events in the Continuation Phase Compared to the Acute Phase: The nature of adverse events reported for the paroxetine group in the continuation study was generally similar to that reported in the acute phase. Most of the more common adverse events in the acute phase were seen less frequently during the continuation phase. Weight gain occurred with greater frequency in the continuation phase than in the acute phase.

Efficacy Results

The continuation phase of this study was designed to estimate the rate of relapse in the three treatment groups. The proportion of patients relapsing at any time during the continuation phase, regardless of HAM-D at endpoint, was similar in the imipramine group (38.7%) to the paroxetine group (36.4%), but slightly less (23.1%) in the placebo group. The mean time to relapse in the imipramine group was 61.5 days, compared to approximately 79 days in each of the other treatment groups. The proportion of patients whose HAM-D at endpoint of the continuation phase was >8 and >50% of the acute baseline HAM-D was similar in all treatment groups.

There were no significant differences between paroxetine and placebo or between imipramine and placebo in withdrawals due to lack of efficacy. The continuation phase of this study was not designed to analyze efficacy, as patients were not re-randomized at the end of the acute phase. In addition, only responders were to enter the continuation phase. Nevertheless, trends suggested that patients who

had responded to therapy in the acute phase continued to respond over the six months of the continuation phase, regardless of treatment assignment.

Conclusions

The long-term safety profile of paroxetine in adolescents appears similar to that reported following short-term dosing. In general, the incidence (new onset) of those adverse events identified as occurring in the acute phase at an incidence of at least 5% and at least twice placebo was less in the continuation phase. Weight gain was the only vital sign of concern that occurred with greater frequency in the paroxetine group than in the other treatment groups, and with greater frequency in the continuation phase than in the acute phase. However, with such a small sample size, in the absence of pre- and post-dose body mass index data, the clinical relevance of such findings is difficult to establish in an actively growing and maturing population such as this.

The proportion of patients relapsing at any time during the continuation phase was similar in the paroxetine and imipramine groups and slightly lower in the placebo group. The proportions of patients relapsing at endpoint were similar in all treatment groups. There were no significant differences between paroxetine and placebo or between imipramine and placebo in withdrawals due to lack of efficacy. Trends suggested that patients who had responded to therapy in the acute phase continued to respond over the six months of the continuation phase.

List of Abbreviations and Definitions

AFC	Autonomous Functioning Checklist
ATC	Anatomical Therapeutic Chemical Code
bpm	Beats per minute
CGI–I	Clinical Global Impressions–Improvement
in.	Inches
L	Liter
lbs.	Pounds
mcg	Microgram
mL	Milliliter
mmHg	Millimeters of mercury
ng	Nanogram
OC	Observed case
OTC	Over-the-counter
RBC	Red blood cells
SAE	Serious adverse event

Note: This table includes only those abbreviations that were not provided in the Acute Phase Report.

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1 Introduction

Protocol 29060/329 was a multicenter, double-blind placebo-controlled study of paroxetine and imipramine in adolescents with unipolar major depression. It was conducted in the United States and Canada. The study included two phases: 1) an initial acute phase in which patients were randomized to receive paroxetine, imipramine or placebo for a duration of 8 weeks, and 2) a continuation phase in which patients who completed the acute phase and were judged to have responded to treatment were permitted to continue to receive their initially assigned double-blind study medication for an additional six months in continued double-blind fashion. The objective of the acute phase was to compare the safety and efficacy of paroxetine and imipramine to placebo in treating depression.

The six-month continuation phase had two objectives: 1) to provide information on the safety profile of paroxetine and imipramine when these agents are given to adolescents for an extended period of time, and 2) to estimate the rate of relapse among paroxetine, imipramine, and placebo responders who were maintained on treatment. There was no intent to assess whether paroxetine or imipramine was effective in preventing relapse, and no hypothesis testing was performed. Rather, the intent was to obtain information for additional studies.

The acute portion of the study was initiated in April 1994, with the final patient entered on 15 March 1997. A total of 275 patients entered the acute phase. The data from the acute phase has been analyzed and reported in detail (see SB Document BRL-029060/RSD-100TW9/1, 24 November 1998). This report summarizes the findings from the continuation phase and serves as an addendum to the Acute Phase Report.

In the continuation phase, all comparisons to baseline were made using the acute phase baseline. Baseline values may be found in the Acute Phase Report.

Data tables were prepared separately for the acute and continuation phases of this report. The tables that are specific to this continuation phase are listed at the end of this report. Individual patient listings were compiled after completion of the continuation phase and include patient information for both phases of the study. These appendices may be found at the end of the acute phase report.

2 Objectives

The primary objective of the acute phase of this study was to compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with unipolar major depression.

In this continuation phase, the objectives were as follows:

To provide information on the safety profile of paroxetine and imipramine when these agents are given to adolescents for an extended period of time.

To estimate the rate of relapse among paroxetine, imipramine, and placebo responders who were maintained on treatment.

3 Methodology

3.1 Overview

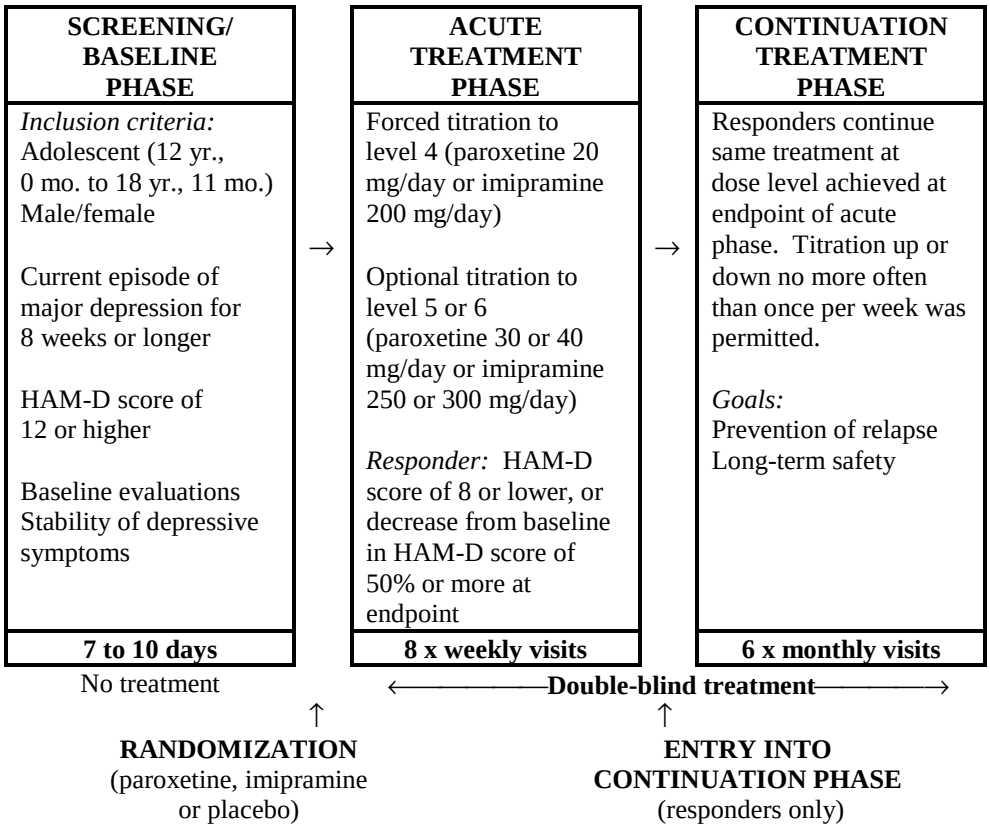
A complete description of the methodology for the study is described in the Acute Phase Report. Briefly, protocol 329 was a multicenter, double-blind parallel-group trial. Eligible for entry into the acute phase of the study were adolescents 12 years 0 months through 18 years 11 months of age who met the DSM-III-R criteria for major depression. Excluded were patients who failed prior antidepressant pharmacological treatment, were suicidal, or had a comorbid psychiatric disorder or other significant medical condition. Eligible patients were randomized to treatment with paroxetine, imipramine or placebo for 8 weeks. During this time, patients made weekly visits to the clinic, and the effects of treatment on depression were evaluated using standardized instruments. At the completion of the 8-week acute phase, patients who met the specific response criteria, defined as having a final (week 8) HAM-D score that was ≤8, or a decrease in HAM-D score at week 8 that was at least 50% of the baseline score (see Section 3.2, Inclusion Criteria: Continuation Phase) had the option of continuing on the same medication in a double-blind manner for an additional 24 weeks. The study medication blind was not to be broken.

Doses could be titrated up to dose level 6 during the continuation phase at the discretion of the investigator, and doses could be decreased in case of severe side effects that appeared to be dose related. The potential range of dosage combined with flexibility in the dosage schedule was designed to ensure an adequate trial of medication for each patient.

In the continuation phase of the study, visits to the clinic were made every four weeks. Efficacy and safety assessments were carried out in a manner similar to that described for the acute phase of the trial. For early terminations a discontinuation taper over a 7- to 17-day period was recommended in a blinded manner. Further treatment of patients who either completed the study or withdrew early was at the discretion of the investigator.

The study design for both phases of the study is illustrated in Figure 1.

Figure 1 Study Design



3.2 Inclusion Criteria: Continuation Phase

Eligible for entry in the continuation phase were patients judged to be responders, defined as having a final (week 8) HAM-D score that was ≤8, or a decrease in HAM-D score at week 8 that was at least 50% of the baseline score. Patients who failed to complete a full 8 weeks of the acute phase were to be denied entry into the continuation phase.

3.3 Study Medication and Administration

The formulation of the study medication used in the continuation phase was identical to that used in the acute phase. A detailed description of the supplies, including strengths and batch numbers, may be found in the Acute Phase Report. Briefly, the medication provided was tablets overencapsulated in Supro B locking capsules that were prepackaged in foil-backed blister cards containing sufficient supply for a 1-week treatment period. Four cards were issued at each visit.

Patients were to enter the continuation phase of the study at the same dose level of blinded study medication at which they completed the acute phase. Table 1 presents the dose levels and corresponding dosages of paroxetine and imipramine.

Table 1 Dosage Schedule

Dose level	Paroxetine	Imipramine
	Daily dose	Daily dose
1	20 mg	50 mg
2	20 mg	100 mg
3	20 mg	150 mg
4	20 mg	200 mg
5	30 mg	250 mg
6	40 mg	300 mg

Source: Appendix A contains the study protocol

If, at any dosage, the patient manifested severe side effects that appeared to be dose related (e.g., anticholinergic effects or drowsiness), the dosage could be decreased to the maximum tolerated dose at that time. If the patient was not responding optimally to the study medication at a given dose level, the dosage could again be increased, up to a maximum of dose level 6 (paroxetine 40 mg/day or imipramine 300 mg/day). Titration was permitted no more frequently than once per week. This potential range of dosage combined with flexibility in the dosage schedule was designed to ensure an adequate trial of medication for each patient.

3.4 Study Procedures

Patients participating in the continuation phase of the trial made visits to the clinic every 4 weeks, for a total of 6 visits. The visits were designated week 12, 16, 20, 24, 28, and 32, respectively, to provide continuity to the visit numbering used in the acute phase (weeks 1–8). Procedures carried out during the continuation phase are as outlined in Table 2 below. A detailed description of each assessment may be found in the Acute Phase Report.

Table 2 Schedule of Assessment–Continuation Phase

Assessments Time (Weeks) *	12	16	20	24	28	32
Adverse Events	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Clinical Laboratory Studies			X			X
Serum Pregnancy Test **				X		
Serum/Plasma Samples for Drug Analyses			X			X
EKG-12 Lead			X			X
EKG Rhythm Strip	X	X		X	X	
Hamilton Depression Scale	X	X	X	X	X	X
CGI–I	X	X	X	X	X	X
Affect Section of K-SADS-L	X	X	X	X	X	X
Full K-SADS-L						X
Supportive Psychotherapy	X	X	X	X	X	X
Study Medication Record	X	X	X	X	X	X
Concomitant Medication Record	X	X	X	X	X	X

Source: Appendix A, Protocol, and Sample Case Report Form (Acute Phase Report)
* Weeks were calculated from Acute Phase baseline.
** On suspicion of pregnancy

3.5 Method of Randomization

The randomization methods are described in the Acute Phase report. The double-blind was maintained for the continuation phase.

3.6 Planned Efficacy Evaluations

No formal hypothesis testing was planned for the continuation phase.

3.6.1 Percent of Patients Who Relapsed

Patients were defined as having relapsed during the continuation phase if they no longer met the acute phase week 8 criteria for response, defined as having a HAM-D score that was ≤8, or a decrease in HAM-D score that was at least 50% of the baseline score. This variable was to be summarized at each visit during the continuation phase and at endpoint.

3.6.2 Percent of Patients Withdrawing for Lack of Efficacy

This variable was evaluated once at the end of the continuation phase for each patient. The number (%) of patients withdrawing for lack of efficacy is summarized for each treatment group.

3.6.3 Statistical Analysis

Although no formal hypothesis tests were planned, the percent of patients who relapsed at endpoint, the percent of patients withdrawing for lack of efficacy, and mean change in scores for all efficacy scales were analyzed using the same statistical methodology as described in the Acute Phase report. Continuous efficacy variables were analyzed by analysis of variance with effects for treatment and investigator. Categorical data were analyzed by logistic analysis, including effects for treatment and investigator. Analysis of the proportion of patients withdrawing due to lack of efficacy was performed using Fisher's Exact test. The results of the statistical analyses are for informational purposes and were not generated for statistical inference.

Efficacy results are presented for each visit (OC) and for the last observation carried forward (LOCF). The last observation carried forward consisted of each patient's last on-therapy assessment during the continuation phase.

3.7 Planned Safety Evaluations

The primary objective of the continuation phase was to provide long-term safety data. Safety evaluations were performed in the same way as described in the Acute Phase report.

4 Study Population

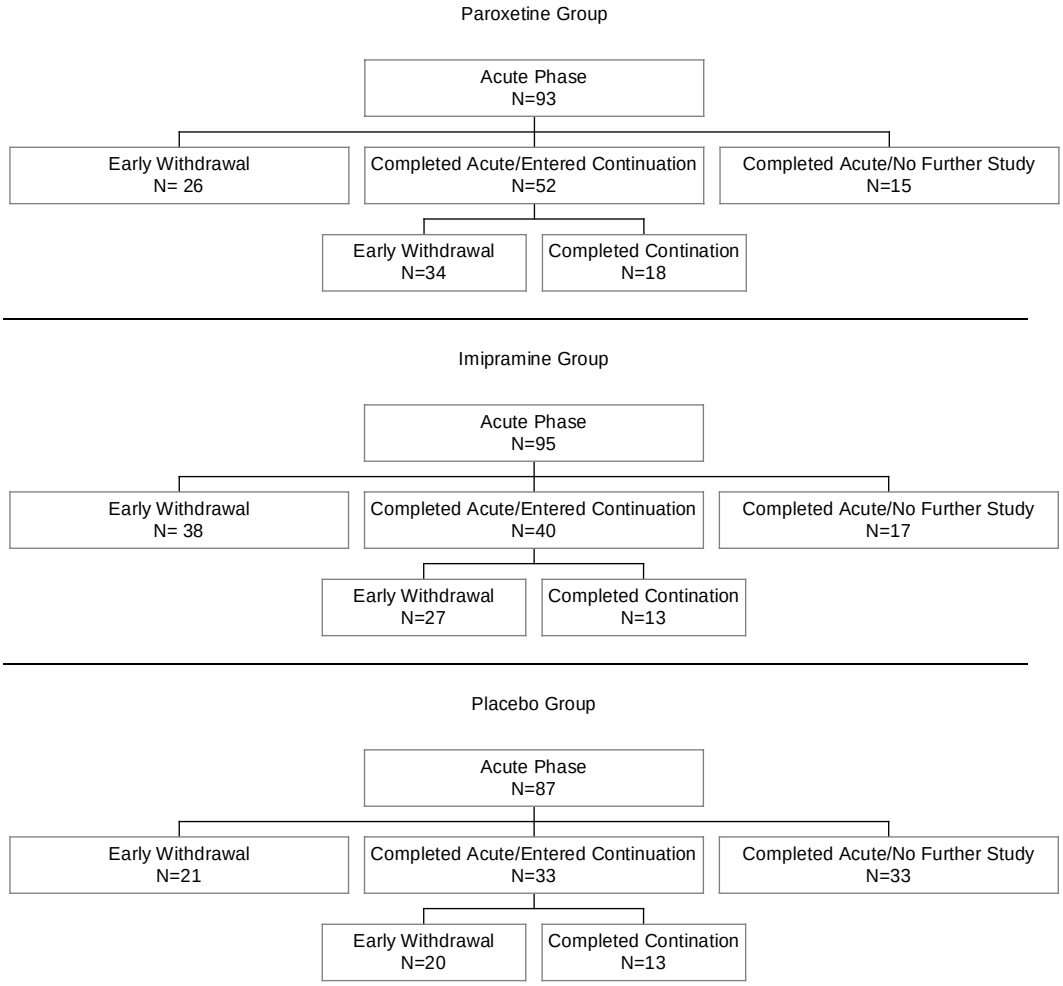
4.1 Entry into the Continuation Phase

The protocol stipulated that a patient was eligible to participate in the continuation phase of the trial if he or she completed 8 weeks of treatment and responded to the treatment. Response was defined as a week-8 HAM-D total score that was less than or equal to 8 or was a decrease of at least 50% from the baseline score. By this definition, 138 (54 paroxetine, 41 imipramine, and 43 placebo) of the 190 patients completing the acute phase of the study were responders and were therefore eligible to enter the continuation phase. However, 77 of these patients did not elect to continue, and therefore 113 of these patients (47 paroxetine, 37 imipramine, and 29 placebo) elected to continue treatment in the continuation phase of the study (Table 12.30 in Section 9).

In addition to the eligible patients who entered the continuation phase, there were 12 patients (five paroxetine, three imipramine, and four placebo) who completed the acute phase but did not meet the HAM-D score response criteria at week 8, but who were permitted by the investigators to participate in the six-month continuation phase. Although entry of these patients is considered a protocol violation, the investigators justified their entry on the basis of global assessment of improvement. Thus 125 patients (52 paroxetine, 40 imipramine and 33 placebo patients) participated in the six-month continuation phase (Table 12.2 in Section 9). The final date on which the last patient took study medication during the continuation phase was 03 September 1997.

The disposition of patients from the time of randomization into the acute phase through the end of the continuation phase is presented in Figure 2.

Figure 2 Disposition of Patients



4.2 Reasons for Not Entering the Continuation Phase

There were 65 patients (15 paroxetine, 17 imipramine and 33 placebo) who completed the 8-week acute phase and did not enter the continuation phase of the study. Table 3 presents the reasons the investigators reported for not entering patients into the continuation phase. Lack of efficacy, as determined by the investigator and not necessarily synonymous with non-response as defined by the protocol, was the predominant reason for patients' not participating in the continuation phase; the proportion was greatest in the placebo group. No patients failed to enter the continuation phase because of being lost to follow-up.

Table 3 Number (%) of Randomized Patients Who Completed the Acute Phase But Did Not Participate in the Continuation Phase, by Reason (ITT Population)

	Treatment Group			
	Paroxetine n = 67	**Imipramine n = 57**	**Placebo n = 66**	**Total n = 190**
Did Not Enter Continuation Phase	15 (22.4 %)	17 (29.8%)	33 (50.0%)	65 (34.2%)
Adverse Event	3 (11.9%)	2 (3.5%)	0 (0.0%)	5 (2.6%)
Lack of Efficacy *	8 (10.4%)	12 (21.1%)	23 (34.8%)	43 (22.6%)
Protocol Violation (including non-compliance)	1 (1.5%)	2 (3.5%)	1 (1.5%)	4 (2.1%)
Other **	3 (4.5%)	1 (1.8%)	9 (13.6%)	13 (6.8%)
Entered Continuation Phase	52 (77.6%)	40 (70.2%)	33 (50.0%)	125 (65.8%)

Source: Data Source Table 12.29 and 12.30 in Section 9; Patient Data Listings in Appendix B.1
* As determined by the investigator
** Other = no study medication available (1 paroxetine, 4 placebo); withdrew consent (1 paroxetine); patient to have surgery (1 paroxetine); ADHD symptoms needed treatment (1 imipramine); patient did not want to continue (2 placebo); patient did not want to be on medication (2 placebo); moving out of state (1 placebo)

There were five patients who completed the acute phase but did not enter the continuation phase because of an adverse event: patients 329.003.00089, 329.009.00201, and 329.009.00324 in the paroxetine group, and patients 329.005.00295 and 329.009.00134 in the imipramine group. The investigators reported that these patients had an adverse event for which the action in regard to study medication was coded "stopped"; however, according to the patients' study records, they completed the full 8 weeks of the acute phase. The adverse event was actually the reason for the patients' not entering the continuation phase (Patient Data Listings in Appendix D.1 and D.3).

4.3 Disposition of Patients in the Continuation Phase

Thirty-five percent of the patients (44/125) who entered the continuation phase completed six additional months of treatment as prescribed by the protocol. There were no substantial differences between the treatment groups with respect to the overall continuation phase completion rates. The number of patients who withdrew and the reasons for withdrawal are listed in Table 4. The proportion of patients who withdrew due to adverse events was 7.7% in the paroxetine group compared to 20.0% in the imipramine group and 12.1% in the placebo group. The proportion of patients withdrawn for lack of efficacy was 13.5% in the paroxetine group compared to 15.0% in the imipramine group and 18.2% in the placebo group.

Table 4 Number (%) of Randomized Patients Who Completed or Were Withdrawn from the Study, by Reason for Withdrawal (ITT Population)

	Treatment Group			
	Paroxetine n = 52	**Imipramine n = 40**	**Placebo n = 33**	**Total n = 125**
Withdrawn Before 6 Months	34 (65.4%)	27 (67.5%)	20 (60.6%)	81 (64.8%)
Adverse Event *	4 (7.7%)	8 (20.0%)	4 (12.1%)	16 (12.8%)
Lack of Efficacy	7 (13.5%)	6 (15.0%)	6 (18.2%)	19 (15.2%)
Protocol Violation (including non-compliance)	12 (23.1%)	7 (17.5%)	4 (12.1%)	23 (18.4%)
Lost to Follow-up	3 (5.8%)	2 (5.0%)	3 (9.1%)	8 (6.4%)
Other **	8 (15.4%)	4 (10.0%)	3 (9.1%)	15 (12.0%)
Completed 6 Months	18 (34.6%)	13 (32.5%)	13 (39.4%)	44 (35.2%)

Source: Data Source Tables 12.2 and 12.3 in Section 9; Patient Data Listings in Appendix B.1 of the Acute Phase Report
* Includes patient 329.009.00194 from the imipramine group and patient 329.009.00169 from the placebo group, who developed nausea and manic reaction, respectively, in the acute phase but were not withdrawn until the continuation phase.
** Other includes 8 patients (or parents) withdrew consent (5 paroxetine, 3 imipramine); 4 believe can improve/have already improved without medication (2 paroxetine, 2 placebo); 1 conflict with studies (paroxetine); 1 wants known therapy (imipramine); and 1 moved from area (placebo).

Withdrawals from study medication for any reason occurred somewhat evenly throughout the study in all treatment groups, except that there were fewer withdrawals at week 28 than at other timepoints (Table 12.4 in Section 9).

4.4 Concomitant Medications

A summary of medications used prior to entry into the acute study is presented in Table 12.11 in Section 10 of the Acute Phase Report. The most common medication used by patients prior to entry was paracetamol.

Table 5 presents concomitant individual medications and medication by ATC classification received by 10% or more of patients in any treatment group during the continuation phase. Similar to the results from the acute phase, paracetamol, ibuprofen, and acetylsalicylic acid were the most commonly taken medications across all three treatment groups. The use of anti-infectives and over-the-counter (OTC) analgesics and cough/cold remedies is not uncommon in an adolescent population. There were no meaningful differences among treatment groups as to concomitant medication use.

Table 5 Concomitant Medications by ATC Classification Received by 10% or More of Patients in Any Treatment Group (number (%) of patients) (ITT Population)

ATC Classification and Concomitant Medication	Treatment Group			Total
	Paroxetine (N = 52)	Imipramine (N = 40)	Placebo (N = 33)	(N = 125)
Any concomitant medication	29 (55.8%)	17 (42.5%)	19 (57.6%)	65 (52.0%)
Alimentary Tract/Metabolic	7 (13.5%)	6 (15.0%)	1 (3.0%)	14 (11.2%)
Anti-infectives, Systemic	12 (23.1%)	2 (5.0%)	8 (24.2%)	22 (17.6%)
Amoxicillin trihydrate	1 (1.9%)	0 (0.0%)	4 (12.1%)	5 (4.0%)
Central Nervous System	17 (32.7%)	11 (27.5%)	10 (30.3%)	38 (30.4%)
Paracetamol	14 (26.9%)	8 (20.0%)	8 (24.2%)	30 (24.0%)
Acetylsalicylic acid	5 (9.6%)	4 (10.0%)	4 (12.1%)	13 (10.4%)
Dermatologicals	7 (13.5%)	3 (7.5%)	2 (6.1%)	12 (9.6%)
Musculo-Skeletal	10 (19.2%)	3 (7.5%)	4 (12.1%)	17 (13.6%)
Ibuprofen	8 (15.4%)	2 (5.0%)	3 (9.1%)	13 (10.4%)
Respiratory	14 (26.9%)	6 (15.0%)	8 (24.2%)	28 (22.4%)

Source: Data Source Table 12.15 in Section 9; Patient Data Listings in Appendix B.13 and B.14 of the Acute Phase Report
Note: Either the medication was started during the continuation phase, or was started prior to randomization or during the acute phase and was continued during the continuation phase.

4.5 Treatment Compliance and Titration

Treatment compliance, defined as taking 80% to 120% of the prescribed study medication over the course of the study, was 78.8% among paroxetine patients during the continuation phase, compared to 82.5% among imipramine patients and 72.7% among placebo patients (Table 12.17 in Section 9).

Data Source Table 12.19 in Section 9 summarizes the dosing information from the continuation phase. Table 12.18 in Section 10 of the Acute Phase Report summarizes the dosing information from the acute phase. Patient details are provided in Patient Data Listings in Appendix B.15 and B.16 of the Acute Phase Report.

For patients in the paroxetine group, the proportion of patients at each dose at the beginning of the continuation phase was similar to that seen at the completion of the acute phase, with paroxetine patients divided somewhat evenly among doses of 20, 30, or 40 mg/day (dose levels 4, 5, and 6). After week 12, a greater proportion of patients took 30 mg/day at each visit than 20 or 40 mg/day; at endpoint, 23/52 patients (44.2%) were taking 30 mg paroxetine per day, compared to 17/52 (32.7%) taking 20 mg and 12/52 (23.1%) taking 40 mg. The mean daily dose at endpoint was 29.0 mg (SD 7.5); this compares to a mean daily dose during the acute phase of 28.0 mg (SD 8.5).

For the imipramine group, the mean dosage during the continuation phase was somewhat higher than at the completion of the acute phase. The mean daily dose of imipramine at endpoint of the continuation phase was 241.3 mg (SD 43.7), compared to 205.8 mg (SD 63.9) at endpoint for the acute phase.

For the placebo patients, the distribution of patients by dose levels at the end of the continuation phase was similar to that observed at the completion of the acute phase.

5 Safety Results

The primary objective of this study was to provide information on the safety profile of paroxetine and imipramine when these agents are given to adolescents for an extended period of time.

Patient listings of adverse events may be found in Appendix D.1 of the Acute Phase report. However, adverse events were tabulated separately for the acute phase and the continuation phase. That is, if a patient had an adverse event during the acute phase and had the same adverse event at the same intensity during the continuation phase, it was counted as occurring in both study phases.

5.1 Extent of Exposure

The exposure of the patients to each dose level of the study medications and the duration of that exposure during the continuation phase are summarized in Table 6. The mean duration of exposure to study medication in the continuation phase was approximately four months in each of the three treatment groups (114 days in the paroxetine group vs. 110 and 111 days in the imipramine and placebo groups, respectively). Exposure to paroxetine in the continuation phase totaled 5,944 patient days.

In both phases combined, the overall duration of exposure to paroxetine was similar to the exposure to imipramine or placebo (Table 16.1.1 in Section 11). Approximately 18% of paroxetine patients had >224 days of exposure, compared to 14% of imipramine patients and 15% of placebo patients. The number of patients in the paroxetine group with long-term exposure (>168 days) was 23/93 (24.7%), compared to 20/95 (21.1%) in the imipramine group and 14/87 (16.1%) in the placebo group.

Table 6 Exposure of Patients to Each Daily Dose of Study Medication and Duration of Exposure (number (%) of patients) (Continuation Phase) (ITT Population)

	Paroxetine (N = 52)			Imipramine (N = 40)			Placebo (N = 33)
	Dose (mg)			Dose (mg)			Dose
Study Medication Exposure	**20**	**30**	**40**	**200**	**250**	**300**	**0**
Total Duration of Exposure (Days)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
1-28	5 (9.6%)	6 (11.5%)	3 (5.8%)	2 (5.0%)	5 (12.5%)	3 (7.5%)	6 (18.2%)
29-56	3 (5.8%)	3 (5.8%)	1 (1.9%)	3 (7.5%)	3 (7.5%)	2 (5.0%)	7 (21.2%)
57-84	3 (5.8%)	3 (5.8%)	4 (7.7%)	3 (7.5%)	1 (2.5%)	1 (2.5%)	4 (12.1%)
85-112	3 (5.8%)	3 (5.8%)	3 (5.8%)	3 (7.5%)	0 (0.0%)	2 (5.0%)	2 (6.1%)
113-140	2 (3.8%)	3 (5.8%)	0 (0.0%)	2 (5.0%)	2 (5.0%)	1 (2.5%)	1 (3.0%)
≥141	5 (9.6%)	6 (11.5%)	5 (9.6%)	7 (17.5%)	0 (0.0%)	5 (12.5%)	13 (39.4%)
Mean ± SE		114.3 ± 9.32			110.2 ± 10.25		110.9 ± 13.30
Median		101			112		98
Range (days)		1–215			1–204		1–222

Source: Data Source Table 16.1 in Section 11; Patient Data Listings in Appendix B.15 and B.16 of the Acute Phase Report
Note: For patients whose dose changed during the course of the study, the number of days at each dose appears in each of the relevant columns.

5.2 Adverse Events

Overall, 85 patients (68.0%) had treatment-emergent adverse events during the continuation phase: 37 patients (71.2%) in the paroxetine group, 27 patients (67.5%) in the imipramine group, and 21 patients (63.6%) in the placebo group. Events occurring during the continuation phase were tabulated even if the patient had the same event at the same intensity during the acute phase.

The most commonly occurring non-gender specific emergent adverse events (i.e., those occurring in at least 5% of patients in any group) are shown in Table 7, presented by body system and preferred term. A display of all events may be found in Table 16.2.1 in Section 11. An analysis of gender-specific events shows no meaningful findings among treatment groups (Tables 16.2.2 [males] and 16.2.3 [females] in Section 11).

Table 7 Number (%) of Patients with Treatment-emergent Adverse Events Most Frequently Reported (≥5% in Any Treatment Group), by Body System and Preferred Term (ITT Population)

Adverse Event		Paroxetine N = 52	Imipramine N = 40	Placebo N = 33
Patients with Adverse Events		37 (71.2%)	27 (67.5%)	21 (63.6%)
Body System	**Preferred Term**			
Body as a Whole	Abdominal Pain	6 (11.5%)	4 (10.0%)	1 (3.0%)
	Asthenia	2 (3.8%)	2 (5.0%)	1 (3.0%)
	Back Pain	0 (0.0%)	0 (0.0%)	2 (6.1%)
	Headache	14 (26.9%)	7 (17.5%)	6 (18.2%)
	Infection	5 (9.6%)	1 (2.5%)	4 (12.1%)
	Trauma	2 (3.8%)	0 (0.0%)	5 (15.2%)
Cardiovascular System	Tachycardia	1 (1.9%)	2 (5.0%)	0 (0.0%)
Digestive System	Diarrhea	0 (0.0%)	3 (7.5%)	3 (9.1%)
	Dry Mouth	1 (1.9%)	3 (7.5%)	0 (0.0%)
	Dyspepsia	0 (0.0%)	2 (5.0%)	0 (0.0%)
	Nausea	9 (17.3%)	3 (7.5%)	3 (9.1%)
	Tooth Disorder	0 (0.0%)	1 (2.5%)	2 (6.1%)
	Vomiting	4 (7.7%)	2 (5.0%)	3 (9.1%)
Hemic and Lymphatic System	WBC Abnormality	0 (0.0%)	0 (0.0%)	2 (6.1%)
Metabolic and Nutritional Disorders	Weight Gain	4 (7.7%)	1 (2.5%)	0 (0.0%)
Musculoskeletal System	Myalgia	1 (1.9%)	3 (7.5%)	0 (0.0%)
Nervous System	Dizziness	9 (17.3%)	3 (7.5%)	4 (12.1%)
	Emotional Lability	4 (7.7%)	1 (2.5%)	1 (3.0%)
	Insomnia	4 (7.7%)	3 (7.5%)	1 (3.0%)
	Tremor	3 (5.8%)	0 (0.0%)	0 (0.0%)
Respiratory System	Pharyngitis	6 (11.5%)	0 (0.0%)	3 (9.1%)
	Respiratory disorder	6 (11.5%)	3 (7.5%)	2 (6.1%)
	Rhinitis	3 (5.8%)	1 (2.5%)	1 (3.0%)
	Sinusitis	1 (1.9%)	1 (2.5%)	3 (9.1%)
Skin and Appendages	Rash	0 (0.0%)	0 (0.0%)	2 (6.1%)
Special Senses	Otitis Media	1 (1.9%)	0 (0.0%)	2 (6.1%)

Source: Data Source Table 16.2.1 in Section 11; Patient Data Listings in Appendix D.1 and D.2 of the Acute Phase Report.

Five adverse events in the paroxetine group and six adverse events in the imipramine group occurred in at least 5% of the patients and with a frequency at least twice that of placebo (Table 8). These events were predominantly associated with gastrointestinal complaints and with the nervous system.

Table 8 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X Placebo (ITT Population)

Adverse Event		Paroxetine N = 52	Imipramine N = 40	Placebo N = 33
Patients with Adverse Events		37 (71.2%)	27 (67.5%)	21 (63.6%)
Body System	**Preferred Term**			
Body as a whole	Abdominal Pain	6 (11.5%)	4 (10.0%)	1 (3.0%)
Cardiovascular system	Tachycardia	1 (1.9%)	2 (5.0%)	0 (0.0%)
Digestive system	Dry Mouth	1 (1.9%)	3 (7.5%)	0 (0.0%)
	Dyspepsia	0 (0.0%)	2 (5.0%)	0 (0.0%)
Metabolic and Nutritional Disorders	Weight Gain	4 (7.7%)	1 (2.5%)	0 (0.0%)
Musculoskeletal system	Myalgia	1 (1.9%)	3 (7.5%)	0 (0.0%)
Nervous system	Emotional Lability	4 (7.7%)	1 (2.5%)	1 (3.0%)
	Insomnia	4 (7.7%)	3 (7.5%)	1 (3.0%)
	Tremor	3 (5.8%)	0 (0.0%)	0 (0.0%)

Source: Data Source Table 16.2.1 in Section 11; Patient Data Listings in Appendix D.1 and D.2 of the Acute Phase Report

Treatment-emergent adverse events are presented by age group (age <15, age ≥15) for all patients and by gender in Tables 16.10.1, 16.10.2, and 16.10.3 in Section 11. There were no meaningful differences in the incidence of treatment-emergent adverse events between age groups or among treatment groups; however, due to the small number of patients aged less than 15 years (n = 18 in the paroxetine group, 15 in the imipramine group and 15 in the placebo group), meaningful comparisons are difficult to make. No meaningful differences were seen in gender-specific adverse events between the two age groups.

Treatment-emergent adverse events are presented by maximum intensity for all patients and by gender in Tables 16.3.1, 16.3.2, and 16.3.3 in Section 11. The severe non-gender specific adverse events that were experienced by ≥5% of patients in any treatment group were headache (9.6% in the paroxetine group, 5.0% in the imipramine group, and 6.1% in the placebo group) and tooth disorder (6.1% in the placebo group and none in the other treatment groups). One female in the paroxetine group and two in the placebo group experienced severe dysmenorrhea. There were no severe male-specific adverse events.

Treatment-emergent adverse events are presented by time of first occurrence for all patients and by gender in Tables 16.4.1, 16.4.2, and 16.4.3 in Section 11. Table 9 shows the time to first occurrence for the five most common events overall by treatment group. The incidence of each event is expressed as a

percentage of the overall number of patients remaining at that timepoint in each group with the event.

In the acute phase of the study, in general, the most commonly reported events occurred during the first week of treatment. No pattern was evident in the continuation phase of the study, as, in general, the most commonly reported adverse events appeared to occur with similar frequency throughout the study.

Table 9 Number (%) of Patients with the Five Most Frequently Reported Treatment-emergent Adverse Events by the Time of First Occurrence During the Continuation Phase (ITT Population)

Adverse Event	Time of First Occurrence							No. of Patients with Event **
	Day 56-71	Day 72-99	Day 100-127	Day 128-155	Day 156-183	Day 184-211	>Day 211	
Paroxetine group								
Patients Who Received Study Medication *	67	52	41	37	28	21	18	37/52 (71.2%)
Headache	3 (4.5%)	7 (13.5%)	1 (2.4%)	0 (0.0%)	1 (3.6%)	2 (9.5%)	0 (0.0%)	14/52 (26.9%)
Nausea	0 (0.0%)	3 (5.8%)	2 (4.9%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	3 (16.7%)	9/52 (17.3%)
Dizziness	0 (0.0%)	4 (7.7%)	1 (2.4%)	2 (5.4%)	1 (3.6%)	0 (0.0%)	1 (5.6%)	9/52 (17.3%)
Abdominal Pain	1 (1.5%)	0 (0.0%)	2 (4.9%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	6/52 (11.5%)
Respiratory Disorder	0 (0.0%)	3 (5.8%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	1 (4.8%)	1 (5.6%)	6/52 (11.5%)
Imipramine group								
Patients Who Received Study Medication *	56	44	32	28	21	15	13	27/40 (67.5%)
Headache	1 (1.8%)	3 (6.8%)	0 (0.0%)	2 (7.1%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	7/40 (17.5%)
Abdominal Pain	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	1 (6.7%)	1 (7.7%)	4/40 (10.0%)
Nausea	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (7.7%)	3/40 (7.5%)
Dizziness	0 (0.0%)	0 (0.0%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	3/40 (7.5%)
Respiratory Disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.1%)	1 (4.8%)	0 (0.0%)	0 (0.0%)	3/40 (7.5%)
Placebo group								
Patients Who Received Study Medication *	66	41	26	19	16	14	13	21/33 (63.6%)
Headache	0 (0.0%)	3 (7.3%)	1 (3.8%)	0 (0.0%)	1 (6.3%)	1 (7.1%)	0 (0.0%)	6/33 (18.2%)
Nausea	1 (1.5%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	3/33 (9.1%)
Dizziness	0 (0.0%)	1 (2.4%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (7.7%)	4/33 (12.1%)
Abdominal Pain	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1/33 (3.0%)
Respiratory Disorder	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	1 (7.1%)	0 (0.0%)	2/33 (6.1%)

Source: Data Source Table 16.4.1 in Section 11; Patient Data Listings in Appendix D.1 and D.2 of the Acute Phase Report

* These n's include patients who were still taking study medication during the acute phase but who did not necessarily enter the continuation phase.

** The number of patients with event includes only patients in the continuation phase. The denominators represent the total N in the continuation phase for each treatment group.

Treatment-emergent adverse events leading to dose reduction are presented for all patients and by gender in Tables 16.5.1, 16.5.2 and 16.5.3 in Section 11. Three patients in the paroxetine group (two with multiple events) and two in the imipramine group (one with multiple events) had dose reductions due to adverse events. Only insomnia led to a dose reduction in more than one patient (2/52 patients, 3.8%, in the paroxetine group). The other events were headache, hypertension, hyperkinesia, and agitation in the paroxetine group and abdominal pain, gastrointestinal disorder and nausea in the imipramine group. There were no gender-specific adverse events leading to dose reduction.

Treatment-emergent adverse events requiring corrective therapy are presented for all patients and by gender in Tables 16.6.1, 16.6.2 and 16.6.3 in Section 11. The most common non-gender specific adverse event requiring corrective therapy across all treatment groups was headache (23.1% in the paroxetine group, 15.0% in the imipramine group, and 9.1% in the placebo group); treatment consisted primarily of paracetamol or other OTC analgesics. Other adverse events requiring corrective therapy in more than 10% of patients in any treatment group were respiratory disorder (11.5%, 7.5%, and 6.1% in the three treatment groups, respectively), with treatment consisting primarily of OTC cold preparations, and infection (3.8%, 2.5%, and 12.1% in the three treatment groups, respectively), with treatment consisting primarily of anti-infectives. One gender-specific adverse event, dysmenorrhea, required corrective therapy (9.1% of females in the paroxetine group and 8.7% of females in the placebo group); treatment consisted primarily of OTC analgesics.

5.3 Deaths

No deaths were reported to the sponsor during the course of the study or at any time since the last dose of study medication (Table 16.7 in Section 11).

5.4 Serious Non-Fatal Adverse Events

Serious adverse events (SAEs) were defined as any event that was fatal, life-threatening, disabling or incapacitating, or resulted in hospitalization, prolonged a hospital stay, or was associated with congenital abnormality, cancer or overdose (whether 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 be associated with the use of the drug was reported as a serious adverse event.

Table 10 shows the number of patients in each treatment group with serious non-fatal adverse events during the continuation phase. Nine patients in the intent-to-treat population, 6/52 (11.5%) in the paroxetine group, 2/40 (5.0%) in the imipramine group, and 1/33 (3.0%) in the placebo group, had a total of 14 serious adverse events. All but two of the patients with serious adverse events were females, as were all the patients in the paroxetine group. Individual SAE narratives for patients listed in Table 10 are provided in Table 16.8.1 in Section 11.

Emotional lability:

Emotional lability that was considered serious occurred in three patients in the paroxetine group and one each in the imipramine and placebo groups. In all cases except the placebo patient, the verbatim term was intentional overdose; the placebo patient had suicide ideation along with hostility (homicidal ideation). All were hospitalized and withdrawn from the study. All events were considered unrelated or probably unrelated to the study medication by the investigator.

In the paroxetine group, patients 329.002.00058, 329.003.00250, and 329.005.00011, all females age 15 or 16, intentionally overdosed with Tylenol (80 tablets), study medication (20 capsules; unknown how many were 10 mg, 20 mg, or placebo), or Bayer extra strength aspirin (approximately 20 tablets), respectively. For patient 329.003.00250, no information was available in regard to precipitating events. However, since the event was asymptomatic, it appears that she self-reported the overdose. This patient had overdosed with study medication in the acute phase as well, but it was not clear whether that overdose was intentional or was accidental overcompliance. For patient 329.002.00058, the overdose followed an argument with her boyfriend, and was also asymptomatic. For patient 329.005.00011, the overdose followed an argument with her mother; she took the overdose in a way that assured that it would be discovered at once.

In the imipramine group, patient 329.012.00221, a 17-year-old male, intentionally overdosed on his father's lorazepam (8 mg oral medication). It is not clear whether he reported the overdose himself, as he was symptomatic (ataxia and drowsiness) when he arrived at the emergency room. However, the patient later stated that the act was impulsive and that he did not intend to die.

In the placebo group, patient 329.002.00241, a 15-year-old male, experienced suicidal and homicidal ideation. There is no evidence that the patient made a suicidal gesture. However, the mother reported finding metal pipes and knives in the patient's room prior to admission.

Other serious adverse events:

Two other patients in the paroxetine group experienced serious adverse events that were psychiatric in nature. Patient 329.004.00017, a 16-year-old female, was hospitalized after her mother expressed concern about hypomania. No hypomanic symptoms were observed during the 3 days she spent in the hospital, and the event was considered by the investigator to be unrelated to study medication. Patient 329.009.00170, a 14-year-old female, completed the study but experienced agitation, fatigue, nausea, drowsiness, and shaky tremors after missing some doses of taper medication. The physician said the patient had an excellent response to therapy after eight months on study medication but experienced "severe withdrawal symptoms." She was restarted on paroxetine by her physician. All events were considered related or possibly related to study medication. The investigator considered the event serious because it involved significant disability or incapacity

Patient 329.005.00109, a 17-year-old female with a past history of bleeding ulcer, experienced a bleeding ulcer on study medication (paroxetine) and was withdrawn from the study. The event was considered unrelated to study medication.

The other serious adverse event in the imipramine group was tricyclic toxicity in patient 329.008.00273, a 12-year-old female, for which she was hospitalized. The patient had near syncope, hypotension and cerebellar findings during the initial exam in the emergency room, and reportedly had electrocardiogram abnormalities, including QRS widening and increased QTC interval. The event was considered serious. There was no evidence that the patient had taken an overdose, intentional or accidental.

Table 10 Serious Non-Fatal Adverse Events (ITT Population)

Patient number	Age/ Gender	Daily Dose *	Adverse Event (Preferred Term)	Adverse Event Verbatim Term	Investigator relationship	Outcome	Comments
Paroxetine Group							
329.002.00058	16 / F	40 mg	Emotional lability	Intentional overdose	Probably unrelated	Resolved	Hospitalized, Withdrawn
329.003.00250	15 / F	30 mg	Emotional lability	Intentional overdose	Unrelated	Resolved	Hospitalized, Withdrawn
329.004.00017	16 / F	30 mg	Manic Reaction	Rule out hypomania	Unrelated	Resolved	Hospitalized
329.005.00011	17 / F	30 mg	Emotional lability	Intentional overdose	Unrelated	Resolved	Hospitalized, Withdrawn
329.005.00109	17 / F	20 mg	Peptic ulcer hemorrhage	Bleeding ulcer	Unrelated	Resolved	Hospitalized, medication stopped for 3 days
329.009.00170	14 / F	20 mg	Asthenia	Fatigue	Possibly related	Resolved	Events began after patient missed taper dose **
		20 mg	Nausea	Nausea	Related	Resolved	
		20 mg	Somnolence	Drowsy	Possibly related	Resolved	
		20 mg	Tremor	Shaky Tremors	Possibly related	Resolved	
		20 mg	Agitation	Agitation	Possibly related	Resolved	
Imipramine Group							
329.008.00273	12 / F	300 mg	Accidental overdose	Tricyclic toxicity	Related	Resolved	Hospitalized, Withdrawn
329.012.00221	17 / M	200 mg	Emotional lability	Intentional overdose	Unrelated	Resolved	ER Visit, Withdrawn
Placebo Group							
329.002.00241	15 / M	0	Emotional lability	Suicidal ideation	Probably unrelated	Not stated	Hospitalized, Withdrawn
			Hostility	Homicidal ideation	Probably unrelated	Not stated	

Source: Data Source Table 16.8 in Section 11; Patient Data Listings in Appendix B1, D1 and D2 of the Acute Phase Report

* Dose at onset of adverse event

** Serious adverse events for patient 329.009.00170 occurred on day 234 except for agitation, which occurred on day 246.

5.5 Withdrawals for Adverse Events

Of the 125 patients who entered the continuation phase, 16 (12.8%) were withdrawn due to an adverse event: four patients (7.7%) in the paroxetine group, eight patients (20.0%) in the imipramine group, and four patients (12.1%) in the placebo group. Adverse events related to the nervous system and leading to withdrawal occurred in three patients in the paroxetine group (all for adverse events of emotional lability), three patients in the imipramine group (one for emotional lability, one for neurosis, and one for convulsion), and one patient in the placebo group (for emotional lability, hostility, and manic reaction). All other events leading to withdrawal occurred in no more than one patient in any group or body system, with the exception of three events in the Body as a Whole category in the imipramine group, in which adverse events of abnormal laboratory value (toxic imipramine level), accidental overdose, and asthenia each led to the withdrawal of a single patient (three total) from the study.

The events leading to withdrawal are provided in Table 11.

Table 11 Treatment-emergent Adverse Events, Regardless of Attribution, Leading to Withdrawal (number (%) of patients (ITT Population)

Body system* Preferred term	Paroxetine (N = 52)	Imipramine (N = 40)	Placebo (N = 33)
Total Number of Patients	**4 (7.7%)**	**8 (20.0%)**	**4 (12.1%)**
Body as a whole	0 (0.0%)	3 (7.5%)	1 (3.0%)
Abnormal Laboratory value	0 (0.0%)	1 (2.5%)	0 (0.0%)
Accidental Overdose	0 (0.0%)	1 (2.5%)	0 (0.0%)
Asthenia	0 (0.0%)	1 (2.5%)	0 (0.0%)
Infection	0 (0.0%)	0 (0.0%)	1 (3.0%)
Digestive System	0 (0.0%)	1 (2.5%)	0 (0.0%)
Nausea	0 (0.0%)	1 (2.5%) *	0 (0.0%)
Metabolic and Nutritional Disorders	0 (0.0%)	1 (2.5%)	0 (0.0%)
Dehydration	0 (0.0%)	1 (2.5%)	0 (0.0%)
Nervous System	3 (5.8%)	3 (7.5%)	1 (3.0%)
Convulsion	0 (0.0%)	1 (2.5%)	0 (0.0%)
Emotional Lability	3 (5.8%)	1 (2.5%)	1 (3.0%)
Hostility	0 (0.0%)	0 (0.0%)	1 (3.0%)
Manic Reaction	0 (0.0%)	0 (0.0%)	1 (3.0%) *
Neurosis	0 (0.0%)	1 (2.5%)	0 (0.0%)
Respiratory System	0 (0.0%)	0 (0.0%)	1 (3.0%)
Sinusitis	0 (0.0%)	0 (0.0%)	1 (3.0%)
Skin and Appendages	1 (1.9%)	0 (0.0%)	0 (0.0%)
Contact Dermatitis	1 (1.9%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	1 (2.5%) *	0 (0.0%)
Urogenital System	0 (0.0%)	1 (2.5%)	0 (0.0%)
Unintended Pregnancy	0 (0.0%)	1 (5.6%) **	0 (0.0%)

Source: Data Source Tables 16.9.1 and 16.9.3 in Section 11; Patient Data Listings in Appendix D.1, D.2, and D.3
* These 3 adverse events started during the acute phase and do not appear in the Data Source Tables.
** Percentage adjusted for gender

Table 12 lists individual patients who were withdrawn and the reason for withdrawal.

Table 12 Adverse Events Leading to Withdrawal in Continuation Phase (ITT Population)

Patient Number	Age/ Gender	Daily Dose *	Day of Onset **	Adverse Event Preferred term (Verbatim term)	Duration	Investigator relationship
				Paroxetine		
329.002.00058	16 / F	40 mg	122, 64	Emotional lability (intentional overdose) †	1 day	Probably unrelated
329.003.00250	15 / F	30 mg	75, 18	Emotional lability (intentional overdose) †	1 hour	Unrelated
329.005.00011	16 / F	30 mg	156, 100	Emotional lability (intentional overdose) †	1 day	Unrelated
329.005.00116	16 / F	30 mg	131, 73	Contact dermatitis (poison ivy)	26 days	Unrelated
				Imipramine		
329.002.00057	15 / F	300 mg	94, 37	Unintended pregnancy (pregnancy)	Not stated	Unrelated
329.005.00006	17 / M	300 mg	116, 56	Neurosis (obsessive thoughts)	Not stated	Probably unrelated
329.005.00007	15 / F	250 mg	197, 134	Convulsion (seizure)	5 minutes	Unrelated
		250 mg	191, 128	Dehydration (dehydration)	8 days	Probably unrelated
		50 mg	2, -62	Rash (rash bilateral forearms) ††	5 days	Probably unrelated
329.008.00273	12 / F	300 mg	116, 53	Accidental overdose (tricyclic toxicity) †	8 days	Related
329.009.00194	12 / M	200 mg	43, -14	Nausea (nausea) ††	153 days	Possibly related
329.010.00281	13 / M	300 mg	152, 91	Asthenia (fatigue)	30 days	Possibly related
329.011.00208	13 / M	300 mg	63, 4	Abnormal laboratory value (toxic imipramine level)††	Not stated	Related
329.012.00221	17 / M	200 mg	132, 69	Emotional lability (intentional overdose) †	19:30 hours	Unrelated
				Placebo		
329.002.00241	15 / M	0	108, 52	Emotional lability (suicidal ideation) †	Not stated	Probably unrelated
		0	108, 52	Hostility (homicidal ideation) †	Not stated	Probably unrelated
329.005.00012	14 / F	0	165, 106	Infection (toxoplasmosis [eye])	Not stated	Unrelated
329.005.00111	16 / F	0	97, 41	Sinusitis (sinus infection)	Not stated	Unrelated
329.009.00169	13 / M	0	64, -2	Manic reaction (hypomania) ††	Not stated	Related

Source: Data Source Tables 16.9.1 and 16.9.3 in Section 11; Patient Data Listings in Appendix B.1, D.1, D.2, and D.3

* Dose at onset of event

** Days relative to start of acute phase, days relative to start of continuation phase

† Serious adverse event

†† Onset occurred in acute phase

Brief descriptions of the adverse events leading to withdrawal are provided below. Detailed individual patient narratives for all patients listed in Table 12 are provided in Table 16.9.4 in Section 11, unless discussed in a narrative for a serious adverse event. The location of the patient narratives may be found in Table 16.0 in Section 11.

As noted above, five patients, three in the paroxetine group and one each in the imipramine and placebo groups, were withdrawn from the study due to adverse events of emotional lability. All five events were considered serious and are discussed in Section 5.4, Serious Non-Fatal Adverse Events. Narratives for these patients are provided in Table 16.8.1 in Section 11.

In the paroxetine group, the other patient who withdrew due to an adverse event was patient 329.005.00116, a 16-year-old Caucasian female who developed contact dermatitis (poison ivy) on day 131 of the study. The event lasted 26 days and the patient was withdrawn from the study. The investigator considered the event to be severe in intensity and unrelated to the study medication.

In the imipramine group, two patients were withdrawn due to toxicity; at the time of the events, each patient was receiving 300 mg imipramine per day. Patient 329.008.00273 developed severe tricyclic toxicity and was hospitalized. The event was considered serious and is discussed in Section 5.4, Serious Non-Fatal Adverse Events. Patient 329.011.00208, a 13-year-old Caucasian male, was found to have a toxic imipramine level (592 ng/mL) on day 63 of the study. No symptoms were reported. The investigator considered this event to be mild in intensity and related to the study medication.

Two patients in the imipramine group had adverse events leading to withdrawal that were considered possibly related to study medication. Patient 329.009.00194, a 12-year-old Caucasian male, developed moderately severe nausea on day 43 of the acute phase. On day 184 of the study (continuation phase), the patient was still experiencing nausea and was withdrawn for this event. The patient was taking 200 mg of imipramine per day. Patient 329.010.00281, 13-year-old Caucasian male, developed severe asthenia (fatigue) on day 152 of the study. The patient was taking 300 mg of imipramine per day.

The three other adverse events leading to withdrawal in the imipramine group were considered unrelated or probably unrelated to study medication. Patient 329.005.00006, a 17-year-old Caucasian male, developed moderately severe neurosis (obsessive thoughts) on day 116 of the study. Adverse events leading to withdrawal in the other patients in the imipramine group were not psychiatric in

nature. Patient 329.005.00007, a 15-year-old Caucasian female, developed severe dehydration on day 191 and had a severe convulsion (seizure) on day 197; the patient was taking 250 mg of imipramine per day. An additional reason given for withdrawal was a moderately severe bilateral rash on the forearms that occurred on day 2 of the acute phase and lasted 5 days. Patient 329.002.00057, a 15-year-old Caucasian female, was withdrawn from the study on day 94 after it was determined that she was pregnant. The patient was taking 300 mg of imipramine per day. No follow-up information is available. This patient was the only patient to withdraw due to a gender-specific adverse event (Tables 16.9.2 and 16.9.3 in Section 11)

One patient in the placebo group had a psychiatric adverse event leading to withdrawal that was considered related to study medication. Patient 329.009.00169, a 13-year-old Hispanic male, developed a severe manic reaction (hypomania) on day 64 of the study. The event was considered by the investigator to be non-serious; the outcome of the event is not stated. The other two placebo patients with adverse events leading to withdrawal had events that were considered unrelated to study medication. Patient 329.005.00012, a 14-year-old Caucasian female, developed a moderately severe eye infection (toxoplasmosis) on day 165 of the study; the patient had a history of the same infection. Patient 329.005.00111, a 16-year-old Caucasian female, developed severe sinusitis (sinus infection) on day 97.

5.6 Vital Signs and Body Weight

5.6.1 Mean Values and Changes in Value

Vital signs were evaluated at every visit. Table 13 presents the group mean values for acute phase baseline, continuation phase endpoint, and change from acute phase baseline to continuation phase endpoint values for the systolic and diastolic blood pressure, pulse rate, and body weight.

The mean changes in vital signs and body weight in the paroxetine group were small and comparable to placebo, and do not appear to be of clinical consequence.

In the imipramine group, the mean pulse rate increased by over 14 beats/min. for measures taken sitting and standing. Sitting systolic and diastolic blood pressures also increased by a mean of 1.4 and 2.2 mm Hg respectively, compared to small decreases in the paroxetine and placebo groups.

Table 13 Vital Signs and Body Weight at Baseline and Endpoint (mean ± SD) (ITT Population)

Vital sign parameter	Treatment Group					
	n	Paroxetine	n	Imipramine	n	Placebo
Sitting systolic BP (mmHg)						
Baseline	49	111.1 ± 12.93	36	113.1 ± 15.75	31	107.2 ± 14.25
Endpoint	49	110.8 ± 13.82	36	114.5 ± 14.96	31	105.0 ± 12.23
Change	49	-0.3 ± 14.62	36	1.4 ± 17.93	31	-2.2 ± 13.28
Sitting diastolic BP (mmHg)						
Baseline	49	68.9 ± 7.64	36	68.1 ± 10.40	31	69.6 ± 10.17
Endpoint	49	67.8 ± 9.61	36	70.3 ± 10.92	31	67.4 ± 9.26
Change	49	-1.1 ± 10.33	36	2.2 ± 10.26	31	-2.2 ± 9.74
Standing systolic BP (mmHg)						
Baseline	49	110.2 ± 13.65	36	108.2 ± 14.70	30	105.3 ± 14.80
Endpoint	49	107.6 ± 14.49	36	107.6 ± 13.03	30	102.5 ± 11.99
Change	49	-2.7 ± 14.62	36	-0.6 ± 18.22	30	-2.8 ± 13.92
Standing diastolic BP (mmHg)						
Baseline	49	69.3 ± 7.36	36	69.6 ± 10.22	30	68.5 ± 9.76
Endpoint	49	68.3 ± 9.40	36	68.5 ± 11.92	30	67.6 ± 10.62
Change	49	-1.0 ± 9.59	36	-1.1 ± 12.24	30	-0.9 ± 12.12
Sitting pulse (bpm)						
Baseline	49	77.6 ± 11.38	36	75.4 ± 10.90	31	79.8 ± 10.27
Endpoint	49	78.1 ± 9.15	36	90.2 ± 13.40	31	76.4 ± 12.34
Change	49	0.5 ± 10.65	36	14.8 ± 13.04	31	-3.5 ± 12.09
Standing pulse (bpm)						
Baseline	49	83.4 ± 13.74	36	82.4 ± 12.07	30	86.6 ± 12.74
Endpoint	49	83.9 ± 11.53	36	97.6 ± 16.63	30	82.9 ± 11.82
Change	49	0.4 ± 13.48	36	15.2 ± 15.63	30	-3.7 ± 12.81
Body weight (lb.)						
Baseline	49	146.3 ± 37.93	36	141.6 ± 30.74	31	140.6 ± 37.00
Endpoint	49	149.7 ± 38.59	36	143.5 ± 33.22	31	143.7 ± 38.42
Change	49	3.4 ± 7.57	36	1.9 ± 10.07	31	3.0 ± 5.89

Source: Data Source Table 16.11 in Section 11; Patient Data Listings in Appendix E.1 of the Acute Phase Report

5.6.2 Patients with Vital Signs of Potential Clinical Concern

Table 14 shows that the number of paroxetine patients with vital signs of potential clinical concern in the continuation phase were few and generally comparable to placebo, with the possible exception of increased body weight, for which 25% of paroxetine patients met the criteria for clinical concern predetermined by the sponsor (increase ≥7%). The proportions of patients meeting this criterion in the placebo and imipramine groups were 18% and 15%, respectively. In the

imipramine group, 17.5% of patients had elevated standing pulse meeting the clinical concern criteria, compared to no patients in the other treatment groups.

Table 14 Number (%) of Patients with Vital Sign or Body Weight Values of Potential Clinical Concern at Any Time During the Continuation Phase (ITT Population)

	Treatment Group		
Vital Sign Parameter of Clinical Concern	**Paroxetine (N = 52)**	**Imipramine (N = 40)**	**Placebo (N = 33)**
Sitting systolic BP (mmHg)			
Low (<90 and decrease ≥30)	1 (1.9%)	1 (2.5%)	0 (0.0%)
Sitting diastolic BP (mmHg)			
Low (<50 and decrease ≥20)	0 (0.0%)	1 (2.5%)	0 (0.0%)
Standing systolic BP (mmHg)			
Low (<90 and decrease ≥30)	1 (1.9%)	1 (2.5%)	2 (6.1%)
Standing diastolic BP (mmHg)			
Low (<50 and decrease ≥20)	1 (1.9%)	2 (5.0%)	0 (0.0%)
Standing pulse (bpm)			
High (>120 and increase ≥30)	0 (0.0%)	7 (17.5%)	0 (0.0%)
Body weight (lbs)			
High (increase ≥7%)	13 (25.0%)	6 (15.0%)	6 (18.2%)
Low (decrease ≥7%)	2 (3.8%)	5 (12.5%)	0 (0.0%)

Source: Data Source Table 16.12 in Section 11; Patient Data Listings in Appendix E.1 of the Acute Phase Report
Note: The number of patients is not additive, since an individual patient may have had more than one value of clinical concern.

Few of the findings meeting the potential clinical concern criteria were reported as adverse events (three patients each in the paroxetine and imipramine groups). Narratives for these patients may be found in Table 16.12.1 in Section 11, Narratives for Patients with Vital Signs of Potential Clinical Concern.

In the paroxetine group, patients 329.005.00151, 329.005.00257, and 329.007.00268 had adverse events of weight gain reported and, in addition ,the increases in weight met the predetermined clinical concern criteria. All were considered by the investigator to be possibly related to study medication. No other adverse events were associated with the weight gain and all patients continued in the study.

In the imipramine group, one patient (329.001.00122) with a weight gain meeting the potential clinical concern criteria had weight gain reported as an adverse event. This patient also had an adverse event of increased appetite. The adverse events were considered by the investigator to be related to study medication. The patient withdrew from the study on day 182 from acute baseline due to lack of efficacy.

For two of the seven patients in the imipramine group with increased pulse rate meeting the clinical concern criteria, the increase was reported as an adverse event. Patient 329.009.00325 had an increase in standing pulse on day 57 of the continuation phase (131 bpm, compared to 97 bpm at baseline). On day 3 the patient had an adverse event of tachycardia, which was reported to last 27 days. The investigator considered the tachycardia moderately severe and possibly related to study medication. The patient withdrew from the study due to lack of efficacy on day 124 from acute baseline. Patient 329.009.00305 had increased pulse and an adverse event of right axis deviation on electrocardiogram. The patient had had an increased pulse at weeks 4, 7 and 8 of the acute phase as well. The investigator considered the adverse event mild and probably unrelated to study medication.

5.7 Laboratory Tests

5.7.1 Change from Baseline in Laboratory Values at Endpoint

Clinical laboratory studies were performed for each patient at baseline and week 8, and at weeks 20 and 32 in the continuation phase. These laboratory parameter results were summarized using descriptive statistics. Review of the mean values at acute phase baseline and continuation phase endpoint did not identify any substantial differences between treatment groups in any of the laboratory parameters studied. A summary of mean laboratory values by treatment group is presented in Table 16.13 in Section 11. Individual laboratory data may be found in Appendix F.1 of the Acute Phase Report.

5.7.2 Laboratory Values of Potential Clinical Concern

In addition to a review of the mean laboratory data, each laboratory parameter was compared to a pre-determined range to identify those values that were considered of potential clinical concern.

These pre-determined ranges are shown in Section 6.10 of the Acute Phase Report. Values above or below these extended ranges were considered to be of potential clinical concern. A total of 19 patients were identified as having one or more laboratory values of potential clinical concern during the continuation phase (Table 15). The percentages of patients in each treatment group with laboratory values meeting the predefined clinical concern criteria were essentially the same (approximately 15% in each group).

Table 15 Number of Patients with Laboratory Values Considered to Be of Clinical Concern (ITT Population)

			Treatment Group		
			Paroxetine	**Imipramine**	**Placebo**
Laboratory Values of Potential Clinical Concern			N = 52 n (%)	N = 40 n (%)	N = 33 n (%)
Total patients with out-of-range values *			8 (15.4%)	6 (15.0%)	5 (15.0%)
	Sponsor-defined Values of Clinical Concern				
Hematology					
Hematocrit	Low	M ≤37.0; F ≤32.0%	0 (0.0%)	2 (5.0%)	0 (0.0%)
WBC count	High	≥16.0 THOU/mcL	1 (1.9%)	0 (0.0%)	0 (0.0%)
Eosinophils	High	≥10%	1 (1.9%)	2 (5.0%)	3 (9.1%)
Platelet count	Low	$\leq 75 \times 10^9/L$	2 (3.8%)	2 (5.0%)	1 (3.0%)
Urinalysis					
RBC	High	M >8/hpf; F >10/hpf	5 (9.6%)	1 (2.5%)	1 (3.0%)
WBC	High	>10/hpf	0 (0.0%)	1 (2.5%)	0 (0.0%)

Source: Data Source Table 16.14 in Section 11; Patient Data Listings in Appendix F.3
* The number of patients is not additive, since a patient may have had more than one abnormal laboratory value.

Seven patients (five paroxetine, one imipramine, and one placebo) had red blood cells (RBCs) in their urine that met the clinical concern criteria. All seven patients were female and no associated adverse events were reported other than hematuria concurrent with menstruation in one patient.

Six patients had high eosinophil counts (one paroxetine, two imipramine, three placebo). No associated adverse events were reported.

Five patients had low platelet counts; however, in all cases the investigator reported clumping of the sample.

Two patients in the imipramine group had low hematocrit. Patient 329.003.00289 had mild anemia reported as an adverse event, considered by the investigator to be unrelated to study medication. A narrative for this patient may be found in Table 16.14.1, Narratives for Patients with Laboratory Values of Potential Clinical Concern. Patient 329.008.00272 had no associated adverse event. Both patients completed the study as planned.

One patient had white blood cells in the urine, patient 329.002.00104 in the imipramine group. No associated adverse events were reported and the patient completed the study as planned.

5.7.3 Serum Concentrations of Imipramine

Sampling for serum concentrations of imipramine and desipramine and for plasma concentrations of paroxetine was to be performed at weeks 4, 8, 20, and 32. The serum was to be analyzed for imipramine and desipramine in real time, and the results blinded on the laboratory report sent to the investigator. However, if a patient had a combined serum concentration of imipramine and desipramine exceeding 500 ng/mL (500 mcg/L), the investigator was to be notified by telephone to withdraw the patient from the trial. The plasma concentrations of imipramine will not be reported since they were analyzed for safety purposes only.

Two patients randomized to imipramine experienced toxic levels of imipramine during the continuation phase. Information regarding these events may be found in Section 5.4 (Serious Non-Fatal Adverse Events) for patient 329.008.00273, and in Section 5.5 (Withdrawals for Adverse Events) for patient 329.011.00208. Both patients were withdrawn from the study.

Pharmacokinetic analyses were not completed on the paroxetine plasma concentration results because the times of the blood draws in relation to the previous dose of paroxetine were not recorded. Paroxetine plasma concentration results are available elsewhere.

5.8 Safety Results in the Continuation Phase Compared to the Acute Phase

Adverse events occurring at an incidence ≥5% in either the paroxetine or imipramine treatment group and at twice the incidence of placebo during either the acute phase or the continuation phase are presented in Table 16. A summary of adverse events during both phases combined may be found in Table 16.2.4 in Section 11.

In general, the long-term safety profile of paroxetine was similar to the short-term safety profile. In the acute phase, there were six adverse events that had occurred at an incidence of at least 5% and at least twice that of placebo (somnolence, insomnia, hostility, emotional lability, tremor, and tooth disorder. In the continuation phase, only insomnia, emotional lability and tremor continued to be reported at an incidence of at least 5% and at least twice that of placebo; of these, however, only emotional lability continued to occur at an incidence equaling that in the acute phase. Only two events occurred at an incidence of at least 5% and at least twice that of placebo in the continuation phase that did not also meet these

criteria in the acute phase. These were abdominal pain and weight gain. Of these two, for only weight gain was the incidence in the paroxetine group in the continuation phase greater than that in the acute phase (7.7% vs. 1.1%, respectively).

In the imipramine group, all the cardiovascular adverse events meeting the above criteria (tachycardia, postural hypotension, and vasodilatation) decreased in the continuation phase. Dry mouth, constipation, somnolence, insomnia, dizziness, tremor, sweating, and abnormal vision also decreased in the continuation phase. Abdominal pain and myalgia were the only adverse events meeting the above criteria that occurred with greater frequency in the continuation phase than in the acute phase.

Table 16 Adverse Events Occurring in ≥5% of Either Paroxetine or Imipramine Patients and at Least 2X Placebo in Either Phase of the Study or Both Phases Combined (ITT Population)

	Paroxetine			Imipramine			Placebo		
Body System	**Acute Phase**	**Continuation Phase**	**Combined Phases ***	**Acute Phase**	**Continuation Phase**	**Combined Phases ***	**Acute Phase**	**Continuation Phase**	**Combined Phases ***
Preferred Term	**N = 93**	**N = 52**	**N = 93**	**N = 95**	**N = 40**	**N = 95**	**N = 87**	**N = 33**	**N = 87**
Body as a whole									
Abdominal Pain	10 (10.8%)	**6 (11.5%)**	15 (16.1%)	7 (7.4%)	**4 (10.0%)**	9 (9.5%)	10 (11.5%)	1 (3.0%)	11 (12.6%)
Chest Pain	2 (2.2%)	1 (1.9%)	3 (3.2%)	**5 (5.3%)**	0 (0.0%)	**5 (5.3%)**	2 (2.3%)	0 (0.0%)	2 (2.3%)
Cardiovascular									
Tachycardia	2 (2.2%)	1 (1.9%)	3 (3.2%)	**18 (18.9%)**	**2 (5.0%)**	**19 (20.0%)**	1 (1.1%)	0 (0.0%)	1 (1.1%)
Postural Hypotension	1 (1.1%)	0 (0.0%)	1 (1.1%)	**13 (13.7%)**	0 (0.0%)	**13 (13.7%)**	1 (1.1%)	0 (0.0%)	1 (1.1%)
Vasodilatation	0 (0.0%)	0 (0.0%)	0 (0.0%)	**6 (6.3%)**	0 (0.0%)	**6 (6.3%)**	2 (2.3%)	0 (0.0%)	2 (2.3%)
Syncope	1 (1.1%)	1 (1.9%)	2 (2.2%)	4 (4.2%)	1 (2.5%)	**5 (5.3%)**	1 (1.1%)	0 (0.0%)	1 (1.1%)
Gastrointestinal									
Dry Mouth	19 (20.4%)	1 (1.9%)	19 (20.4%)	**43 (45.3%)**	**3 (7.5%)**	**43 (45.3%)**	12 (13.8%)	0 (0.0%)	12 (13.8%)
Dyspepsia	6 (6.5%)	0 (0.0%)	6 (6.5%)	**9 (9.5%)**	**2 (5.0%)**	**10 (10.5%)**	4 (4.6%)	0 (0.0%)	4 (4.6%)
Constipation	5 (5.4%)	2 (3.8%)	7 (7.5%)	**9 (9.5%)**	1 (2.5%)	**10 (10.5%)**	4 (4.6%)	0 (0.0%)	4 (4.6%)
Tooth Disorder	**5 (5.4%)**	0 (0.0%)	5 (5.4%)	2 (2.1%)	1 (2.5%)	3 (3.2%)	2 (2.3%)	2 (6.1%)	4 (4.6%)
Nervous System									
Somnolence	**16 (17.2%)**	1 (1.9%)	**16 (17.2%)**	**13 (13.7%)**	1 (2.5%)	**14 (14.7%)**	3 (3.4%)	0 (0.0%)	3 (3.4%)
Insomnia	**14 (15.1%)**	**4 (7.7%)**	**17 (18.3%)**	**13 (13.7%)**	**3 (7.5%)**	**16 (16.8%)**	4 (4.6%)	1 (3.0%)	5 (5.7%)
Hostility	**7 (7.5%)**	0 (0.0%)	**7 (7.5%)**	3 (3.2%)	0 (0.0%)	3 (3.2%)	0 (0.0%)	1 (3.0%)	1 (1.1%)
Emotional Lability	**6 (6.5%)**	**4 (7.7%)**	**8 (8.6%)**	3 (3.2%)	1 (2.5%)	4 (4.2%)	1 (1.1%)	1 (3.0%)	2 (2.3%)
Dizziness	22 (23.7%)	9 (17.3%)	26 (28.0%)	**45 (47.4%)**	3 (7.5%)	**46 (48.4%)**	16 (18.4%)	4 (12.1%)	20 (23.0%)
Tremor	**10 (10.8%)**	**3 (5.8%)**	**11 (11.8%)**	**14 (14.7%)**	0 (0.0%)	**14 (14.7%)**	2 (2.3%)	0 (0.0%)	2 (2.3%)
Other									
Weight Gain	1 (1.1%)	**4 (7.7%)**	**5 (5.4%)**	0 (0.0%)	1 (2.5%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Myalgia	3 (3.2%)	1 (1.9%)	4 (4.3%)	0 (0.0%)	**3 (7.5%)**	3 (3.2%)	2 (2.3%)	0 (0.0%)	2 (2.3%)
Sweating	1 (1.1%)	0 (0.0%)	1 (1.1%)	**6 (6.3%)**	1 (2.5%)	**7 (7.4%)**	1 (1.1%)	0 (0.0%)	1 (1.1%)
Abnormal Vision	1 (1.1%)	1 (1.9%)	2 (2.2%)	**7 (7.4%)**	1 (2.5%)	**7 (7.4%)**	2 (2.3%)	0 (0.0%)	2 (2.3%)

Source: Data Source Tables 16.2.1 and 16.2.4 in Section 11; Table 14.2.1 in Section 12 of the Acute Phase Report and Patient Data Listings in Appendix D.1 and D.2 of the Acute Phase Report
Note: Bold text indicates an incidence of ≥5% in any group and at least 2X placebo
*Adverse events during both phases combined are not additive where a patient had the same adverse event at the same intensity in both phases.

5.8.1 Serious Adverse Events in Both Phases Combined

Table 17 presents the incidence of serious adverse events in both study phases combined (acute plus continuation) by treatment. The overall incidence of serious adverse events was 17.2% in the paroxetine group, compared to 7.4% in the imipramine group and 3.4% in the placebo group. During the acute phase of the study, 11/93 patients in the paroxetine group experienced 16 serious adverse events (14 of which were psychiatric in nature). This acute phase incidence rate (11.8%) of serious adverse events is similar to the proportion of paroxetine patients in the continuation phase who experienced serious adverse events (6/52, 11.5%). In the imipramine group, 5.3% of patients experienced serious adverse events during the acute phase, comparable to 5.0% in the continuation phase. In the placebo group, 2.3% of patients experienced serious adverse events during the acute phase, comparable to 3.0% in the continuation phase.

In the paroxetine group, emotional lability was the only serious adverse event reported at an incidence ≥5% and twice that of placebo in both phases combined. Serious adverse events of emotional lability were reported for five paroxetine patients (5.4%) during the acute phase and three paroxetine patients (5.8%) in the continuation phase; of these, one patient had a serious adverse event of emotional lability in both phases (see Section 5.4, Serious Non-Fatal Adverse Events). The incidence of emotional lability considered serious in the imipramine group was comparable to placebo. No serious adverse events occurred in the imipramine or placebo group at an incidence of 5% or greater.

Table 17 Number (%) of Patients with Serious Adverse Events in Each Phase of the Study and Both Phases Combined (ITT Population)

	Paroxetine			Imipramine			Placebo		
Serious Adverse Event Preferred Term	**Acute N = 93 n (%)**	**Continuation N = 52 n (%)**	**Total N = 93 n (%)**	**Acute N = 95 n (%)**	**Continuation N = 40 n (%)**	**Total N = 95 n (%)**	**Acute N = 87 n (%)**	**Continuation N = 33 n (%)**	**Total N = 87 n (%)**
Total patients with an SAE	11 (11.8%)	6 (11.5%)	16 (17.2%)*	5 (5.3%)	2 (5.0%)	7 (7.4%)	2 (2.3%)	1 (3.0%)	3 (3.4%)
Abnormal Dream	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Accidental Overdose	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Agitation	1 (1.1%)	1 (1.9%)	2 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asthenia	0 (0.0%)	1 (1.9%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chest Pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Depression	2 (2.2%)	0 (0.0%)	2 (2.2%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	2 (2.3%)	0 (0.0%)	2 (2.3%)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspnea	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Emotional lability *	5 (5.4%)	3 (5.8%)	7 (7.5%) *	1 (1.1%)	1 (2.5%)	2 (2.1%)	1 (1.1%)	1 (3.0%)	2 (2.3%)
Euphoria	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hallucinations	1 (1.1%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hostility	3 (3.2%)	0 (0.0%)	3 (3.2%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (3.0%)	1 (1.1%)
Hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Insomnia	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Maculopapular Rush	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Manic Reaction	0 (0.0%)	1 (1.9%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nausea	0 (0.0%)	1 (1.9%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervousness	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Paranoid reaction	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Peptic ulcer hemorrhage	0 (0.0%)	1 (1.9%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence	0 (0.0%)	1 (1.9%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tremor	0 (0.0%)	1 (1.9%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal Syndrome	1 (1.1%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Data Source Table 16.8 in Section 11; Table 48 in Acute Phase report; Patient Data Listings in Appendix D.1 and D.2

* Patient 329.003.00250 had an adverse event of emotional lability in both phases of the study.

6 Efficacy Results

All analyses for the continuation phase were conducted using the ITT population. No Per Protocol population was defined or identified, since there were no hypotheses to be tested.

The continuation phase of this study was designed to provide long-term safety information and to estimate the rate of relapse in the three treatment groups. It was not designed to formally evaluate efficacy, as patients were not re-randomized at the end of the acute phase. In addition, only responders were eligible to enter the continuation phase. Nevertheless, the results suggested that patients who had responded to therapy in the acute phase (irrespective of treatment assignment) continued to respond over the six months of the continuation phase.

6.1 Withdrawals Due to Lack of Efficacy

Table 18 present the numbers of patients withdrawing in each treatment group due to lack of efficacy. There were no significant differences between paroxetine and placebo or between imipramine and placebo in withdrawals due to lack of efficacy during the continuation phase.

Table 18 Number (%) of Patients Withdrawing for Lack of Efficacy (Intent to Treat Population)

	Paroxetine	Imipramine	Placebo	Pairwise Comparisons	
	N = 52 n (%)	N = 40 n (%)	N = 33 n (%)	Paroxetine vs. Placebo	Imipramine vs. Placebo
Patients withdrawing for lack of efficacy	7 (13.5%)	6 (15.0%)	6 (18.2)	0.554	0.759

Source: Data Source Table 15.1 in Section 10; Patient Data Listings in Appendix D.3

6.2 Analysis of Relapse

Relapse during the continuation phase was summarized at each visit during the continuation phase and at endpoint, and the patients who relapsed are presented by treatment group at each visit and at endpoint (Patient Data Listings in Appendix C.1). The number (%) of patients who relapsed at any time during the continuation phase is presented for each treatment group (Data Source Table 15.2 in Section 10).

Relapse during the continuation phase was summarized only for patients who had a HAM-D ≤8 at the end of the acute phase. Relapse was defined as a HAM-D total score greater than 8 or a decrease from acute baseline less than 50%. Table 19 presents a summary of relapse during the continuation phase. Also included is the mean time to relapse in days for each treatment group.

The proportion of patients relapsing at any time during the continuation phase was similar in the imipramine group (38.7%) and in the paroxetine group (36.4%) but slightly lower in the placebo group (23.1%). The mean time to relapse in the imipramine group was 61.5 days, compared to approximately 79 days in each of the other treatment groups.

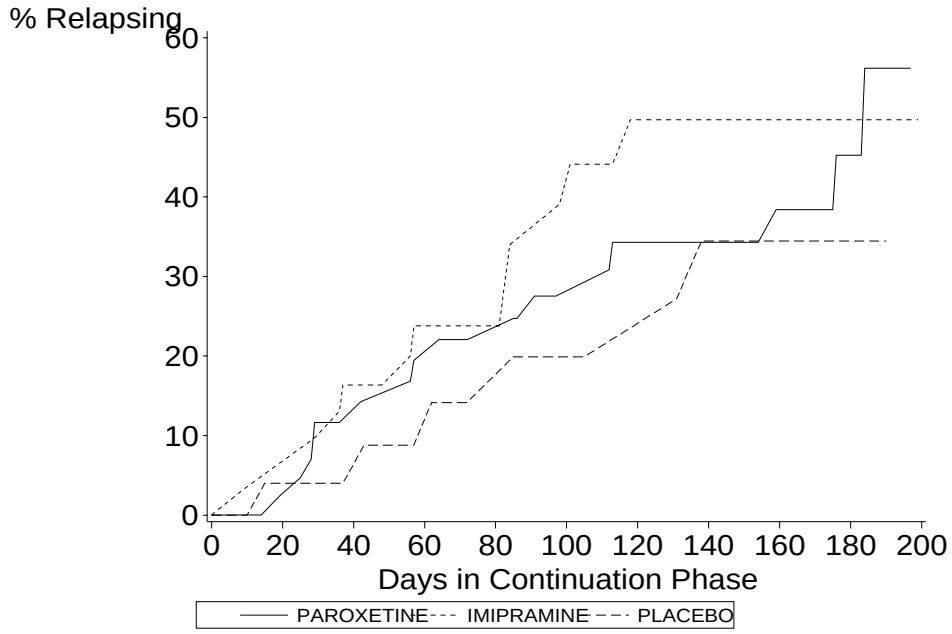
Table 19 Summary of Relapse During the Continuation Phase for Patients Who Had a HAM-D ≤8 at End of Acute Phase (ITT Population)

	Paroxetine N = 44	**Imipramine N = 31**	**Placebo N = 26**
Relapse (%)	16 (36.4%)	12 (38.7%)	6 (23.1%)
Mean time to relapse (days) *	79.3	61.5	79.0
Median time to relapse (days) *	60.5	56.5	73.5

Source: Data Source Table 15.2 in Section 10; Patient Data Listings in Appendix C.1 of the Acute Phase Report
Relapse = HAM-D total score greater than 8 or a decrease from baseline less than 50%
* Time to relapse relative to start of continuation phase. Median and mean are not adjusted for censored data.

Figure 3 shows the Kaplan Meier survival curves for relapse during the continuation phase. There is no clinically meaningful difference between paroxetine and placebo or between imipramine and placebo in the proportion of patients relapsing over time.

Figure 3 Kaplan Meier Survival Curves for Relapse During the Continuation Phase (ITT Population)



Source: Data Source Figure 2 in Section 12

The estimate of rate of relapse was based on counting patients as relapsers if at any time during the continuation phase they failed to meet the definition of a responder, even if such relapse occurred early in the continuation phase and at only one visit.

A post-hoc summary of relapse at endpoint was conducted, defining relapsers as those patients whose HAM-D at endpoint of the continuation phase was >8 and >50% of the acute baseline HAM-D. The proportions of relapsers in each treatment group were similar: 10/44 (22.7%) in the paroxetine group, 8/31 (25.8%) in the imipramine group, and 6/26 (23.1%) in the placebo group (Patient Data Listings in Appendix C.1). Since the number of patients in each group was small, it is difficult to draw any meaningful conclusions about any differences between the groups.

6.3 Hamilton Depression Scale

Table 20 presents the change in HAM-D total score from the acute study baseline for the observed cases (OC) at each treatment week and the LOCF at week 32 (month 6 of the continuation phase). HAM-D scores were comparable among the treatment groups at baseline of the acute phase (Table 13.1 in Section 11 of the Acute Phase Report). For those patients who completed the continuation phase, all groups continued to show improvement (decreased scores) over the 32-week study. However, at week 32 of the LOCF, mean changes in all treatment groups were smaller than mean changes at week 12. For both OC and LOCF at week 32, there were no significant differences for either the paroxetine group ($p = 0.877$ for OC and $p = 0.622$ for LOCF) or the imipramine group ($p = 0.874$ for OC and $p = 0.527$ for LOCF) compared to placebo.

Table 20 Baseline Mean (±SE) and Mean Change from Baseline at Each Visit– HAM-D Scale (ITT Population)

	Treatment Group					
Visit	**Paroxetine**	**n**	**Imipramine**	**n**	**Placebo**	**n**
Acute Baseline *	18.39 ± 0.63	50	17.37 ± 0.69	37	18.33 ± 0.78	31
Week 12	-12.23 ± 1.03	48	-12.24 ± 1.18	32	-12.32 ± 1.29	29
Week 16	-13.19 ± 1.15	38	-12.18 ± 1.15	32	-13.69 ± 1.37	23
Week 20	-12.69 ± 1.10	37	-10.02 ± 1.18	25	-13.43 ± 1.51	17
Week 24	-12.60 ± 1.39	27	-10.84 ± 1.42	17	-14.46 ± 1.62	16
Week 28	-13.56 ± 1.33	19	-12.31 ± 1.30	15	-11.58 ± 1.77	9
Week 32 OC	-14.81 ± 1.24	18	-14.80 ± 1.29	14	-15.10 ± 1.38	13
Week 32 LOCF	-11.29 ± 1.18	50	-10.95 ± 1.30	37	-12.13 ± 1.46	31

Source: Data Source Table 15.3 in Section 10; Patient Data Listings in Appendix C.1 of the Acute Phase Report
Note: A minus sign represents an improvement (decrease in score).
* n = number of patients with at least one on-therapy efficacy assessment during the continuation phase

6.4 Clinical Global Impression of Improvement

Table 21 presents the distribution of patients in each class of CGI Global Improvement at week 32 LOCF endpoint. This instrument is described in Section 5.2.5 of the Acute Phase report.

There were no meaningful differences in the distribution of patients in each class of CGI Global Improvement at endpoint. In the paroxetine group, 35/50 patients (70.0%) had a score of 1 (very much improved) or 2 (much improved) at endpoint, compared to 25/37 imipramine patients (67.6%) and 22/30 placebo patients (73.3%).

Table 21 Distribution of Patients in Each Class of CGI Global Improvement at Week 32 LOCF Endpoint (Intent to Treat Population)

	Paroxetine	Imipramine	Placebo
	N = 50	N = 37	N = 30
	n (%)	n (%)	n (%)
Very Much Improved	20 (40%)	14 (37.8%)	17 (56.7%)
Much Improved	15 (30%)	11 (29.7%)	5 16.7%)
Minimally Improved	5 (10%)	2 (5.4%)	4 (13.3%)
No Change	2 (4.0%)	5 (13.5%)	3 (10.0%)
Minimally Worse	3 (6.0%)	1 (2.7)	1 (3.3%)
Much Worse	3 (6.0%)	3 (8.1%)	0 (0.0%)
Very Much Worse	2 (4.0%)	1 (2.7)	0 (0.0%)

Source: Data Source Table 15.6 in Section 10; Patient Data Listings in Appendix C.4

Table 22 presents the mean CGI Global Improvement scores for all OC weeks and LOCF week 32. Briefly, for this instrument, a mean score of 4 indicates an average of "no change" for the group. Mean scores above 4 indicate worsening and scores below 4 indicate improvement.

All treatment groups showed similar improvements over the 32-week study and neither the paroxetine or imipramine group was significantly different from the placebo group at OC week 32 ($p = 0.186$ and 0.547 for the paroxetine and imipramine treatment groups, respectively) or at LOCF week 32 ($p = 0.056$ and 0.099 for the paroxetine and imipramine treatment groups, respectively).

Table 22 Mean (±SE) CGI Global Improvement at Each Visit (ITT Population)

	Treatment Group					
Visit	**Paroxetine**	**n**	**Imipramine**	**n**	**Placebo**	**n**
Week 12	1.89 ± 0.21	48	1.60 ± 0.24	32	1.83 ± 0.27	28
Week 16	1.73 ± 0.21	38	1.87 ± 0.21	33	1.58 ± 0.25	22
Week 20	2.54 ± 0.26	37	2.25 ± 0.28	25	1.91 ± 0.36	17
Week 24	2.35 ± 0.29	28	2.29 ± 0.30	17	1.82 ± 0.34	16
Week 28	1.63 ± 0.21	18	1.57 ± 0.20	15	1.97 ± 0.27	9
Week 32 OC	1.80 ± 0.28	18	1.50 ± 0.29	14	1.24 ± 0.31	13
Week 32 LOCF	2.58 ± 0.25	50	2.54 ± 0.27	37	1.87 ± 0.31	30

Source: Data Source Table 15.5 in Section 10; Patient Data Listings in Appendix C.4 of the Acute Phase Report

6.5 Other Secondary Scales

There were no clinically meaningful advantages found for either paroxetine or imipramine over placebo in any of the other secondary efficacy measures: K-SADS-L Depression 9-item Scale; HAM-D Anxiety, Sleep, Cognitive

Disturbance, Retardation, and Depressed Mood Scales; Self Perception Profile Scale; Autonomous Functioning Scale and Subscores; and Sickness Impact Profile Scale and Subscores. In general, patients continued to respond to treatment or maintained the improvement seen at the end of the acute study.

The analyses of the secondary outcome measures are presented in Section 10 of this report (Tables 15.4 and 15.7–15.26). Individual patient data may be found in Patient Data Listings in Appendix C.2, C.3, and C.5-C.7 of the Acute Phase Report.

7 Discussion

The continuation phase of this multi-center, double-blind, placebo-controlled study represents the only long-term placebo-controlled safety data as well as estimation of relapse rate for paroxetine in pediatric patients with depression. In general, the safety data do not suggest that there are any specific risks associated with long-term (6 months) use of paroxetine in this population. The data also suggest that patients who had responded to therapy in the acute phase, regardless of treatment assignment, in general continued to maintain their response during the continuation phase. However, the number of patients completing the additional six months of study medication in the continuation phase was small (18 in the paroxetine group and 13 each in the imipramine and placebo groups), which limits any conclusions that can be drawn regarding long-term efficacy.

Additionally, compliance in the continuation phase, defined as taking 80% to 120% of study medication over the course of the continuation phase, was less than ideal in all three treatment groups: 78.8% among paroxetine patients, 82.5% among imipramine patients and 72.7% among placebo patients. The small sample size along with poor compliance makes it difficult to draw meaningful conclusions about the results of the study.

Safety:

The nature and incidence of adverse events reported for the paroxetine group during long-term (continuation phase) exposure were generally similar in nature to those reported in the acute phase. In general, the frequency was less during the continuation phase for many of the adverse events that were identified in the acute phase as occurring in at least 5% of patients in the paroxetine group and at an incidence at least twice that of placebo, in particular those adverse events that are psychiatric in nature (somnolence, insomnia, hostility, and tremor). The incidence of emotional lability was similar in both phases. The only adverse event meeting these criteria (≥5% of patients and ≥2 times placebo) that occurred with greater frequency in the paroxetine group in the continuation phase than in the acute phase was weight gain.

In the imipramine group, all the cardiovascular adverse events meeting the above criteria (tachycardia, postural hypotension, and vasodilatation) decreased in the continuation phase, as did most of the other adverse events meeting these criteria. No adverse event meeting the above criteria occurred with greater frequency in the continuation phase than in the acute phase.

There were no deaths during the trial. During the continuation phase, serious adverse events occurred in nine patients, six in the paroxetine group, two in the imipramine group, and one in the placebo group. Emotional lability (verbatim: intentional overdose) (in all three cases in the paroxetine group by overdose of study medication or OTC analgesic medication) occurred with long-term use of paroxetine with similar frequency to that seen in the acute phase, and did not appear to be related to the degree of improvement or deterioration seen in the patient. Emotional lability occurred in patients taking imipramine and placebo as well, but in fewer patients.

During the 32 weeks of the continuation phase, there were no serious adverse events of hostility or aggression among paroxetine patients, whereas there was one patient in the placebo group with a serious adverse event of hostility.

The proportion of patients who were withdrawn from the study due to adverse events was 7.7% in the paroxetine group compared to 20.0% in the imipramine group and 12.1% in the placebo group. Adverse events related to the nervous system were the most common event leading to withdrawal, occurring in three patients in the paroxetine group, three patients in the imipramine group, and one patient in the placebo group. Two patients in the imipramine group were withdrawn due to tricyclic toxicity. All other events leading to withdrawal occurred in no more than one patient in any group.

In the paroxetine group, 13 patients (25.0%) were identified as having weight gain of potential clinical concern, defined as a weight gain of ≥7%. For three of these patients, the weight gain was reported as an adverse event. It is not unexpected for some adolescents to experience this degree of weight gain in an eight-month period. Similarly, in the imipramine group, 6 patients (15.0%) had a weight gain ≥7%, as did 6 patients (18.2%) in the placebo group. There were no other changes in vital signs of clinical significance in the paroxetine group.

In the imipramine group, seven patients were identified as having increases in the standing pulse rate of potential clinical concern, one of which was reported as an adverse event of tachycardia. Among placebo patients, there were no changes in vital signs of clinical significance.

Clinical laboratory abnormalities meeting concern criteria were few in number and none were identified by investigators as related to the study medication.

Efficacy:

It must be kept in mind that the six-month continuation phase of this double-blind placebo-controlled trial was primarily designed to assess long-term safety. In this continuation phase of the study, patients were not re-randomized, which would be necessary in order to establish long-term efficacy. In addition, only responders were eligible to enter the continuation phase. As in the acute phase of the study, the difference in the paroxetine response relative to imipramine and to placebo in the change in most efficacy scores was small.

The results of this study suggest that patients who had responded to therapy in the acute phase, regardless of treatment regimen, continued to maintain their response over the six months of the continuation phase. The data to support this statement was derived from the analyses of eight prospectively defined measures of depression. For each of these measures, the analysis of the week 32 endpoint using the LOCF shows that the acute phase response achieved in the paroxetine group generally continued over the six months of the continuation phase. The analysis of the OC generally paralleled or showed more improvement than the analysis of the LOCF.

Relapse during the continuation phase was defined as a HAM-D total score greater than 8 or a decrease from acute baseline less than 50% at any time during the continuation phase. The proportion of patients relapsing was similar in the imipramine group (39%) to the paroxetine group (36%), but slightly less (23%) in the placebo group. However, a post-hoc summary of relapse at endpoint was conducted, defining relapsers as those patients whose HAM-D at endpoint of the continuation phase was >8 and >50% of the acute baseline HAM-D. The proportions of relapsers in each treatment group were similar: 23% in the paroxetine and placebo groups and 26% in the imipramine group. Since the number of patients in each group was small, it is difficult to draw meaningful conclusions about any differences between the groups.

There is no clinically meaningful difference between paroxetine and placebo or between imipramine and placebo in the proportion of patients relapsing over time. The number of withdrawals due to lack of efficacy was also similar among groups.

8 Conclusions

The long-term safety profile of paroxetine in adolescents appears similar to that reported following short-term dosing. In general, the incidence (new onset) of those adverse events identified as occurring in the acute phase at an incidence of at least 5% and at least twice placebo was less in the continuation phase. Weight gain was the only vital sign of concern that occurred with greater frequency in the paroxetine group than in the other treatment groups, and with greater frequency in the continuation phase than in the acute phase. However, with such a small sample size, in the absence of pre- and post-dose body mass index data, the clinical relevance of such findings is difficult to establish in an actively growing and maturing population such as this.

The proportion of patients relapsing at any time during the continuation phase was similar in the paroxetine and imipramine groups and slightly lower in the placebo group. The proportions of patients relapsing at endpoint were similar in all treatment groups. There were no significant differences between paroxetine and placebo or between imipramine and placebo in withdrawals due to lack of efficacy. Trends suggested that patients who had responded to therapy in the acute phase continued to respond over the six months of the continuation phase.

9 Data Source Tables: Study Population

PAROXETINE - PROTOCOL 329

Table 12.2

Summary of Patients Remaining in the Study at Weekly Intervals
Intent-to-Treat Population

PHASE=Acute Phase

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Completed Acute Phase
PAROXETINE	93	86	80	78	76	75	72	68	67	67
IMIPRAMINE	95	91	83	79	75	68	61	57	57	57
PLACEBO	87	85	80	76	75	70	70	67	66	66
TOTAL	275	262	243	233	226	213	203	192	190	190

PAROXETINE - PROTOCOL 329

Table 12.2

Summary of Patients Remaining in the Study at Weekly Intervals
Intent-to-Treat Population

PHASE=Continuation Phase

	Entered Cont. Phase	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Completed Cont. Phase
PAROXETINE	52	42	37	28	21	18	18	18
IMIPRAMINE	40	33	28	21	16	13	13	13
PLACEBO	33	26	19	16	14	13	13	13
TOTAL	125	101	84	65	51	44	44	44

PAROXETINE - PROTOCOL 329

Table 12.3

Summary of Patient Withdrawals
Intent-to-Treat Population

PHASE=Acute Phase

Reason for Withdrawal	PAROXETINE N = 93 n	%	IMIPRAMINE N = 95 n	%	PLACEBO N = 87 n	%	TOTAL N = 275 n	%
Adverse event, including intercurrent illness	9	9.7	30	31.6	6	6.9	45	16.4
Lack of Efficacy	4	4.3	1	1.1	6	6.9	11	4.0
Protocol violation, including non-compliance	3	3.2	5	5.3	7	8.0	15	5.5
Lost to follow-up	5	5.4	1	1.1	1	1.1	7	2.5
Other reason	5	5.4	1	1.1	1	1.1	7	2.5
Total	26	28.0	38	40.0	21	24.1	85	30.9

PAROXETINE - PROTOCOL 329

Table 12.3

Summary of Patient Withdrawals
Intent-to-Treat Population

PHASE=Continuation Phase

Reason for Withdrawal	PAROXETINE N = 52 n	%	IMIPRAMINE N = 40 n	%	PLACEBO N = 33 n	%	TOTAL N = 125 n	%
Adverse event, including intercurrent illness	4	7.7	8	20.0	4	12.1	16	12.8
Lack of Efficacy	7	13.5	6	15.0	6	18.2	19	15.2
Protocol violation, including non-compliance	12	23.1	7	17.5	4	12.1	23	18.4
Lost to follow-up	3	5.8	2	5.0	3	9.1	8	6.4
Other reason	8	15.4	4	10.0	3	9.1	15	12.0
Total	34	65.4	27	67.5	20	60.6	81	64.8

PAROXETINE - PROTOCOL 329

Table 12.4

Distribution of Patient Withdrawals by Reason and Week
Intent-to-Treat Population

Treatment Group=PAROXETINE PHASE=Acute Phase

N = 93

Reason for Withdrawal	Baseline n	Baseline %	Week 1 n	Week 1 %	Week 2 n	Week 2 %	Week 3 n	Week 3 %	Week 4 n	Week 4 %	Week 5 n	Week 5 %	Week 6 n	Week 6 %	Week 7 n	Week 7 %	Week 8 n	Week 8 %
Adverse event, including intercurrent illness	0	0.0	2	2.2	4	4.3	0	0.0	0	0.0	0	0.0	0	0.0	2	2.2	1	1.1
Lack of Efficacy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.1	2	2.2	1	1.1	0	0.0
Protocol violation, including non-compliance	0	0.0	1	1.1	0	0.0	2	2.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Lost to follow-up	0	0.0	1	1.1	2	2.2	0	0.0	1	1.1	0	0.0	1	1.1	0	0.0	0	0.0
Other reason	0	0.0	3	3.2	0	0.0	0	0.0	1	1.1	0	0.0	0	0.0	1	1.1	0	0.0

Table 12.4

Distribution of Patient Withdrawals by Reason and Week
Intent-to-Treat Population

Treatment Group=PAROXETINE PHASE=Continuation Phase

N = 52

Reason for Withdrawal	Week 12 n	Week 12 %	Week 16 n	Week 16 %	Week 20 n	Week 20 %	Week 24 n	Week 24 %	Week 28 n	Week 28 %
Adverse event, including intercurrent illness	1	1.9	1	1.9	1	1.9	1	1.9	0	0.0
Lack of Efficacy	2	3.8	1	1.9	2	3.8	2	3.8	0	0.0
Protocol violation, including non-compliance	3	5.8	2	3.8	5	9.6	2	3.8	0	0.0
Lost to follow-up	2	3.8	0	0.0	0	0.0	0	0.0	1	1.9
Other reason	2	3.8	1	1.9	1	1.9	2	3.8	2	3.8

PAROXETINE - PROTOCOL 329

Table 12.4

Distribution of Patient Withdrawals by Reason and Week
Intent-to-Treat Population

Treatment Group=IMIPRAMINE PHASE=Acute Phase

N = 95

Reason for Withdrawal	Baseline n	Baseline %	Week 1 n	Week 1 %	Week 2 n	Week 2 %	Week 3 n	Week 3 %	Week 4 n	Week 4 %	Week 5 n	Week 5 %	Week 6 n	Week 6 %	Week 7 n	Week 7 %	Week 8 n	Week 8 %
Adverse event, including intercurrent illness	0	0.0	2	2.1	7	7.4	4	4.2	3	3.2	5	5.3	6	6.3	3	3.2	0	0.0
Lack of Efficacy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.1	0	0.0	0	0.0
Protocol violation, including non-compliance	0	0.0	2	2.1	0	0.0	0	0.0	1	1.1	1	1.1	0	0.0	1	1.1	0	0.0
Lost to follow-up	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0
Other reason	0	0.0	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 12.4

Distribution of Patient Withdrawals by Reason and Week
Intent-to-Treat Population

Treatment Group=IMIPRAMINE PHASE=Continuation Phase

N = 40

Reason for Withdrawal	Week 12 n	Week 12 %	Week 16 n	Week 16 %	Week 20 n	Week 20 %	Week 24 n	Week 24 %	Week 28 n	Week 28 %
Adverse event, including intercurrent illness	1	2.5	1	2.5	2	5.0	2	5.0	2	5.0
Lack of Efficacy	1	2.5	2	5.0	1	2.5	2	5.0	0	0.0
Protocol violation, including non-compliance	2	5.0	1	2.5	3	7.5	1	2.5	0	0.0
Lost to follow-up	1	2.5	0	0.0	0	0.0	0	0.0	1	2.5
Other reason	2	5.0	1	2.5	1	2.5	0	0.0	0	0.0

Table 12.4

Distribution of Patient Withdrawals by Reason and Week
Intent-to-Treat Population

Treatment Group=PLACEBO PHASE=Acute Phase

N = 87

Reason for Withdrawal	Baseline n	Baseline %	Week 1 n	Week 1 %	Week 2 n	Week 2 %	Week 3 n	Week 3 %	Week 4 n	Week 4 %	Week 5 n	Week 5 %	Week 6 n	Week 6 %	Week 7 n	Week 7 %	Week 8 n	Week 8 %
Adverse event, including intercurrent illness	0	0.0	1	1.1	2	2.3	3	3.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Lack of Efficacy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	2.3	0	0.0	3	3.4	1	1.1
Protocol violation, including non-compliance	0	0.0	1	1.1	2	2.3	1	1.1	1	1.1	2	2.3	0	0.0	0	0.0	0	0.0
Lost to follow-up	0	0.0	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other reason	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0

Table 12.4

Distribution of Patient Withdrawals by Reason and Week
Intent-to-Treat Population

Treatment Group=PLACEBO PHASE=Continuation Phase

N = 33

Reason for Withdrawal	Week 12 n	Week 12 %	Week 16 n	Week 16 %	Week 20 n	Week 20 %	Week 24 n	Week 24 %	Week 28 n	Week 28 %
Adverse event, including intercurrent illness	1	3.0	2	6.1	0	0.0	1	3.0	0	0.0
Lack of Efficacy	3	9.1	0	0.0	2	6.1	0	0.0	1	3.0
Protocol violation, including non-compliance	0	0.0	3	9.1	0	0.0	1	3.0	0	0.0
Lost to follow-up	2	6.1	1	3.0	0	0.0	0	0.0	0	0.0
Other reason	1	3.0	1	3.0	1	3.0	0	0.0	0	0.0

Table 12.15

Summary of Concomitant Medications by WHO ATC Classification
Continuation Phase
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH MEDICATIONS :	29	55.8%	17	42.5%	19	57.6%	65	52.0%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
ALIMENTARY TRACT/METAB:	7	13.5	6	15.0	1	3.0	14	11.2
ALUMINIUM HYDROXIDE	2	3.8	1	2.5	0	0.0	3	2.4
BISACODYL	1	1.9	0	0.0	0	0.0	1	0.8
BISMUTH SUBSALICYLATE	0	0.0	1	2.5	1	3.0	2	1.6
CAFFEINE	0	0.0	1	2.5	0	0.0	1	0.8
CALCIUM CARBONATE	2	3.8	2	5.0	0	0.0	4	3.2
CHARCOAL, ACTIVATED	1	1.9	0	0.0	0	0.0	1	0.8
CORN SYRUP	0	0.0	1	2.5	0	0.0	1	0.8
DIMETICONE, ACTIVATED	0	0.0	1	2.5	0	0.0	1	0.8
LAXATIVES, NOS	0	0.0	1	2.5	0	0.0	1	0.8
MAGNESIUM HYDROXIDE	2	3.8	1	2.5	0	0.0	3	2.4
NATURAL FLAVORS	0	0.0	1	2.5	0	0.0	1	0.8
NEOMYCIN	1	1.9	0	0.0	0	0.0	1	0.8
NIZATIDINE	0	0.0	1	2.5	0	0.0	1	0.8
POLYMYXIN B	1	1.9	0	0.0	0	0.0	1	0.8
RANITIDINE HYDROCHLORIDE	1	1.9	0	0.0	0	0.0	1	0.8
SODIUM CHLORIDE	1	1.9	0	0.0	0	0.0	1	0.8
ANTIINFECTIVES,SYSTEMIC:	12	23.1	2	5.0	8	24.2	22	17.6
AMOXICILLIN	4	7.7	1	2.5	2	6.1	7	5.6
AMOXICILLIN TRIHYDRATE	1	1.9	0	0.0	4	12.1	5	4.0
ANTIBIOTIC NOS	1	1.9	0	0.0	0	0.0	1	0.8
CEFACLOR	1	1.9	0	0.0	0	0.0	1	0.8
CEFALEXIN	1	1.9	0	0.0	0	0.0	1	0.8
CEFALEXIN MONOHYDRATE	1	1.9	0	0.0	0	0.0	1	0.8
CEFUROXIME AXETIL	1	1.9	0	0.0	0	0.0	1	0.8
CLAVULANIC ACID	1	1.9	0	0.0	3	9.1	4	3.2
ERYTHROMYCIN	2	3.8	1	2.5	0	0.0	3	2.4
ERYTHROMYCIN ETHYLSUCCINATE	0	0.0	0	0.0	1	3.0	1	0.8
MICONAZOLE NITRATE	2	3.8	0	0.0	0	0.0	2	1.6
NEOMYCIN	1	1.9	0	0.0	0	0.0	1	0.8
PENICILLIN NOS	1	1.9	0	0.0	0	0.0	1	0.8
POLYMYXIN B	1	1.9	0	0.0	0	0.0	1	0.8
SULFAFURAZOLE ACETYL	0	0.0	0	0.0	1	3.0	1	0.8
SULFAMETHOXAZOLE	1	1.9	0	0.0	1	3.0	2	1.6
TRIMETHOPRIM	1	1.9	0	0.0	1	3.0	2	1.6
BLOOD/BLOOD FORM ORGANS:	2	3.8	0	0.0	0	0.0	2	1.6
I.V. FLUIDS	1	1.9	0	0.0	0	0.0	1	0.8
SODIUM CHLORIDE	1	1.9	0	0.0	0	0.0	1	0.8

Table 12.15

Summary of Concomitant Medications by WHO ATC Classification
Continuation Phase
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH MEDICATIONS :	29	55.8%	17	42.5%	19	57.6%	65	52.0%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
CENTRAL NERVOUS SYSTEM:	17	32.7	11	27.5	10	30.3	38	30.4
ACETYLSALICYLIC ACID	5	9.6	4	10.0	4	12.1	13	10.4
BUTALBITAL	1	1.9	0	0.0	0	0.0	1	0.8
CAFFEINE	3	5.8	2	5.0	1	3.0	6	4.8
CAFFEINE CITRATE	0	0.0	0	0.0	1	3.0	1	0.8
CINNAMEDRINE HYDROCHLORIDE	0	0.0	1	2.5	1	3.0	2	1.6
CODEINE PHOSPHATE	1	1.9	0	0.0	2	6.1	3	2.4
CYCLOBENZAPRINE	0	0.0	1	2.5	0	0.0	1	0.8
DEXTROMETHORPHAN	0	0.0	0	0.0	1	3.0	1	0.8
EPINEPHRINE	1	1.9	0	0.0	0	0.0	1	0.8
FENTANYL	1	1.9	0	0.0	0	0.0	1	0.8
FLUOXETINE	0	0.0	0	0.0	1	3.0	1	0.8
LIDOCAINE HYDROCHLORIDE	1	1.9	0	0.0	0	0.0	1	0.8
LORAZEPAM	0	0.0	1	2.5	0	0.0	1	0.8
MEPYRAMINE MALEATE	0	0.0	1	2.5	1	3.0	2	1.6
METHOHEXITAL SODIUM	1	1.9	0	0.0	0	0.0	1	0.8
MIDAZOLAM HYDROCHLORIDE	1	1.9	0	0.0	0	0.0	1	0.8
NEFAZODONE	1	1.9	0	0.0	0	0.0	1	0.8
NITROUS OXIDE	1	1.9	0	0.0	0	0.0	1	0.8
PAMABROM	0	0.0	1	2.5	1	3.0	2	1.6
PARACETAMOL	14	26.9	8	20.0	8	24.2	30	24.0
PHENACETIN	0	0.0	0	0.0	1	3.0	1	0.8
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	0.0	0	0.0	1	3.0	1	0.8
PHENYLTOLOXAMINE CITRATE	0	0.0	0	0.0	1	3.0	1	0.8
PROCHLORPERAZINE	1	1.9	1	2.5	0	0.0	2	1.6
PSEUDOEPHEDRINE	0	0.0	0	0.0	1	3.0	1	0.8
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0.0	0	0.0	1	3.0	1	0.8
DERMATOLOGICALS:	7	13.5	3	7.5	2	6.1	12	9.6
BENZOYL PEROXIDE	0	0.0	1	2.5	0	0.0	1	0.8
CALAMINE	0	0.0	0	0.0	1	3.0	1	0.8
CAMPHOR	0	0.0	1	2.5	1	3.0	2	1.6
CHLOROPHYLLIN SODIUM	0	0.0	1	2.5	0	0.0	1	0.8
CLOBETASOL PROPIONATE	0	0.0	1	2.5	0	0.0	1	0.8
DIPHENHYDRAMINE HYDROCHLORIDE	2	3.8	2	5.0	2	6.1	6	4.8
EDETIC ACID	0	0.0	1	2.5	0	0.0	1	0.8
ERYTHROMYCIN	2	3.8	1	2.5	0	0.0	3	2.4
ETHANOL	0	0.0	1	2.5	0	0.0	1	0.8
GLYCEROL	0	0.0	1	2.5	1	3.0	2	1.6
HYDROCORTISONE ACETATE	0	0.0	1	2.5	0	0.0	1	0.8

Table 12.15

Summary of Concomitant Medications by WHO ATC Classification
Continuation Phase
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH MEDICATIONS :	29	55.8%	17	42.5%	19	57.6%	65	52.0%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
ISOPROPANOL	0	0.0	1	2.5	0	0.0	1	0.8
MICONAZOLE NITRATE	2	3.8	0	0.0	0	0.0	2	1.6
NEOMYCIN	1	1.9	0	0.0	0	0.0	1	0.8
PARABENS	0	0.0	1	2.5	0	0.0	1	0.8
PARAFFIN, LIQUID	0	0.0	1	2.5	0	0.0	1	0.8
PROPYLENE GLYCOL	0	0.0	1	2.5	0	0.0	1	0.8
TANNIC ACID	0	0.0	1	2.5	0	0.0	1	0.8
ZINC OXIDE	0	0.0	1	2.5	0	0.0	1	0.8
GU SYSTEM/SEX HORMONES:	2	3.8	0	0.0	0	0.0	2	1.6
MICONAZOLE NITRATE	2	3.8	0	0.0	0	0.0	2	1.6
MUSCULO-SKELETAL:	10	19.2	3	7.5	4	12.1	17	13.6
CYCLOBENZAPRINE	0	0.0	1	2.5	0	0.0	1	0.8
IBUPROFEN	8	15.4	2	5.0	3	9.1	13	10.4
NAPROXEN SODIUM	2	3.8	0	0.0	2	6.1	4	3.2
RESPIRATORY:	14	26.9	6	15.0	8	24.2	28	22.4
BECLOMETASONE DIPROPIONATE	0	0.0	0	0.0	1	3.0	1	0.8
BROMPHENIRAMINE MALEATE	0	0.0	1	2.5	0	0.0	1	0.8
CHLORPHENAMINE MALEATE	2	3.8	1	2.5	0	0.0	3	2.4
CLEMASTINE FUMARATE	0	0.0	0	0.0	1	3.0	1	0.8
COUGH COLD PREPARATIONS NOS	1	1.9	0	0.0	0	0.0	1	0.8
COUGH SYRUP/MED	1	1.9	0	0.0	2	6.1	3	2.4
DEXBROMPHENIRAMINE MALEATE	1	1.9	1	2.5	0	0.0	2	1.6
DEXTROMETHORPHAN	0	0.0	0	0.0	1	3.0	1	0.8
DEXTROMETHORPHAN HYDROBROMIDE	2	3.8	1	2.5	0	0.0	3	2.4
DIMENHYDRINATE	1	1.9	0	0.0	1	3.0	2	1.6
DIPHENHYDRAMINE HYDROCHLORIDE	2	3.8	2	5.0	1	3.0	5	4.0
DOXYLAMINE SUCCINATE	1	1.9	0	0.0	0	0.0	1	0.8
EPHEDRINE SULFATE	1	1.9	0	0.0	0	0.0	1	0.8
GUAIFENESIN	3	5.8	1	2.5	0	0.0	4	3.2
HYDROCODONE	1	1.9	0	0.0	0	0.0	1	0.8
HYDROXYZINE HYDROCHLORIDE	1	1.9	0	0.0	0	0.0	1	0.8
LORATADINE	1	1.9	0	0.0	0	0.0	1	0.8
MEPYRAMINE MALEATE	0	0.0	1	2.5	0	0.0	1	0.8
PARACETAMOL	2	3.8	2	5.0	1	3.0	5	4.0
PHENIRAMINE MALEATE	0	0.0	1	2.5	0	0.0	1	0.8
PHENYLEPHRINE HYDROCHLORIDE	0	0.0	2	5.0	0	0.0	2	1.6
PHENYLPROPANOLAMINE HYDROCHLORIDE	2	3.8	2	5.0	1	3.0	5	4.0

Table 12.15

Summary of Concomitant Medications by WHO ATC Classification
Continuation Phase
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH MEDICATIONS :	29	55.8%	17	42.5%	19	57.6%	65	52.0%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
PREDNISONE	2	3.8	0	0.0	1	3.0	3	2.4
PSEUDOEPHEDRINE	0	0.0	0	0.0	1	3.0	1	0.8
PSEUDOEPHEDRINE HYDROCHLORIDE	1	1.9	2	5.0	2	6.1	5	4.0
PSEUDOEPHEDRINE SULFATE	2	3.8	1	2.5	0	0.0	3	2.4
SALBUTAMOL	1	1.9	0	0.0	3	9.1	4	3.2
SODIUM CHLORIDE	1	1.9	0	0.0	0	0.0	1	0.8
TERBUTALINE SULFATE	0	0.0	0	0.0	1	3.0	1	0.8
THEOPHYLLINE	1	1.9	0	0.0	0	0.0	1	0.8
SENSORY ORGANS:	5	9.6	1	2.5	1	3.0	7	5.6
ERYTHROMYCIN	2	3.8	1	2.5	0	0.0	3	2.4
NEOMYCIN	1	1.9	0	0.0	0	0.0	1	0.8
POLYVIDONE	1	1.9	0	0.0	0	0.0	1	0.8
POLYVINYL ALCOHOL	1	1.9	0	0.0	0	0.0	1	0.8
SODIUM CHLORIDE	2	3.8	0	0.0	0	0.0	2	1.6
STEROID EYE DROPS, NOS	0	0.0	0	0.0	1	3.0	1	0.8
SYSTEMIC HORMONAL:	2	3.8	0	0.0	2	6.1	4	3.2
CORTICOSTEROIDS	0	0.0	0	0.0	1	3.0	1	0.8
PREDNISONE	2	3.8	0	0.0	1	3.0	3	2.4
VARIOUS:	1	1.9	2	5.0	0	0.0	3	2.4
ALLERGENIC EXTRACT, NOS	0	0.0	1	2.5	0	0.0	1	0.8
NUTRITIONAL SUPPLEMENT NOS	1	1.9	1	2.5	0	0.0	2	1.6

PAROXETINE - PROTOCOL 329

Table 12.17

Summary of Patient Compliance
Continuation Phase
Intent-to-Treat Population

	PAROXETINE N = 52		IMIPRAMINE N = 40		PLACEBO N = 33	
	n	%	n	%	n	%
Unknown	2	3.8	2	5.0	4	12.1
< 80 %	9	17.3	4	10.0	5	15.2
80 - 120 %	41	78.8	33	82.5	24	72.7
> 120 %	0	0.0	1	2.5	0	0.0
Mean compliance	88.6		92.9		87.8	

Compliance is calculated by comparing total number of capsules taken with total number of capsules required according to the study medication records during a given assessment period.

PAROXETINE - PROTOCOL 329

Table 12.19

Summary of Patient Dose Levels
Continuation Phase
Intent-to-Treat Population

	PAROXETINE N = 52 Dose Level						IMIPRAMINE N = 40 Dose Level						PLACEBO N = 33 Dose Level					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Week 12	0	0	0	20	17	15	0	0	0	19	7	14	0	0	0	14	5	14
Week 16	0	0	0	11	16	13	0	0	0	17	4	11	0	0	0	8	3	12
Week 20	0	0	0	10	15	10	0	0	0	14	3	8	0	0	0	8	2	9
Week 24	0	0	0	9	10	6	0	0	0	10	2	8	0	0	0	5	2	8
Week 28	0	0	0	6	10	5	0	0	0	7	2	6	0	0	0	5	2	7
Week 32	0	0	0	4	9	5	0	0	0	7	2	4	0	0	0	5	1	7
Endpoint	0	0	0	17	23	12	0	0	0	19	9	12	0	0	0	13	6	14
Maximum	0	0	0	16	20	16	0	0	0	18	8	14	0	0	0	13	6	14

Frequencies represent the highest dose level achieved during a given assessment period.

PAROXETINE - PROTOCOL 329

Table 12.19

Summary of Patient Dose Levels
Continuation Phase
Intent-to-Treat Population

	PAROXETINE N = 52			IMIPRAMINE N = 40			PLACEBO N = 33		
	n	mean	s.d.	n	mean	s.d.	n	mean	s.d.
Mean Dose (mg) at Endpoint	52	29.0	7.48	40	241.3	43.69	33	0.0	0.00

PAROXETINE - PROTOCOL 329

Table 12.29

Summary of Patients Completing the Acute Phase and Not Entering Continuation Phase
Intent-to-Treat Population

PAROXETINE N = 93		IMIPRAMINE N = 95		PLACEBO N = 87	
n	%	n	%	n	%
15	16.1	17	17.9	33	37.9

PAROXETINE - PROTOCOL 329

Table 12.30

Summary of Continuation Phase Status for Responders at the End of Acute Phase Who Completed the Acute Phase
Intent-to-Treat Population

		PAROXETINE N = 93		IMIPRAMINE N = 95		PLACEBO N = 87	
		n	%	n	%	n	%
Responder	Entered Continuation Phase	47	50.5	37	38.9	29	33.3
	Did Not Enter Continuation Phase	7	7.5	4	4.2	14	16.1
Non-responder	Entered Continuation Phase	5	5.4	3	3.2	4	4.6
	Did Not Enter Continuation Phase	8	8.6	13	13.7	19	21.8
Number Completing Acute Phase		67	72.0	57	60.0	66	75.9

Responder: HAMD Total <= 8 or >= 50% improvement from baseline in HAMD Total

10 Data Source Tables: Efficacy

Paroxetine - Protocol 329
Table 15.1
Number (%) of Patients Withdrawing for Lack of Efficacy
Continuation Phase
Intent to Treat Population

Variable	PAROXETINE n/N	%	IMIPRAMINE n/N	%	PLACEBO n/N	%	-- Pairwise Comparisons -- Par vs Pla	Imp vs Pla
Withdrawing for Lack of Efficacy	7 /52	(13.5)	6 /40	(15.0)	6 /33	(18.2)	0.554	0.759

* - significantly different from placebo for alpha = 0.05
Treatment p-value obtained from Fisher's Exact test.

OAKESR8
S329RECU.SAS
13APR98 11:55

Paroxetine - Protocol 329
Table 15.2
Summary of Relapse During Continuation Phase
for Patients Who Had HAMD <=8 at the End of Acute Phase
Intent to Treat Population

	PAROXETINE				IMIPRAMINE				PLACEBO			
		%	Median Time (days)	Mean Time (days)		%	Median Time (days)	Mean Time (days)		%	Median Time (days)	Mean Time (days)
Relapses	16 /44	36.4	60.5	79.3	12 /31	38.7	56.5	61.5	6 /26	23.1	73.5	79.0

Median and Mean Time (days) to Relapse relative to start of continuation phase. Median and mean are not adjusted for censored data.

Relapse = HAMD Total Score greater than 8 OR decrease from baseline is less than 50%.

Paroxetine - Protocol 329
Table 15.3
Baseline Mean and Mean Change from Baseline at Monthly Intervals--HAMD Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	50	18.39	(0.63)	37	17.37	(0.69)	31	18.33	(0.78)	0.946	0.337
Week 12	48	-12.23	(1.03)	32	-12.24	(1.18)	29	-12.32	(1.29)	0.950	0.960
Week 16	38	-13.19	(1.15)	32	-12.18	(1.15)	23	-13.69	(1.37)	0.759	0.382
Week 20	37	-12.69	(1.10)	25	-10.02	(1.18)	17	-13.43	(1.51)	0.666	0.076
Week 24	27	-12.60	(1.39)	17	-10.84	(1.42)	16	-14.46	(1.62)	0.317	0.092
Week 28	19	-13.56	(1.33)	15	-12.31	(1.30)	9	-11.58	(1.77)	0.342	0.740
Week 32	18	-14.81	(1.24)	14	-14.80	(1.29)	13	-15.10	(1.38)	0.877	0.874
Endpoint	50	-11.29	(1.18)	37	-10.95	(1.30)	31	-12.13	(1.46)	0.622	0.527

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.4
Baseline Mean and Mean Change from Baseline at Monthly Intervals-- K-SADS-L Depression 9-Item Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO		-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	49	26.95	(0.73)	37	26.77	(0.79)	30	27.61	(0.90)	0.533	0.465
Week 12	47	-12.99	(1.03)	32	-12.43	(1.17)	28	-12.91	(1.30)	0.959	0.770
Week 16	37	-11.73	(1.24)	31	-13.07	(1.21)	22	-14.61	(1.45)	0.102	0.401
Week 20	35	-11.54	(1.13)	24	-12.06	(1.20)	16	-14.03	(1.54)	0.163	0.314
Week 24	27	-11.29	(1.58)	17	-12.22	(1.61)	16	-14.27	(1.84)	0.162	0.397
Week 28	19	-13.29	(1.50)	15	-14.97	(1.46)	9	-14.14	(2.00)	0.713	0.737
Week 32	18	-13.12	(1.62)	13	-16.70	(1.74)	13	-17.04	(1.81)	0.110	0.891
Endpoint	49	-11.18	(1.17)	37	-11.59	(1.28)	30	-13.04	(1.46)	0.279	0.433

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.5
Mean at Monthly Intervals--CGI Global Improvement
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Week 12	48	1.89	(0.21)	32	1.60	(0.24)	28	1.83	(0.27)	0.849	0.515
Week 16	38	1.73	(0.21)	33	1.87	(0.21)	22	1.58	(0.25)	0.608	0.348
Week 20	37	2.54	(0.26)	25	2.25	(0.28)	17	1.91	(0.36)	0.131	0.457
Week 24	28	2.35	(0.29)	17	2.29	(0.30)	16	1.82	(0.34)	0.176	0.300
Week 28	18	1.63	(0.21)	15	1.57	(0.20)	9	1.97	(0.27)	0.288	0.238
Week 32	18	1.80	(0.28)	14	1.50	(0.29)	13	1.24	(0.31)	0.186	0.547
Endpoint	50	2.58	(0.25)	37	2.54	(0.27)	30	1.87	(0.31)	0.056	0.099

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.6
Distribution Of Patients in Each Class of CGI Global Improvement at Endpoint
Continuation Phase
Intent to Treat Population

	PAROXETINE		IMIPRAMINE		PLACEBO	
	Endpoint		Endpoint		Endpoint	
	n/N	(%)	n/N	(%)	n/N	(%)
Very Much Improved (1)	20 /50	(40.0)	14 /37	(37.8)	17 /30	(56.7)
Much Improved (2)	15 /50	(30.0)	11 /37	(29.7)	5 /30	(16.7)
Minimally Improved (3)	5 /50	(10.0)	2 /37	(5.4)	4 /30	(13.3)
No Change (4)	2 /50	(4.0)	5 /37	(13.5)	3 /30	(10.0)
Minimally Worse (5)	3 /50	(6.0)	1 /37	(2.7)	1 /30	(3.3)
Much Worse (6)	3 /50	(6.0)	3 /37	(8.1)	0 /30	(0.0)
Very Much Worse (7)	2 /50	(4.0)	1 /37	(2.7)	0 /30	(0.0)

Only patients with one or more on-therapy evaluations are included.

Paroxetine - Protocol 329
Table 15.7
Baseline Mean and Mean Change from Baseline at Monthly Intervals--HAMD Anxiety Somatization Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	50	5.94	(0.32)	37	4.92	(0.35)	31	5.31	(0.40)	0.180	0.444
Week 12	48	-3.62	(0.41)	32	-3.36	(0.47)	29	-3.28	(0.52)	0.566	0.896
Week 16	38	-4.52	(0.49)	32	-3.38	(0.49)	23	-3.89	(0.58)	0.363	0.484
Week 20	37	-4.54	(0.49)	25	-2.73	(0.53)	17	-3.70	(0.68)	0.280	0.257
Week 24	27	-4.86	(0.70)	17	-2.59	(0.72)	16	-4.41	(0.82)	0.637	0.092
Week 28	19	-4.87	(0.67)	15	-3.50	(0.65)	9	-3.23	(0.89)	0.120	0.807
Week 32	18	-5.57	(0.73)	14	-4.21	(0.75)	13	-4.18	(0.81)	0.201	0.972
Endpoint	50	-3.84	(0.49)	37	-2.71	(0.54)	31	-3.36	(0.61)	0.507	0.408

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Anxiety/Somatization Scale includes items 10, 11, 12, 13, 15, 17

Paroxetine - Protocol 329
Table 15.8
Baseline Mean and Mean Change from Baseline at Monthly Intervals--HAMD Sleep Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	50	2.00	(0.28)	37	2.33	(0.30)	31	2.21	(0.34)	0.613	0.785
Week 12	48	-1.39	(0.33)	32	-1.63	(0.38)	29	-1.31	(0.42)	0.865	0.548
Week 16	38	-1.28	(0.37)	32	-1.59	(0.37)	23	-1.76	(0.44)	0.361	0.753
Week 20	37	-1.75	(0.36)	25	-1.21	(0.38)	17	-1.41	(0.49)	0.539	0.743
Week 24	27	-1.39	(0.42)	17	-1.86	(0.43)	16	-1.66	(0.49)	0.636	0.754
Week 28	19	-1.12	(0.35)	15	-1.73	(0.34)	9	-0.76	(0.47)	0.508	0.096
Week 32	18	-1.44	(0.41)	14	-2.44	(0.43)	13	-1.41	(0.46)	0.958	0.101
Endpoint	50	-1.32	(0.30)	37	-1.69	(0.33)	31	-1.49	(0.37)	0.708	0.665

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Sleep Scale includes items 4, 5, 6

Paroxetine - Protocol 329
Table 15.9
Baseline Mean and Mean Change from Baseline at Monthly Intervals--HAMD Cognitive Disturbance Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---			
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla		Imp vs Pla	
Baseline	50	3.04	(0.29)	37	3.12	(0.32)	31	3.47	(0.36)	0.312		0.446	
Week 12	48	-1.63	(0.34)	32	-2.24	(0.39)	29	-2.67	(0.43)	0.037	*	0.436	
Week 16	38	-1.82	(0.38)	32	-2.09	(0.38)	23	-2.54	(0.46)	0.191		0.437	
Week 20	37	-1.66	(0.39)	25	-1.35	(0.42)	17	-2.73	(0.53)	0.082		0.044	*
Week 24	27	-1.77	(0.52)	17	-1.17	(0.53)	16	-3.18	(0.60)	0.045	*	0.013	*
Week 28	19	-2.46	(0.48)	15	-2.00	(0.47)	9	-2.86	(0.64)	0.588		0.276	
Week 32	18	-2.65	(0.48)	14	-2.46	(0.50)	13	-3.41	(0.54)	0.297		0.198	
Endpoint	50	-1.42	(0.34)	37	-1.92	(0.37)	31	-2.41	(0.42)	0.046	*	0.352	

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Cognitive Disturbance Scale includes items 2, 3, 9

Paroxetine - Protocol 329
Table 15.10
Baseline Mean and Mean Change from Baseline at Monthly Intervals--HAMD Retardation Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO		-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	50	7.15	(0.26)	37	6.60	(0.29)	31	6.91	(0.32)	0.522	0.445
Week 12	48	-5.52	(0.43)	32	-4.77	(0.49)	29	-4.88	(0.54)	0.310	0.871
Week 16	38	-5.33	(0.55)	32	-4.85	(0.55)	23	-5.22	(0.65)	0.884	0.653
Week 20	37	-4.57	(0.43)	25	-4.42	(0.46)	17	-5.26	(0.58)	0.300	0.253
Week 24	27	-4.56	(0.54)	17	-4.76	(0.55)	16	-5.07	(0.63)	0.478	0.706
Week 28	19	-5.09	(0.58)	15	-4.68	(0.57)	9	-4.43	(0.77)	0.467	0.790
Week 32	18	-4.99	(0.51)	14	-5.16	(0.53)	13	-6.05	(0.57)	0.174	0.253
Endpoint	50	-4.53	(0.48)	37	-4.41	(0.53)	31	-4.66	(0.60)	0.848	0.747

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Retardation Scale includes items 1, 7, 8, 14

Paroxetine - Protocol 329
Table 15.11
Baseline Mean and Mean Change from Baseline at Monthly Intervals--Self Perception Profile Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	60.63	(3.55)	23	60.12	(4.10)	15	54.77	(4.74)	0.309	0.379
Week 32	17	19.99	(5.68)	13	28.94	(6.16)	12	23.33	(6.35)	0.695	0.525
Endpoint	28	21.29	(3.75)	23	22.35	(4.33)	15	23.61	(5.01)	0.702	0.844

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.12
Baseline Mean and Mean Change from Baseline at Monthly Intervals--Autonomous Functioning Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	24	87.26	(6.83)	22	98.01	(7.57)	15	94.33	(8.37)	0.505	0.734
Week 32	14	28.30	(8.32)	13	20.02	(8.42)	12	27.67	(8.55)	0.958	0.519
Endpoint	24	24.39	(5.64)	22	17.93	(6.25)	15	22.32	(6.91)	0.812	0.624

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.13
Baseline Mean and Mean Change from Baseline at Monthly Intervals--Autonomous Functioning Scale:Self/Family Care Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	24	24.11	(2.30)	22	27.44	(2.55)	15	30.17	(2.82)	0.094	0.457
Week 32	14	8.34	(3.09)	13	6.14	(3.13)	12	8.09	(3.18)	0.954	0.658
Endpoint	24	6.74	(2.20)	22	5.48	(2.43)	15	5.38	(2.69)	0.688	0.976

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.14
Baseline Mean and Mean Change from Baseline at Monthly Intervals--Autonomous Functioning Scale:Management Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	24	36.85	(3.23)	22	37.03	(3.58)	15	35.74	(3.95)	0.824	0.801
Week 32	14	12.01	(3.36)	13	9.09	(3.40)	12	10.48	(3.45)	0.754	0.771
Endpoint	24	10.22	(2.24)	22	7.67	(2.49)	15	9.96	(2.75)	0.941	0.521

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.15
Baseline Mean and Mean Change from Baseline at Monthly Intervals--Autonomous Functioning Scale:Recreational Activity Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	24	20.09	(2.09)	22	26.51	(2.32)	15	21.95	(2.56)	0.566	0.174
Week 32	14	5.08	(2.66)	13	2.53	(2.69)	12	6.88	(2.73)	0.643	0.256
Endpoint	24	4.74	(1.90)	22	3.05	(2.10)	15	5.04	(2.32)	0.918	0.508

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.16
Baseline Mean and Mean Change from Baseline at Monthly Intervals--Autonomous Functioning Scale:Social/Vocational Activities Subscor
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	24	6.24	(0.73)	22	7.06	(0.81)	15	6.53	(0.90)	0.798	0.644
Week 32	14	2.81	(0.95)	13	2.52	(0.96)	12	2.19	(0.97)	0.650	0.806
Endpoint	24	2.70	(0.59)	22	1.97	(0.66)	15	1.87	(0.73)	0.365	0.912

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.17
Baseline Mean and Mean Change from Baseline at Monthly Intervals--Sickness Impact Profile Scale
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	30.08	(2.00)	22	31.08	(2.33)	15	31.99	(2.67)	0.554	0.790
Week 32	17	-18.36	(3.29)	12	-17.38	(3.65)	12	-18.46	(3.68)	0.985	0.835
Endpoint	28	-15.18	(2.55)	22	-14.39	(2.98)	15	-17.45	(3.41)	0.582	0.485

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.18
Baseline Mean and Mean Change from Baseline at Monthly Intervals--SIP Scale:Present Health Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	2.38	(0.16)	22	2.50	(0.19)	15	2.74	(0.21)	0.159	0.377
Week 32	17	-0.15	(0.25)	12	-0.61	(0.27)	12	-0.52	(0.28)	0.330	0.806
Endpoint	28	-0.05	(0.18)	22	-0.41	(0.21)	15	-0.62	(0.24)	0.052	0.484

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.19
Baseline Mean and Mean Change from Baseline at Monthly Intervals--SIP Scale:Present Quality of Life Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	3.46	(0.15)	22	3.42	(0.18)	15	3.47	(0.21)	0.955	0.840
Week 32	17	-1.02	(0.34)	12	-1.35	(0.38)	12	-1.12	(0.38)	0.854	0.669
Endpoint	28	-0.96	(0.22)	22	-1.14	(0.26)	15	-1.16	(0.29)	0.572	0.955

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.20
Baseline Mean and Mean Change from Baseline at Monthly Intervals--SIP Scale:Sleep/Rest Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	3.23	(0.36)	22	3.33	(0.42)	15	3.74	(0.48)	0.386	0.506
Week 32	17	-1.75	(0.59)	12	-1.50	(0.65)	12	-2.38	(0.66)	0.477	0.343
Endpoint	28	-1.46	(0.43)	22	-1.08	(0.50)	15	-2.27	(0.57)	0.243	0.110

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.21
Baseline Mean and Mean Change from Baseline at Monthly Intervals--SIP Scale:Home Maintenance Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	2.72	(0.39)	22	2.39	(0.46)	14	2.46	(0.53)	0.688	0.909
Week 32	17	-1.85	(0.45)	12	-0.92	(0.50)	12	-1.16	(0.51)	0.308	0.741
Endpoint	28	-1.43	(0.37)	22	-0.75	(0.43)	14	-1.39	(0.50)	0.938	0.321

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.22
Baseline Mean and Mean Change from Baseline at Monthly Intervals--SIP Scale:Social Interaction Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	6.92	(0.74)	22	7.66	(0.87)	15	8.31	(0.99)	0.249	0.608
Week 32	17	-5.90	(1.12)	12	-4.14	(1.24)	12	-6.65	(1.25)	0.654	0.160
Endpoint	28	-4.54	(0.88)	22	-3.90	(1.02)	15	-6.05	(1.17)	0.289	0.157

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.23
Baseline Mean and Mean Change from Baseline at Monthly Intervals--SIP Scale:Alertness Behavior Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	27	5.12	(0.54)	22	6.04	(0.62)	15	4.79	(0.70)	0.699	0.171
Week 32	16	-2.81	(0.84)	12	-4.65	(0.90)	12	-2.72	(0.91)	0.940	0.138
Endpoint	27	-2.79	(0.65)	22	-3.54	(0.74)	15	-2.27	(0.84)	0.613	0.243

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.24
Baseline Mean and Mean Change from Baseline at Monthly Intervals--SIP Scale:Communication Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	2.22	(0.25)	22	2.00	(0.29)	15	2.11	(0.33)	0.788	0.783
Week 32	17	-1.75	(0.42)	12	-1.17	(0.47)	12	-1.04	(0.47)	0.267	0.848
Endpoint	28	-1.39	(0.27)	22	-0.94	(0.32)	15	-1.06	(0.36)	0.447	0.798

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.25
Baseline Mean and Mean Change from Baseline at Monthly Intervals--SIP Scale:Recreational Pastimes Subscore
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---	
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla	Imp vs Pla
Baseline	28	3.79	(0.43)	22	3.86	(0.50)	15	4.37	(0.58)	0.406	0.493
Week 32	17	-2.91	(0.77)	12	-3.06	(0.85)	12	-2.80	(0.86)	0.923	0.831
Endpoint	28	-2.39	(0.55)	22	-2.67	(0.64)	15	-2.66	(0.74)	0.757	0.998

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

Paroxetine - Protocol 329
Table 15.26
Baseline Mean and Mean Change from Baseline at Monthly Intervals--HAMD Depressed Mood Item
Continuation Phase
Intent to Treat Population

	PAROXETINE			IMIPRAMINE			PLACEBO			-- Pairwise Comparisons ---		
	n	mean	(s.e.)	n	mean	(s.e.)	n	mean	(s.e.)	Par vs Pla		Imp vs Pla
Baseline	50	2.92	(0.12)	37	2.53	(0.14)	31	2.55	(0.15)	0.045	*	0.929
Week 12	48	-2.43	(0.23)	32	-1.83	(0.26)	29	-1.76	(0.29)	0.044	*	0.846
Week 16	38	-2.21	(0.26)	32	-1.69	(0.26)	23	-1.94	(0.31)	0.462		0.524
Week 20	37	-1.85	(0.23)	25	-1.69	(0.24)	17	-1.94	(0.31)	0.790		0.526
Week 24	27	-2.06	(0.26)	17	-1.99	(0.26)	16	-2.08	(0.30)	0.935		0.814
Week 28	19	-1.97	(0.32)	15	-1.69	(0.31)	9	-1.58	(0.42)	0.426		0.833
Week 32	18	-2.10	(0.22)	14	-2.03	(0.23)	13	-2.64	(0.25)	0.112		0.079
Endpoint	50	-1.86	(0.23)	37	-1.69	(0.25)	31	-1.77	(0.29)	0.780		0.822

Treatment differences and p-values are computed using analysis of variance with a model including effects for treatment and investigator.
* - significantly different from placebo for alpha = 0.05

HAMD Depressed Mood Item is HAMD item 1

11 Data Source Tables: Safety

16.0 Location of Patient Narratives

Study 29060/329 Continuation Phase

PID	Serious AE (non-fatal)	AE Leading to Withdrawal	Vital Signs of Potential Clinical Concern	Laboratory Values of Potential Clinical Concern
	Table No.	**Table No.**	**Table No.**	**Table No.**
329.001.00122			16.12.1	
329.002.00057		16.9.4		
329.002.00058	16.8.1	X		
329.002.00241	16.8.1	X		
329.003.00250	16.8.1	X		
329.003.00289				16.14.1
329.004.00017	16.8.1			
329.005.00006		16.9.4		
329.005.00007		16.9.4		
329.005.00011	16.8.1	X		
329.005.00012		16.9.4		
329.005.00109	16.8.1			
329.005.00111		16.9.4		
329.005.00116		16.9.4		
329.005.00151			16.12.1	
329.005.00257			16.12.1	
329.007.00268			16.12.1	
329.008.00273	16.8.1	X		
329.009.00169		16.9.4		
329.009.00170	16.8.1			
329.009.00194		16.9.4		
329.009.00305			16.12.1	
329.009.00325			16.12.1	
329.010.00281		16.9.4		
329.011.00208		16.9.4		
329.012.00221	16.8.1	X		

PAROXETINE - PROTOCOL 329

Table 16.1

Summary of Exposure to Study Medication
Continuation Phase
Intent-to-Treat Population

Total Duration of Exposure (Days)	PAROXETINE N = 52 Dose (mg) 20		30		40		200		IMIPRAMINE N = 40 Dose (mg) 250		300		PLACEBO N = 33 Dose (mg) 0	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1 - 28	5	9.6	6	11.5	3	5.8	2	5.0	5	12.5	3	7.5	6	18.2
29 - 56	3	5.8	3	5.8	1	1.9	3	7.5	3	7.5	2	5.0	7	21.2
57 - 84	3	5.8	3	5.8	4	7.7	3	7.5	1	2.5	1	2.5	4	12.1
85 - 112	3	5.8	3	5.8	3	5.8	3	7.5	0	0.0	2	5.0	2	6.1
113 - 140	2	3.8	3	5.8	0	0.0	2	5.0	2	5.0	1	2.5	1	3.0
>= 141	5	9.6	6	11.5	5	9.6	7	17.5	0	0.0	5	12.5	13	39.4

PAROXETINE - PROTOCOL 329

Table 16.1

Summary of Exposure to Study Medication
Continuation Phase
Intent-to-Treat Population

	PAROXETINE N = 52						IMIPRAMINE N = 40						PLACEBO N = 33					
	n	mean	sem	median	min	max	n	mean	sem	median	min	max	n	mean	sem	median	min	max
Days of Total Exposure	52	114.3	9.32	101	1	215	40	110.2	10.25	112	1	204	33	110.9	13.30	98	1	222

PAROXETINE - PROTOCOL 329

Table 16.1.1

Overall Duration of Exposure to Study Medication
Intent-to-Treat Population

Total Duration of Exposure (Days)	PAROXETINE N = 93 n	%	IMIPRAMINE N = 95 n	%	PLACEBO N = 87 n	%
<=28	93	100.0	95	100.0	87	100.0
>28	78	83.9	77	81.1	75	86.2
>56	67	72.0	56	58.9	64	73.6
>84	47	50.5	36	37.9	30	34.5
>112	40	43.0	31	32.6	21	24.1
>140	35	37.6	22	23.2	18	20.7
>168	23	24.7	20	21.1	14	16.1
>196	21	22.6	14	14.7	14	16.1
>224	17	18.3	13	13.7	13	14.9

Table 16.2.1

Summary of Treatment-Emergent Adverse Experiences during Continuation Phase by ADECS Body System and Preferred Term
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	37	71.2%	27	67.5%	21	63.6%	85	68.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Body as a Whole	23	44.2	14	35.0	15	45.5	52	41.6
ABDOMINAL PAIN	6	11.5	4	10.0	1	3.0	11	8.8
ABNORMAL LABORATORY VALUE	0	0.0	1	2.5	0	0.0	1	0.8
ACCIDENTAL OVERDOSE	0	0.0	1	2.5	0	0.0	1	0.8
ALLERGIC REACTION	1	1.9	0	0.0	0	0.0	1	0.8
ASTHENIA	2	3.8	2	5.0	1	3.0	5	4.0
BACK PAIN	0	0.0	0	0.0	2	6.1	2	1.6
CHEST PAIN	1	1.9	0	0.0	0	0.0	1	0.8
FEVER	2	3.8	0	0.0	0	0.0	2	1.6
HEADACHE	14	26.9	7	17.5	6	18.2	27	21.6
INFECTION	5	9.6	1	2.5	4	12.1	10	8.0
PAIN	0	0.0	0	0.0	1	3.0	1	0.8
TRAUMA	2	3.8	0	0.0	5	15.2	7	5.6
Cardiovascular System	5	9.6	4	10.0	2	6.1	11	8.8
ARRHYTHMIA	1	1.9	0	0.0	1	3.0	2	1.6
ELECTROCARDIOGRAM ABNORMAL	0	0.0	1	2.5	0	0.0	1	0.8
HYPERTENSION	1	1.9	1	2.5	0	0.0	2	1.6
PALPITATION	1	1.9	0	0.0	1	3.0	2	1.6
SYNCOPE	1	1.9	1	2.5	0	0.0	2	1.6
TACHYCARDIA	1	1.9	2	5.0	0	0.0	3	2.4
Digestive System	12	23.1	13	32.5	6	18.2	31	24.8
CONSTIPATION	2	3.8	1	2.5	0	0.0	3	2.4
DECREASED APPETITE	1	1.9	0	0.0	0	0.0	1	0.8
DIARRHEA	0	0.0	3	7.5	3	9.1	6	4.8
DRY MOUTH	1	1.9	3	7.5	0	0.0	4	3.2
DYSPEPSIA	0	0.0	2	5.0	0	0.0	2	1.6
GASTROINTESTINAL DISORDER	0	0.0	1	2.5	0	0.0	1	0.8
GINGIVITIS	1	1.9	0	0.0	0	0.0	1	0.8
INCREASED APPETITE	1	1.9	1	2.5	0	0.0	2	1.6
NAUSEA	9	17.3	3	7.5	3	9.1	15	12.0
PEPTIC ULCER HEMORRHAGE	1	1.9	0	0.0	0	0.0	1	0.8
TOOTH DISORDER	0	0.0	1	2.5	2	6.1	3	2.4
ULCERATIVE STOMATITIS	0	0.0	1	2.5	0	0.0	1	0.8
VOMITING	4	7.7	2	5.0	3	9.1	9	7.2
Hemic and Lymphatic System	2	3.8	1	2.5	3	9.1	6	4.8
ANEMIA	0	0.0	1	2.5	0	0.0	1	0.8
LYMPHADENOPATHY	0	0.0	0	0.0	1	3.0	1	0.8

Table 16.2.1

Summary of Treatment-Emergent Adverse Experiences during Continuation Phase by ADECS Body System and Preferred Term
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	37	71.2%	27	67.5%	21	63.6%	85	68.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
THROMBOCYTHEMIA	1	1.9	0	0.0	0	0.0	1	0.8
THROMBOCYTOPENIA	1	1.9	0	0.0	0	0.0	1	0.8
WBC ABNORMALITY	0	0.0	0	0.0	2	6.1	2	1.6
Metabolic and Nutritional Disorders	4	7.7	2	5.0	0	0.0	6	4.8
DEHYDRATION	0	0.0	1	2.5	0	0.0	1	0.8
WEIGHT GAIN	4	7.7	1	2.5	0	0.0	5	4.0
Musculoskeletal System	1	1.9	3	7.5	0	0.0	4	3.2
MYALGIA	1	1.9	3	7.5	0	0.0	4	3.2
Nervous System	21	40.4	11	27.5	8	24.2	40	32.0
ABNORMAL DREAMS	0	0.0	1	2.5	0	0.0	1	0.8
AGITATION	2	3.8	0	0.0	0	0.0	2	1.6
AMNESIA	1	1.9	0	0.0	0	0.0	1	0.8
ANXIETY	0	0.0	1	2.5	0	0.0	1	0.8
CONVULSION	0	0.0	1	2.5	0	0.0	1	0.8
DIZZINESS	9	17.3	3	7.5	4	12.1	16	12.8
DRUG DEPENDENCE	1	1.9	0	0.0	1	3.0	2	1.6
EMOTIONAL LABILITY	4	7.7	1	2.5	1	3.0	6	4.8
HOSTILITY	0	0.0	0	0.0	1	3.0	1	0.8
HYPERKINESIA	2	3.8	0	0.0	0	0.0	2	1.6
HYPERTONIA	1	1.9	0	0.0	0	0.0	1	0.8
HYPESTHESIA	0	0.0	0	0.0	1	3.0	1	0.8
INSOMNIA	4	7.7	3	7.5	1	3.0	8	6.4
MANIC REACTION	1	1.9	0	0.0	0	0.0	1	0.8
NERVOUSNESS	1	1.9	0	0.0	0	0.0	1	0.8
NEUROSIS	0	0.0	1	2.5	0	0.0	1	0.8
PERSONALITY DISORDER	1	1.9	0	0.0	0	0.0	1	0.8
SOMNOLENCE	1	1.9	1	2.5	0	0.0	2	1.6
TREMOR	3	5.8	0	0.0	0	0.0	3	2.4
VESTIBULAR DISORDER	1	1.9	0	0.0	0	0.0	1	0.8
Respiratory System	14	26.9	5	12.5	8	24.2	27	21.6
ASTHMA	1	1.9	0	0.0	1	3.0	2	1.6
BRONCHITIS	2	3.8	0	0.0	1	3.0	3	2.4
COUGH INCREASED	2	3.8	0	0.0	1	3.0	3	2.4
EPISTAXIS	1	1.9	0	0.0	1	3.0	2	1.6
PHARYNGITIS	6	11.5	0	0.0	3	9.1	9	7.2
RESPIRATORY DISORDER	6	11.5	3	7.5	2	6.1	11	8.8

Table 16.2.1

Summary of Treatment-Emergent Adverse Experiences during Continuation Phase by ADECS Body System and Preferred Term
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	37	71.2%	27	67.5%	21	63.6%	85	68.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
RHINITIS	3	5.8	1	2.5	1	3.0	5	4.0
SINUSITIS	1	1.9	1	2.5	3	9.1	5	4.0
Skin and Appendages	2	3.8	3	7.5	3	9.1	8	6.4
ACNE	0	0.0	1	2.5	0	0.0	1	0.8
CONTACT DERMATITIS	1	1.9	1	2.5	0	0.0	2	1.6
DRY SKIN	0	0.0	1	2.5	0	0.0	1	0.8
PHOTOSENSITIVITY	1	1.9	0	0.0	0	0.0	1	0.8
RASH	0	0.0	0	0.0	2	6.1	2	1.6
SWEATING	0	0.0	1	2.5	0	0.0	1	0.8
URTICARIA	0	0.0	0	0.0	1	3.0	1	0.8
Special Senses	4	7.7	1	2.5	2	6.1	7	5.6
ABNORMAL VISION	1	1.9	1	2.5	0	0.0	2	1.6
EAR PAIN	1	1.9	0	0.0	0	0.0	1	0.8
OTITIS EXTERNA	1	1.9	0	0.0	0	0.0	1	0.8
OTITIS MEDIA	1	1.9	0	0.0	2	6.1	3	2.4
Urogenital System	2	3.8	3	7.5	1	3.0	6	4.8
ALBUMINURIA	1	1.9	0	0.0	1	3.0	2	1.6
DYSURIA	0	0.0	1	2.5	0	0.0	1	0.8
HAEMATURIA	1	1.9	0	0.0	0	0.0	1	0.8
PYURIA	0	0.0	1	2.5	0	0.0	1	0.8
URINARY CASTS	1	1.9	0	0.0	0	0.0	1	0.8
URINARY RETENTION	0	0.0	1	2.5	0	0.0	1	0.8
URINARY TRACT INFECTION	1	1.9	0	0.0	0	0.0	1	0.8
URINATION IMPAIRED	0	0.0	1	2.5	0	0.0	1	0.8

PAROXETINE - PROTOCOL 329

Table 16.2.2

Summary of Treatment-Emergent Adverse Experiences during Continuation Phase by ADECS Body System and Preferred Term
Male Specific Adverse Experiences
Intent-to-Treat Population

NO DATA AVAILABLE FOR THIS REPORT

PAROXETINE - PROTOCOL 329

Table 16.2.3

Summary of Treatment-Emergent Adverse Experiences during Continuation Phase by ADECS Body System and Preferred Term
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP		PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS	:	33	100.0%	18	100.0%	23	100.0%	74	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	4	12.1%	2	11.1%	3	13.0%	9	12.2%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%	N	%
Urogenital System		4	12.1	2	11.1	3	13.0	9	12.2
DYSMENORRHEA		3	9.1	1	5.6	2	8.7	6	8.1
FEMALE GENITAL DISORDERS		1	3.0	0	0.0	0	0.0	1	1.4
MENSTRUAL DISORDER		0	0.0	0	0.0	1	4.3	1	1.4
UNINTENDED PREGNANCY		0	0.0	1	5.6	0	0.0	1	1.4

Paroxetine - Protocol 329
Table 16.2.4
Summary of Treatment-Emergent Adverse Experiences During Both Phases Combined
by ADECS Body System and Preferred Term
Intent-to-Treat Population

Body System Preferred Term	PAROXETINE N = 93 n (%)	IMIPRAMINE N = 95 n (%)	PLACEBO N = 87 n (%)
Body as a Whole	57 (61.3%)	59 (62.1%)	56 (64.4%)
Abdominal Pain	15 (16.1%)	9 (9.5%)	11 (12.6%)
Abnormal Laboratory Value	0 (0.0%)	1 (1.1%)	0 (0.0%)
Accidental Overdose	0 (0.0%)	1 (1.1%)	0 (0.0%)
Allergic Reaction	3 (3.2%)	1 (1.1%)	3 (3.4%)
Asthenia	12 (12.9%)	9 (9.5%)	11 (12.6%)
Back Pain	4 (4.3%)	2 (2.1%)	11 (12.6%)
Chest Pain	3 (3.2%)	5 (5.3%)	2 (2.3%)
Chills	1 (1.1%)	3 (3.2%)	0 (0.0%)
Fever	2 (2.2%)	2 (2.1%)	4 (4.6%)
Headache	39 (41.9%)	42 (44.2%)	37 (42.5%)
Infection	14 (15.1%)	6 (6.3%)	12 (13.8%)
Pain	0 (0.0%)	0 (0.0%)	4 (4.6%)
Trauma	4 (4.3%)	3 (3.2%)	8 (9.2%)

* Percentage corrected for gender

Paroxetine - Protocol 329
Table 16.2.4
Summary of Treatment-Emergent Adverse Experiences During Both Phases Combined
by ADECS Body System and Preferred Term
Intent-to-Treat Population

Body System Preferred Term	PAROXETINE N = 93 n (%)	IMIPRAMINE N = 95 n (%)	PLACEBO N = 87 n (%)
Cardiovascular System	11 (11.8%)	43 (45.3%)	13 (14.9%)
Arrhythmia	1 (1.1%)	1 (1.1%)	2 (2.3%)
Av Block	1 (1.1%)	2 (2.1%)	2 (2.3%)
Bradycardia	0 (0.0%)	0 (0.0%)	1 (1.1%)
Bundle Branch Block	0 (0.0%)	1 (1.1%)	1 (1.1%)
Electrocardiogram Abnormal	0 (0.0%)	4 (4.2%)	0 (0.0%)
Extrasystoles	0 (0.0%)	2 (2.1%)	0 (0.0%)
Heart Malformation	0 (0.0%)	1 (1.1%)	1 (1.1%)
Hypertension	1 (1.1%)	3 (3.2%)	0 (0.0%)
Migraine	1 (1.1%)	1 (1.1%)	0 (0.0%)
Nodal Arrhythmia	0 (0.0%)	0 (0.0%)	1 (1.1%)
Palpitation	2 (2.2%)	3 (3.2%)	1 (1.1%)
Postural Hypotension	1 (1.1%)	13 (13.7%)	1 (1.1%)
Qt Interval Prolonged	0 (0.0%)	3 (3.2%)	0 (0.0%)
Supraventricular Extrasystoles	0 (0.0%)	0 (0.0%)	1 (1.1%)
Syncope	2 (2.2%)	5 (5.3%)	1 (1.1%)
Tachycardia	3 (3.2%)	19 (20.0%)	1 (1.1%)
Vasodilatation	0 (0.0%)	6 (6.3%)	2 (2.3%)

* Percentage corrected for gender

Paroxetine - Protocol 329
Table 16.2.4
Summary of Treatment-Emergent Adverse Experiences During Both Phases Combined
by ADECS Body System and Preferred Term
Intent-to-Treat Population

Body System Preferred Term	PAROXETINE N = 93 n (%)	IMIPRAMINE N = 95 n (%)	PLACEBO N = 87 n (%)
Digestive System	53 (57.0%)	66 (69.5%)	42 (48.3%)
Constipation	7 (7.5%)	10 (10.5%)	4 (4.6%)
Decreased Appetite	8 (8.6%)	2 (2.1%)	4 (4.6%)
Diarrhea	7 (7.5%)	6 (6.3%)	7 (8.0%)
Dry Mouth	19 (20.4%)	43 (45.3%)	12 (13.8%)
Dyspepsia	6 (6.5%)	10 (10.5%)	4 (4.6%)
Dysphagia	0 (0.0%)	3 (3.2%)	0 (0.0%)
Esophagitis	1 (1.1%)	1 (1.1%)	0 (0.0%)
Gastritis	0 (0.0%)	1 (1.1%)	0 (0.0%)
Gastroenteritis	0 (0.0%)	1 (1.1%)	0 (0.0%)
Gastrointestinal Disorder	2 (2.2%)	2 (2.1%)	1 (1.1%)
Gingivitis	1 (1.1%)	0 (0.0%)	0 (0.0%)
Increased Appetite	4 (4.3%)	2 (2.1%)	1 (1.1%)
Nausea	26 (28.0%)	25 (26.3%)	19 (21.8%)
Peptic Ulcer Hemorrhage	1 (1.1%)	0 (0.0%)	0 (0.0%)
Tooth Disorder	5 (5.4%)	3 (3.2%)	4 (4.6%)
Ulcerative Stomatitis	0 (0.0%)	2 (2.1%)	1 (1.1%)
Vomiting	7 (7.5%)	10 (10.5%)	9 (10.3%)
Hemic and Lymphatic System	3 (3.2%)	3 (3.2%)	6 (6.9%)
Anemia	1 (1.1%)	1 (1.1%)	0 (0.0%)
Eosinophilia	0 (0.0%)	1 (1.1%)	1 (1.1%)
Leukopenia	0 (0.0%)	1 (1.1%)	0 (0.0%)
Lymphadenopathy	0 (0.0%)	0 (0.0%)	2 (2.3%)
Thrombocythemia	1 (1.1%)	0 (0.0%)	1 (1.1%)
Thrombocytopenia	1 (1.1%)	0 (0.0%)	0 (0.0%)
Wbc Abnormality	0 (0.0%)	0 (0.0%)	2 (2.3%)

* Percentage corrected for gender

Paroxetine - Protocol 329
Table 16.2.4
Summary of Treatment-Emergent Adverse Experiences During Both Phases Combined
by ADECS Body System and Preferred Term
Intent-to-Treat Population

Body System Preferred Term	PAROXETINE N = 93 n (%)	IMIPRAMINE N = 95 n (%)	PLACEBO N = 87 n (%)
Metabolic and Nutritional Disorders	7 (7.5%)	6 (6.3%)	6 (6.9%)
Dehydration	0 (0.0%)	1 (1.1%)	0 (0.0%)
Hyperglycemia	0 (0.0%)	1 (1.1%)	1 (1.1%)
Thirst	0 (0.0%)	2 (2.1%)	3 (3.4%)
Weight Gain	5 (5.4%)	1 (1.1%)	0 (0.0%)
Weight Loss	2 (2.2%)	1 (1.1%)	2 (2.3%)
Musculoskeletal System	4 (4.3%)	4 (4.2%)	6 (6.9%)
Arthralgia	1 (1.1%)	1 (1.1%)	4 (4.6%)
Myalgia	4 (4.3%)	3 (3.2%)	2 (2.3%)
Myasthenia	1 (1.1%)	0 (0.0%)	0 (0.0%)

* Percentage corrected for gender

Paroxetine - Protocol 329
Table 16.2.4
Summary of Treatment-Emergent Adverse Experiences During Both Phases Combined
by ADECS Body System and Preferred Term
Intent-to-Treat Population

Body System Preferred Term	PAROXETINE N = 93 n (%)	IMIPRAMINE N = 95 n (%)	PLACEBO N = 87 n (%)
Nervous System	64 (68.8%)	73 (76.8%)	36 (41.4%)
Abnormal Dreams	2 (2.2%)	5 (5.3%)	2 (2.3%)
Agitation	4 (4.3%)	2 (2.1%)	0 (0.0%)
Amnesia	1 (1.1%)	1 (1.1%)	0 (0.0%)
Anxiety	2 (2.2%)	1 (1.1%)	2 (2.3%)
Concentration Impaired	1 (1.1%)	1 (1.1%)	0 (0.0%)
Convulsion	0 (0.0%)	1 (1.1%)	0 (0.0%)
Depersonalization	0 (0.0%)	1 (1.1%)	1 (1.1%)
Depression	4 (4.3%)	1 (1.1%)	2 (2.3%)
Dizziness	26 (28.0%)	46 (48.4%)	20 (23.0%)
Drug Dependence	1 (1.1%)	1 (1.1%)	1 (1.1%)
Emotional Lability	8 (8.6%)	4 (4.2%)	2 (2.3%)
Euphoria	1 (1.1%)	1 (1.1%)	1 (1.1%)
Hallucinations	1 (1.1%)	1 (1.1%)	0 (0.0%)
Hostility	7 (7.5%)	3 (3.2%)	1 (1.1%)
Hyperkinesia	3 (3.2%)	2 (2.1%)	1 (1.1%)
Hypertonia	2 (2.2%)	1 (1.1%)	1 (1.1%)
Hypesthesia	0 (0.0%)	1 (1.1%)	1 (1.1%)
Insomnia	17 (18.3%)	16 (16.8%)	5 (5.7%)
Manic Reaction	3 (3.2%)	0 (0.0%)	1 (1.1%)
Myoclonus	2 (2.2%)	1 (1.1%)	0 (0.0%)
Nervousness	9 (9.7%)	6 (6.3%)	5 (5.7%)
Neurosis	0 (0.0%)	1 (1.1%)	0 (0.0%)
Paranoid Reaction	1 (1.1%)	0 (0.0%)	0 (0.0%)
Paresthesia	1 (1.1%)	0 (0.0%)	0 (0.0%)
Personality Disorder	1 (1.1%)	0 (0.0%)	0 (0.0%)
Somnolence	16 (17.2%)	14 (14.7%)	3 (3.4%)
Thinking Abnormal	0 (0.0%)	2 (2.1%)	0 (0.0%)
Tremor	11 (11.8%)	14 (14.7%)	2 (2.3%)
Vestibular Disorder	1 (1.1%)	0 (0.0%)	0 (0.0%)
Withdrawal Syndrome	1 (1.1%)	0 (0.0%)	0 (0.0%)

* Percentage corrected for gender

Paroxetine - Protocol 329
Table 16.2.4
Summary of Treatment-Emergent Adverse Experiences During Both Phases Combined
by ADECS Body System and Preferred Term
Intent-to-Treat Population

Body System Preferred Term	PAROXETINE N = 93 n (%)	IMIPRAMINE N = 95 n (%)	PLACEBO N = 87 n (%)
Respiratory System	35 (37.6%)	28 (29.5%)	32 (36.8%)
Asthma	2 (2.2%)	0 (0.0%)	2 (2.3%)
Bronchitis	3 (3.2%)	0 (0.0%)	4 (4.6%)
Cough Increased	6 (6.5%)	3 (3.2%)	6 (6.9%)
Dyspnea	2 (2.2%)	4 (4.2%)	1 (1.1%)
Epistaxis	1 (1.1%)	1 (1.1%)	1 (1.1%)
Larynx Disorder	1 (1.1%)	0 (0.0%)	0 (0.0%)
Pharyngitis	11 (11.8%)	12 (12.6%)	10 (11.5%)
Respiratory Disorder	15 (16.1%)	10 (10.5%)	12 (13.8%)
Rhinitis	10 (10.8%)	4 (4.2%)	5 (5.7%)
Sinusitis	6 (6.5%)	3 (3.2%)	7 (8.0%)
Skin and Appendages	14 (15.1%)	17 (17.9%)	11 (12.6%)
Acne	3 (3.2%)	3 (3.2%)	1 (1.1%)
Contact Dermatitis	1 (1.1%)	2 (2.1%)	1 (1.1%)
Dry Skin	0 (0.0%)	1 (1.1%)	0 (0.0%)
Fungal Dermatitis	1 (1.1%)	1 (1.1%)	0 (0.0%)
Herpes Zoster	0 (0.0%)	0 (0.0%)	1 (1.1%)
Maculopapular Rash	0 (0.0%)	2 (2.1%)	1 (1.1%)
Photosensitivity	2 (2.2%)	0 (0.0%)	0 (0.0%)
Pruritus	0 (0.0%)	1 (1.1%)	0 (0.0%)
Rash	4 (4.3%)	3 (3.2%)	5 (5.7%)
Skin Disorder	1 (1.1%)	0 (0.0%)	0 (0.0%)
Sweating	1 (1.1%)	7 (7.4%)	1 (1.1%)
Urticaria	1 (1.1%)	1 (1.1%)	1 (1.1%)

* Percentage corrected for gender

Paroxetine - Protocol 329
Table 16.2.4
Summary of Treatment-Emergent Adverse Experiences During Both Phases Combined
by ADECS Body System and Preferred Term
Intent-to-Treat Population

Body System Preferred Term	PAROXETINE N = 93 n (%)	IMIPRAMINE N = 95 n (%)	PLACEBO N = 87 n (%)
Special Senses	10 (10.8%)	14 (14.7%)	5 (5.7%)
Abnormal Vision	2 (2.2%)	7 (7.4%)	2 (2.3%)
Conjunctivitis	3 (3.2%)	0 (0.0%)	0 (0.0%)
Ear Pain	2 (2.2%)	2 (2.1%)	0 (0.0%)
Eye Disorder	0 (0.0%)	0 (0.0%)	1 (1.1%)
Keratoconjunctivitis	0 (0.0%)	1 (1.1%)	0 (0.0%)
Mydriasis	0 (0.0%)	1 (1.1%)	0 (0.0%)
Otitis Externa	1 (1.1%)	0 (0.0%)	0 (0.0%)
Otitis Media	2 (2.2%)	0 (0.0%)	2 (2.3%)
Photophobia	0 (0.0%)	1 (1.1%)	0 (0.0%)
Taste Perversion	0 (0.0%)	3 (3.2%)	0 (0.0%)
Tinnitus	0 (0.0%)	2 (2.1%)	0 (0.0%)

* Percentage corrected for gender

Paroxetine - Protocol 329
Table 16.2.4
Summary of Treatment-Emergent Adverse Experiences During Both Phases Combined
by ADECS Body System and Preferred Term
Intent-to-Treat Population

Body System Preferred Term	PAROXETINE N = 93 n (%)	IMIPRAMINE N = 95 n (%)	PLACEBO N = 87 n (%)
Urogenital System	12 (12.9%)	19 (20.0%)	8 (9.2%)
Albuminuria	1 (1.1%)	0 (0.0%)	3 (3.4%)
* Amenorrhea	1 (1.7%)	0 (0.0%)	0 (0.0%)
* Breast Enlargement	1 (1.7%)	0 (0.0%)	0 (0.0%)
Cystitis	1 (1.1%)	1 (1.1%)	0 (0.0%)
* Dysmenorrhea	4 (6.9%)	5 (8.9%)	4 (7.0%)
Dysuria	0 (0.0%)	1 (1.1%)	0 (0.0%)
* Female Genital Disorders	1 (1.7%)	0 (0.0%)	0 (0.0%)
Haematuria	1 (1.1%)	0 (0.0%)	0 (0.0%)
* Menstrual Disorder	0 (0.0%)	0 (0.0%)	1 (1.8%)
Nocturia	0 (0.0%)	1 (1.1%)	0 (0.0%)
Polyuria	0 (0.0%)	1 (1.1%)	0 (0.0%)
Pyuria	0 (0.0%)	1 (1.1%)	1 (1.1%)
* Unintended Pregnancy	0 (0.0%)	2 (3.6%)	0 (0.0%)
Urinary Casts	1 (1.1%)	0 (0.0%)	0 (0.0%)
Urinary Frequency	0 (0.0%)	1 (1.1%)	0 (0.0%)
Urinary Retention	0 (0.0%)	3 (3.2%)	0 (0.0%)
Urinary Tract Infection	2 (2.2%)	0 (0.0%)	0 (0.0%)
Urination Impaired	0 (0.0%)	3 (3.2%)	0 (0.0%)
Urine Abnormality	2 (2.2%)	0 (0.0%)	0 (0.0%)
* Vaginal Moniliasis	0 (0.0%)	1 (1.8%)	0 (0.0%)

* Percentage corrected for gender

Table 16.3.1

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE PATIENTS RECEIVING STUDY MEDICATION: 52

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	22	42.3%	24	46.2%	14	26.9%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	9	17.3	14	26.9	6	11.5
ABDOMINAL PAIN	4	7.7	2	3.8	0	0.0
ALLERGIC REACTION	0	0.0	1	1.9	0	0.0
ASTHENIA	1	1.9	1	1.9	0	0.0
CHEST PAIN	1	1.9	0	0.0	0	0.0
FEVER	1	1.9	1	1.9	0	0.0
HEADACHE	3	5.8	6	11.5	5	9.6
INFECTION	0	0.0	4	7.7	1	1.9
TRAUMA	1	1.9	1	1.9	0	0.0
Cardiovascular System	3	5.8	2	3.8	0	0.0
ARRHYTHMIA	1	1.9	0	0.0	0	0.0
HYPERTENSION	0	0.0	1	1.9	0	0.0
PALPITATION	0	0.0	1	1.9	0	0.0
SYNCOPE	1	1.9	0	0.0	0	0.0
TACHYCARDIA	1	1.9	0	0.0	0	0.0
Digestive System	7	13.5	6	11.5	3	5.8
CONSTIPATION	1	1.9	1	1.9	0	0.0
DECREASED APPETITE	1	1.9	0	0.0	0	0.0
DRY MOUTH	1	1.9	0	0.0	0	0.0
GINGIVITIS	0	0.0	0	0.0	1	1.9
INCREASED APPETITE	0	0.0	1	1.9	0	0.0
NAUSEA	4	7.7	4	7.7	1	1.9
PEPTIC ULCER HEMORRHAGE	0	0.0	0	0.0	1	1.9
VOMITING	0	0.0	2	3.8	2	3.8
Hemic and Lymphatic System	2	3.8	0	0.0	0	0.0
THROMBOCYTHEMIA	1	1.9	0	0.0	0	0.0
THROMBOCYTOPENIA	1	1.9	0	0.0	0	0.0
Metabolic and Nutritional Disorders	1	1.9	3	5.8	0	0.0
WEIGHT GAIN	1	1.9	3	5.8	0	0.0
Musculoskeletal System	1	1.9	0	0.0	0	0.0
MYALGIA	1	1.9	0	0.0	0	0.0
Nervous System	8	15.4	13	25.0	6	11.5
AGITATION	1	1.9	1	1.9	0	0.0
AMNESIA	1	1.9	0	0.0	0	0.0
DIZZINESS	3	5.8	6	11.5	0	0.0

Table 16.3.1

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE PATIENTS RECEIVING STUDY MEDICATION: 52

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	22	42.3%	24	46.2%	14	26.9%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
DRUG DEPENDENCE	0	0.0	0	0.0	1	1.9
EMOTIONAL LABILITY	1	1.9	1	1.9	2	3.8
HYPERKINESIA	1	1.9	1	1.9	0	0.0
HYPERTONIA	0	0.0	1	1.9	0	0.0
INSOMNIA	0	0.0	2	3.8	2	3.8
MANIC REACTION	1	1.9	0	0.0	0	0.0
NERVOUSNESS	0	0.0	1	1.9	0	0.0
PERSONALITY DISORDER	0	0.0	0	0.0	1	1.9
SOMNOLENCE	0	0.0	1	1.9	0	0.0
TREMOR	1	1.9	2	3.8	0	0.0
VESTIBULAR DISORDER	0	0.0	1	1.9	0	0.0
Respiratory System	6	11.5	11	21.2	1	1.9
ASTHMA	0	0.0	1	1.9	0	0.0
BRONCHITIS	0	0.0	2	3.8	0	0.0
COUGH INCREASED	0	0.0	2	3.8	0	0.0
EPISTAXIS	1	1.9	0	0.0	0	0.0
PHARYNGITIS	1	1.9	4	7.7	1	1.9
RESPIRATORY DISORDER	4	7.7	2	3.8	0	0.0
RHINITIS	0	0.0	3	5.8	0	0.0
SINUSITIS	0	0.0	1	1.9	0	0.0
Skin and Appendages	0	0.0	1	1.9	1	1.9
CONTACT DERMATITIS	0	0.0	0	0.0	1	1.9
PHOTOSENSITIVITY	0	0.0	1	1.9	0	0.0
Special Senses	1	1.9	3	5.8	0	0.0
ABNORMAL VISION	0	0.0	1	1.9	0	0.0
EAR PAIN	1	1.9	0	0.0	0	0.0
OTITIS EXTERNA	0	0.0	1	1.9	0	0.0
OTITIS MEDIA	0	0.0	1	1.9	0	0.0
Urogenital System	0	0.0	2	3.8	0	0.0
ALBUMINURIA	0	0.0	1	1.9	0	0.0
HAEMATURIA	0	0.0	1	1.9	0	0.0
URINARY CASTS	0	0.0	1	1.9	0	0.0
URINARY TRACT INFECTION	0	0.0	1	1.9	0	0.0

Table 16.3.1

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE PATIENTS RECEIVING STUDY MEDICATION: 40

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	19	47.5%	15	37.5%	6	15.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	7	17.5	4	10.0	4	10.0
ABDOMINAL PAIN	3	7.5	1	2.5	0	0.0
ABNORMAL LABORATORY VALUE	1	2.5	0	0.0	0	0.0
ACCIDENTAL OVERDOSE	0	0.0	0	0.0	1	2.5
ASTHENIA	1	2.5	0	0.0	1	2.5
HEADACHE	3	7.5	2	5.0	2	5.0
INFECTION	0	0.0	1	2.5	0	0.0
Cardiovascular System	3	7.5	2	5.0	0	0.0
ELECTROCARDIOGRAM ABNORMAL	1	2.5	0	0.0	0	0.0
HYPERTENSION	0	0.0	1	2.5	0	0.0
SYNCOPE	1	2.5	0	0.0	0	0.0
TACHYCARDIA	1	2.5	1	2.5	0	0.0
Digestive System	5	12.5	7	17.5	1	2.5
CONSTIPATION	0	0.0	1	2.5	0	0.0
DIARRHEA	2	5.0	1	2.5	0	0.0
DRY MOUTH	1	2.5	1	2.5	1	2.5
DYSPEPSIA	0	0.0	2	5.0	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	1	2.5	0	0.0
INCREASED APPETITE	0	0.0	1	2.5	0	0.0
NAUSEA	2	5.0	1	2.5	0	0.0
TOOTH DISORDER	0	0.0	1	2.5	0	0.0
ULCERATIVE STOMATITIS	0	0.0	1	2.5	0	0.0
VOMITING	1	2.5	1	2.5	0	0.0
Hemic and Lymphatic System	1	2.5	0	0.0	0	0.0
ANEMIA	1	2.5	0	0.0	0	0.0
Metabolic and Nutritional Disorders	0	0.0	1	2.5	1	2.5
DEHYDRATION	0	0.0	0	0.0	1	2.5
WEIGHT GAIN	0	0.0	1	2.5	0	0.0
Musculoskeletal System	1	2.5	2	5.0	0	0.0
MYALGIA	1	2.5	2	5.0	0	0.0
Nervous System	7	17.5	2	5.0	2	5.0
ABNORMAL DREAMS	0	0.0	0	0.0	1	2.5
ANXIETY	1	2.5	0	0.0	0	0.0
CONVULSION	0	0.0	0	0.0	1	2.5
DIZZINESS	3	7.5	0	0.0	0	0.0

Table 16.3.1

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE PATIENTS RECEIVING STUDY MEDICATION: 40

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	19	47.5%	15	37.5%	6	15.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
EMOTIONAL LABILITY	0	0.0	0	0.0	1	2.5
INSOMNIA	2	5.0	1	2.5	0	0.0
NEUROSIS	0	0.0	1	2.5	0	0.0
SOMNOLENCE	1	2.5	0	0.0	0	0.0
Respiratory System	4	10.0	1	2.5	0	0.0
RESPIRATORY DISORDER	2	5.0	1	2.5	0	0.0
RHINITIS	1	2.5	0	0.0	0	0.0
SINUSITIS	1	2.5	0	0.0	0	0.0
Skin and Appendages	2	5.0	1	2.5	0	0.0
ACNE	0	0.0	1	2.5	0	0.0
CONTACT DERMATITIS	0	0.0	1	2.5	0	0.0
DRY SKIN	1	2.5	0	0.0	0	0.0
SWEATING	1	2.5	0	0.0	0	0.0
Special Senses	1	2.5	0	0.0	0	0.0
ABNORMAL VISION	1	2.5	0	0.0	0	0.0
Urogenital System	1	2.5	2	5.0	0	0.0
DYSURIA	0	0.0	1	2.5	0	0.0
PYURIA	1	2.5	0	0.0	0	0.0
URINARY RETENTION	0	0.0	1	2.5	0	0.0
URINATION IMPAIRED	0	0.0	1	2.5	0	0.0

Table 16.3.1

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO PATIENTS RECEIVING STUDY MEDICATION: 33

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	15	45.5%	14	42.4%	4	12.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	5	15.2	9	27.3	2	6.1
ABDOMINAL PAIN	1	3.0	0	0.0	0	0.0
ASTHENIA	1	3.0	0	0.0	0	0.0
BACK PAIN	0	0.0	2	6.1	0	0.0
HEADACHE	2	6.1	2	6.1	2	6.1
INFECTION	1	3.0	3	9.1	0	0.0
PAIN	0	0.0	0	0.0	1	3.0
TRAUMA	1	3.0	4	12.1	0	0.0
Cardiovascular System	2	6.1	0	0.0	0	0.0
ARRHYTHMIA	1	3.0	0	0.0	0	0.0
PALPITATION	1	3.0	0	0.0	0	0.0
Digestive System	4	12.1	2	6.1	2	6.1
DIARRHEA	2	6.1	1	3.0	0	0.0
NAUSEA	2	6.1	1	3.0	0	0.0
TOOTH DISORDER	0	0.0	0	0.0	2	6.1
VOMITING	1	3.0	1	3.0	1	3.0
Hemic and Lymphatic System	2	6.1	1	3.0	0	0.0
LYMPHADENOPATHY	1	3.0	0	0.0	0	0.0
WBC ABNORMALITY	1	3.0	1	3.0	0	0.0
Nervous System	5	15.2	2	6.1	1	3.0
DIZZINESS	3	9.1	1	3.0	0	0.0
DRUG DEPENDENCE	0	0.0	1	3.0	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0	1	3.0
HOSTILITY	0	0.0	0	0.0	1	3.0
HYPESTHESIA	1	3.0	0	0.0	0	0.0
INSOMNIA	1	3.0	0	0.0	0	0.0
Respiratory System	3	9.1	5	15.2	2	6.1
ASTHMA	0	0.0	1	3.0	0	0.0
BRONCHITIS	0	0.0	1	3.0	0	0.0
COUGH INCREASED	0	0.0	1	3.0	0	0.0
EPISTAXIS	0	0.0	0	0.0	1	3.0
PHARYNGITIS	1	3.0	1	3.0	1	3.0
RESPIRATORY DISORDER	1	3.0	1	3.0	0	0.0
RHINITIS	0	0.0	0	0.0	1	3.0
SINUSITIS	1	3.0	1	3.0	1	3.0

Table 16.3.1

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO PATIENTS RECEIVING STUDY MEDICATION: 33

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	15	45.5%	14	42.4%	4	12.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Skin and Appendages	1	3.0	2	6.1	0	0.0
RASH	1	3.0	1	3.0	0	0.0
URTICARIA	0	0.0	1	3.0	0	0.0
Special Senses	0	0.0	2	6.1	0	0.0
OTITIS MEDIA	0	0.0	2	6.1	0	0.0
Urogenital System	1	3.0	0	0.0	0	0.0
ALBUMINURIA	1	3.0	0	0.0	0	0.0

PAROXETINE - PROTOCOL 329

Table 16.3.2

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Male Specific Adverse Experiences
Intent-to-Treat Population

NO DATA AVAILABLE FOR THIS REPORT

PAROXETINE - PROTOCOL 329

Table 16.3.3

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE PATIENTS RECEIVING STUDY MEDICATION: 33

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	2	6.1%	1	3.0%	1	3.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Urogenital System	2	6.1	1	3.0	1	3.0
DYSMENORRHEA	1	3.0	1	3.0	1	3.0
FEMALE GENITAL DISORDERS	1	3.0	0	0.0	0	0.0

Table 16.3.3

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE PATIENTS RECEIVING STUDY MEDICATION: 18

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	1	5.6%	1	5.6%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Urogenital System	1	5.6	1	5.6	0	0.0
DYSMENORRHEA	1	5.6	0	0.0	0	0.0
UNINTENDED PREGNANCY	0	0.0	1	5.6	0	0.0

Table 16.3.3

Summary of Treatment-Emergent Adverse Experiences by ADECS Body System and Preferred Term and by Maximum Intensity
Continuation Phase - Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO PATIENTS RECEIVING STUDY MEDICATION: 23

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	0	0.0%	1	4.3%	2	8.7%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Urogenital System	0	0.0	1	4.3	2	8.7
DYSMENORRHEA	0	0.0	0	0.0	2	8.7
MENSTRUAL DISORDER	0	0.0	1	4.3	0	0.0

PAROXETINE - PROTOCOL 329

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	67	--	52	--	41	--	37	--	28	-
PATIENTS WITH ADVERSE EXPERIENCES :	9	13.4%	23	44.2%	10	24.4%	12	32.4%	9	32.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Body as a Whole	4	6.0	8	15.4	4	9.8	5	13.5	3	10.7
ABDOMINAL PAIN	1	1.5	0	0.0	2	4.9	2	5.4	0	0.0
ALLERGIC REACTION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ASTHENIA	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
CHEST PAIN	1	1.5	0	0.0	0	0.0	0	0.0	0	0.0
FEVER	0	0.0	0	0.0	0	0.0	1	2.7	1	3.6
HEADACHE	3	4.5	7	13.5	1	2.4	0	0.0	1	3.6
INFECTION	0	0.0	1	1.9	0	0.0	1	2.7	1	3.6
TRAUMA	0	0.0	0	0.0	1	2.4	1	2.7	0	0.0
Cardiovascular System	0	0.0	1	1.9	4	9.8	0	0.0	0	0.0
ARRHYTHMIA	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0
HYPERTENSION	0	0.0	0	0.0	1	2.4	0	0.0	0	0.0
PALPITATION	0	0.0	0	0.0	1	2.4	0	0.0	0	0.0
SYNCOPE	0	0.0	0	0.0	1	2.4	0	0.0	0	0.0
TACHYCARDIA	0	0.0	0	0.0	1	2.4	0	0.0	0	0.0
Digestive System	1	1.5	5	9.6	3	7.3	2	5.4	0	0.0
CONSTIPATION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
DECREASED APPETITE	1	1.5	0	0.0	0	0.0	0	0.0	0	0.0
DRY MOUTH	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0
GINGIVITIS	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0
INCREASED APPETITE	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
NAUSEA	0	0.0	3	5.8	2	4.9	0	0.0	0	0.0
PEPTIC ULCER HEMORRHAGE	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
VOMITING	0	0.0	0	0.0	1	2.4	1	2.7	0	0.0
Hemic and Lymphatic System	1	1.5	0	0.0	0	0.0	1	2.7	0	0.0
THROMBOCYTHEMIA	1	1.5	0	0.0	0	0.0	0	0.0	0	0.0
THROMBOCYTOPENIA	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
Metabolic and Nutritional Disorders	0	0.0	2	3.8	1	2.4	0	0.0	1	3.6
WEIGHT GAIN	0	0.0	2	3.8	1	2.4	0	0.0	1	3.6
Musculoskeletal System	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0
MYALGIA	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0
Nervous System	1	1.5	9	17.3	3	7.3	4	10.8	5	17.9
AGITATION	0	0.0	0	0.0	0	0.0	0	0.0	1	3.6
AMNESIA	0	0.0	0	0.0	1	2.4	0	0.0	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

DAYS	DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION :	21	--	18	-
PATIENTS WITH ADVERSE EXPERIENCES :	5	23.8%	8	44.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	4	19.0	3	16.7
ABDOMINAL PAIN	0	0.0	1	5.6
ALLERGIC REACTION	1	4.8	0	0.0
ASTHENIA	0	0.0	1	5.6
CHEST PAIN	0	0.0	0	0.0
FEVER	0	0.0	0	0.0
HEADACHE	2	9.5	0	0.0
INFECTION	1	4.8	1	5.6
TRAUMA	0	0.0	0	0.0
Cardiovascular System	0	0.0	0	0.0
ARRHYTHMIA	0	0.0	0	0.0
HYPERTENSION	0	0.0	0	0.0
PALPITATION	0	0.0	0	0.0
SYNCOPE	0	0.0	0	0.0
TACHYCARDIA	0	0.0	0	0.0
Digestive System	1	4.8	4	22.2
CONSTIPATION	0	0.0	2	11.1
DECREASED APPETITE	0	0.0	0	0.0
DRY MOUTH	0	0.0	0	0.0
GINGIVITIS	0	0.0	0	0.0
INCREASED APPETITE	0	0.0	0	0.0
NAUSEA	1	4.8	3	16.7
PEPTIC ULCER HEMORRHAGE	0	0.0	0	0.0
VOMITING	0	0.0	2	11.1
Hemic and Lymphatic System	0	0.0	0	0.0
THROMBOCYTHEMIA	0	0.0	0	0.0
THROMBOCYTOPENIA	0	0.0	0	0.0
Metabolic and Nutritional Disorders	0	0.0	0	0.0
WEIGHT GAIN	0	0.0	0	0.0
Musculoskeletal System	0	0.0	0	0.0
MYALGIA	0	0.0	0	0.0
Nervous System	0	0.0	4	22.2
AGITATION	0	0.0	1	5.6
AMNESIA	0	0.0	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	67	--	52	--	41	--	37	--	28	-
PATIENTS WITH ADVERSE EXPERIENCES :	9	13.4%	23	44.2%	10	24.4%	12	32.4%	9	32.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
DIZZINESS	0	0.0	4	7.7	1	2.4	2	5.4	1	3.6
DRUG DEPENDENCE	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
EMOTIONAL LABILITY	0	0.0	2	3.8	1	2.4	0	0.0	1	3.6
HYPERKINESIA	0	0.0	0	0.0	1	2.4	0	0.0	1	3.6
HYPERTONIA	0	0.0	0	0.0	0	0.0	0	0.0	1	3.6
INSOMNIA	0	0.0	2	3.8	0	0.0	0	0.0	1	3.6
MANIC REACTION	0	0.0	0	0.0	0	0.0	0	0.0	1	3.6
NERVOUSNESS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
PERSONALITY DISORDER	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0
SOMNOLENCE	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
TREMOR	1	1.5	0	0.0	0	0.0	1	2.7	0	0.0
VESTIBULAR DISORDER	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0
Respiratory System	3	4.5	6	11.5	1	2.4	3	8.1	4	14.3
ASTHMA	0	0.0	0	0.0	0	0.0	0	0.0	1	3.6
BRONCHITIS	1	1.5	0	0.0	1	2.4	0	0.0	0	0.0
COUGH INCREASED	1	1.5	1	1.9	0	0.0	0	0.0	0	0.0
EPISTAXIS	0	0.0	0	0.0	0	0.0	0	0.0	1	3.6
PHARYNGITIS	1	1.5	2	3.8	0	0.0	1	2.7	1	3.6
RESPIRATORY DISORDER	0	0.0	3	5.8	0	0.0	0	0.0	1	3.6
RHINITIS	0	0.0	1	1.9	0	0.0	1	2.7	0	0.0
SINUSITIS	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
Skin and Appendages	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
CONTACT DERMATITIS	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
PHOTOSENSITIVITY	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Special Senses	0	0.0	1	1.9	0	0.0	2	5.4	1	3.6
ABNORMAL VISION	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
EAR PAIN	0	0.0	0	0.0	0	0.0	0	0.0	1	3.6
OTITIS EXTERNA	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
OTITIS MEDIA	0	0.0	1	1.9	0	0.0	0	0.0	0	0.0
Urogenital System	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
ALBUMINURIA	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
HAEMATURIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
URINARY CASTS	0	0.0	0	0.0	0	0.0	1	2.7	0	0.0
URINARY TRACT INFECTION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

DAYS	DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION :	21	--	18	-
PATIENTS WITH ADVERSE EXPERIENCES :	5	23.8%	8	44.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
DIZZINESS	0	0.0	1	5.6
DRUG DEPENDENCE	0	0.0	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0
HYPERKINESIA	0	0.0	0	0.0
HYPERTONIA	0	0.0	0	0.0
INSOMNIA	0	0.0	1	5.6
MANIC REACTION	0	0.0	0	0.0
NERVOUSNESS	0	0.0	1	5.6
PERSONALITY DISORDER	0	0.0	0	0.0
SOMNOLENCE	0	0.0	1	5.6
TREMOR	0	0.0	1	5.6
VESTIBULAR DISORDER	0	0.0	0	0.0
Respiratory System	1	4.8	2	11.1
ASTHMA	0	0.0	0	0.0
BRONCHITIS	0	0.0	0	0.0
COUGH INCREASED	0	0.0	0	0.0
EPISTAXIS	0	0.0	0	0.0
PHARYNGITIS	0	0.0	1	5.6
RESPIRATORY DISORDER	1	4.8	1	5.6
RHINITIS	0	0.0	1	5.6
SINUSITIS	0	0.0	0	0.0
Skin and Appendages	0	0.0	1	5.6
CONTACT DERMATITIS	0	0.0	0	0.0
PHOTOSENSITIVITY	0	0.0	1	5.6
Special Senses	0	0.0	0	0.0
ABNORMAL VISION	0	0.0	0	0.0
EAR PAIN	0	0.0	0	0.0
OTITIS EXTERNA	0	0.0	0	0.0
OTITIS MEDIA	0	0.0	0	0.0
Urogenital System	0	0.0	1	5.6
ALBUMINURIA	0	0.0	0	0.0
HAEMATURIA	0	0.0	1	5.6
URINARY CASTS	0	0.0	0	0.0
URINARY TRACT INFECTION	0	0.0	1	5.6

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	56	--	44	--	32	--	28	--	21	-
PATIENTS WITH ADVERSE EXPERIENCES :	8	14.3%	11	25.0%	10	31.3%	7	25.0%	4	19.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Body as a Whole	3	5.4	4	9.1	1	3.1	2	7.1	1	4.8
ABDOMINAL PAIN	1	1.8	0	0.0	0	0.0	1	3.6	0	0.0
ABNORMAL LABORATORY VALUE	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0
ACCIDENTAL OVERDOSE	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
ASTHENIA	0	0.0	1	2.3	0	0.0	1	3.6	0	0.0
HEADACHE	1	1.8	3	6.8	0	0.0	2	7.1	1	4.8
INFECTION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Cardiovascular System	1	1.8	2	4.5	0	0.0	1	3.6	0	0.0
ELECTROCARDIOGRAM ABNORMAL	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
HYPERTENSION	0	0.0	0	0.0	0	0.0	1	3.6	0	0.0
SYNCOPE	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0
TACHYCARDIA	1	1.8	1	2.3	0	0.0	0	0.0	0	0.0
Digestive System	3	5.4	3	6.8	2	6.3	4	14.3	2	9.5
CONSTIPATION	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
DIARRHEA	0	0.0	1	2.3	0	0.0	0	0.0	1	4.8
DRY MOUTH	2	3.6	0	0.0	0	0.0	1	3.6	0	0.0
DYSPEPSIA	1	1.8	0	0.0	0	0.0	1	3.6	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	1	4.8
INCREASED APPETITE	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
NAUSEA	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0
TOOTH DISORDER	0	0.0	0	0.0	0	0.0	1	3.6	0	0.0
ULCERATIVE STOMATITIS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
VOMITING	0	0.0	1	2.3	0	0.0	1	3.6	0	0.0
Hemic and Lymphatic System	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ANEMIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Metabolic and Nutritional Disorders	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
DEHYDRATION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
WEIGHT GAIN	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
Musculoskeletal System	0	0.0	1	2.3	0	0.0	1	3.6	0	0.0
MYALGIA	0	0.0	1	2.3	0	0.0	1	3.6	0	0.0
Nervous System	0	0.0	1	2.3	4	12.5	3	10.7	1	4.8
CONVULSION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ABNORMAL DREAMS	0	0.0	0	0.0	0	0.0	1	3.6	0	0.0
ANXIETY	0	0.0	0	0.0	0	0.0	0	0.0	1	4.8

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION :	15	--	13	-
PATIENTS WITH ADVERSE EXPERIENCES :	4	26.7%	6	46.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	1	6.7	2	15.4
ABDOMINAL PAIN	1	6.7	1	7.7
ABNORMAL LABORATORY VALUE	0	0.0	0	0.0
ACCIDENTAL OVERDOSE	0	0.0	0	0.0
ASTHENIA	0	0.0	0	0.0
HEADACHE	0	0.0	0	0.0
INFECTION	0	0.0	1	7.7
Cardiovascular System	0	0.0	1	7.7
ELECTROCARDIOGRAM ABNORMAL	0	0.0	1	7.7
HYPERTENSION	0	0.0	0	0.0
SYNCOPE	0	0.0	0	0.0
TACHYCARDIA	0	0.0	0	0.0
Digestive System	1	6.7	1	7.7
CONSTIPATION	0	0.0	0	0.0
DIARRHEA	0	0.0	1	7.7
DRY MOUTH	0	0.0	0	0.0
DYSPEPSIA	0	0.0	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	0	0.0
INCREASED APPETITE	0	0.0	0	0.0
NAUSEA	1	6.7	1	7.7
TOOTH DISORDER	0	0.0	0	0.0
ULCERATIVE STOMATITIS	1	6.7	0	0.0
VOMITING	0	0.0	0	0.0
Hemic and Lymphatic System	0	0.0	1	7.7
ANEMIA	0	0.0	1	7.7
Metabolic and Nutritional Disorders	1	6.7	0	0.0
DEHYDRATION	1	6.7	0	0.0
WEIGHT GAIN	0	0.0	0	0.0
Musculoskeletal System	0	0.0	1	7.7
MYALGIA	0	0.0	1	7.7
Nervous System	3	20.0	0	0.0
CONVULSION	1	6.7	0	0.0
ABNORMAL DREAMS	0	0.0	0	0.0
ANXIETY	0	0.0	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	56	--	44	--	32	--	28	--	21	-
PATIENTS WITH ADVERSE EXPERIENCES :	8	14.3%	11	25.0%	10	31.3%	7	25.0%	4	19.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
DIZZINESS	0	0.0	0	0.0	2	6.3	0	0.0	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0	0	0.0	1	3.6	0	0.0
INSOMNIA	0	0.0	1	2.3	0	0.0	1	3.6	0	0.0
NEUROSIS	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
SOMNOLENCE	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
Respiratory System	0	0.0	1	2.3	1	3.1	2	7.1	1	4.8
SINUSITIS	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0
RESPIRATORY DISORDER	0	0.0	0	0.0	0	0.0	2	7.1	1	4.8
RHINITIS	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
Skin and Appendages	0	0.0	1	2.3	3	9.4	0	0.0	0	0.0
DRY SKIN	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
CONTACT DERMATITIS	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
ACNE	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0
SWEATING	0	0.0	0	0.0	1	3.1	0	0.0	0	0.0
Special Senses	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0
ABNORMAL VISION	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0
Urogenital System	1	1.8	1	2.3	0	0.0	0	0.0	1	4.8
URINATION IMPAIRED	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0
DYSURIA	0	0.0	1	2.3	0	0.0	0	0.0	0	0.0
PYURIA	0	0.0	0	0.0	0	0.0	0	0.0	1	4.8
URINARY RETENTION	1	1.8	0	0.0	0	0.0	0	0.0	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION :	15	--	13	-
PATIENTS WITH ADVERSE EXPERIENCES :	4	26.7%	6	46.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
DIZZINESS	1	6.7	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0
INSOMNIA	1	6.7	0	0.0
NEUROSIS	0	0.0	0	0.0
SOMNOLENCE	0	0.0	0	0.0
Respiratory System	0	0.0	0	0.0
SINUSITIS	0	0.0	0	0.0
RESPIRATORY DISORDER	0	0.0	0	0.0
RHINITIS	0	0.0	0	0.0
Skin and Appendages	0	0.0	0	0.0
DRY SKIN	0	0.0	0	0.0
CONTACT DERMATITIS	0	0.0	0	0.0
ACNE	0	0.0	0	0.0
SWEATING	0	0.0	0	0.0
Special Senses	0	0.0	0	0.0
ABNORMAL VISION	0	0.0	0	0.0
Urogenital System	0	0.0	0	0.0
URINATION IMPAIRED	0	0.0	0	0.0
DYSURIA	0	0.0	0	0.0
PYURIA	0	0.0	0	0.0
URINARY RETENTION	0	0.0	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	66	--	41	--	26	--	19	--	16	-
PATIENTS WITH ADVERSE EXPERIENCES :	4	6.1%	12	29.3%	8	30.8%	5	26.3%	6	37.5%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Body as a Whole	2	3.0	5	12.2	5	19.2	1	5.3	3	18.8
ABDOMINAL PAIN	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0
ASTHENIA	0	0.0	0	0.0	1	3.8	0	0.0	0	0.0
BACK PAIN	0	0.0	0	0.0	2	7.7	0	0.0	0	0.0
HEADACHE	0	0.0	3	7.3	1	3.8	0	0.0	1	6.3
INFECTION	0	0.0	1	2.4	1	3.8	0	0.0	1	6.3
PAIN	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0
TRAUMA	2	3.0	0	0.0	0	0.0	1	5.3	1	6.3
Cardiovascular System	0	0.0	1	2.4	0	0.0	0	0.0	1	6.3
ARRHYTHMIA	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0
PALPITATION	0	0.0	0	0.0	0	0.0	0	0.0	1	6.3
Digestive System	1	1.5	2	4.9	1	3.8	0	0.0	0	0.0
DIARRHEA	0	0.0	1	2.4	1	3.8	0	0.0	0	0.0
NAUSEA	1	1.5	1	2.4	0	0.0	0	0.0	0	0.0
TOOTH DISORDER	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0
VOMITING	0	0.0	1	2.4	1	3.8	0	0.0	0	0.0
Hemic and Lymphatic System	0	0.0	1	2.4	0	0.0	1	5.3	0	0.0
LYMPHADENOPATHY	0	0.0	0	0.0	0	0.0	1	5.3	0	0.0
WBC ABNORMALITY	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0
Nervous System	0	0.0	2	4.9	4	15.4	0	0.0	0	0.0
DIZZINESS	0	0.0	1	2.4	1	3.8	0	0.0	0	0.0
DRUG DEPENDENCE	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0	1	3.8	0	0.0	0	0.0
HOSTILITY	0	0.0	0	0.0	1	3.8	0	0.0	0	0.0
HYPESTHESIA	0	0.0	0	0.0	1	3.8	0	0.0	0	0.0
INSOMNIA	0	0.0	0	0.0	1	3.8	0	0.0	0	0.0
Respiratory System	2	3.0	3	7.3	1	3.8	1	5.3	2	12.5
ASTHMA	0	0.0	0	0.0	1	3.8	0	0.0	0	0.0
BRONCHITIS	0	0.0	0	0.0	0	0.0	0	0.0	1	6.3
COUGH INCREASED	1	1.5	0	0.0	0	0.0	0	0.0	0	0.0
EPISTAXIS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
PHARYNGITIS	1	1.5	0	0.0	0	0.0	1	5.3	0	0.0
RESPIRATORY DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	1	6.3
RHINITIS	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0
SINUSITIS	0	0.0	3	7.3	0	0.0	0	0.0	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

DAYS	DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION :	14	--	13	-
PATIENTS WITH ADVERSE EXPERIENCES :	4	28.6%	4	30.8%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	1	7.1	2	15.4
ABDOMINAL PAIN	0	0.0	0	0.0
ASTHENIA	0	0.0	0	0.0
BACK PAIN	0	0.0	0	0.0
HEADACHE	1	7.1	0	0.0
INFECTION	0	0.0	1	7.7
PAIN	0	0.0	0	0.0
TRAUMA	0	0.0	1	7.7
Cardiovascular System	0	0.0	0	0.0
ARRHYTHMIA	0	0.0	0	0.0
PALPITATION	0	0.0	0	0.0
Digestive System	2	14.3	1	7.7
DIARRHEA	1	7.1	0	0.0
NAUSEA	0	0.0	1	7.7
TOOTH DISORDER	1	7.1	0	0.0
VOMITING	0	0.0	1	7.7
Hemic and Lymphatic System	0	0.0	1	7.7
LYMPHADENOPATHY	0	0.0	0	0.0
WBC ABNORMALITY	0	0.0	1	7.7
Nervous System	1	7.1	1	7.7
DIZZINESS	1	7.1	1	7.7
DRUG DEPENDENCE	0	0.0	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0
HOSTILITY	0	0.0	0	0.0
HYPESTHESIA	0	0.0	0	0.0
INSOMNIA	0	0.0	0	0.0
Respiratory System	1	7.1	2	15.4
ASTHMA	0	0.0	0	0.0
BRONCHITIS	0	0.0	0	0.0
COUGH INCREASED	0	0.0	0	0.0
EPISTAXIS	0	0.0	1	7.7
PHARYNGITIS	0	0.0	1	7.7
RESPIRATORY DISORDER	1	7.1	0	0.0
RHINITIS	0	0.0	0	0.0
SINUSITIS	0	0.0	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	66	--	41	--	26	--	19	--	16	-
PATIENTS WITH ADVERSE EXPERIENCES :	4	6.1%	12	29.3%	8	30.8%	5	26.3%	6	37.5%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Skin and Appendages	0	0.0	2	4.9	0	0.0	1	5.3	0	0.0
RASH	0	0.0	1	2.4	0	0.0	1	5.3	0	0.0
URTICARIA	0	0.0	1	2.4	0	0.0	0	0.0	0	0.0
Special Senses	0	0.0	0	0.0	2	7.7	0	0.0	0	0.0
OTITIS MEDIA	0	0.0	0	0.0	2	7.7	0	0.0	0	0.0
Urogenital System	0	0.0	0	0.0	0	0.0	1	5.3	0	0.0
ALBUMINURIA	0	0.0	0	0.0	0	0.0	1	5.3	0	0.0

Table 16.4.1

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

DAYS	DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION :	14	--	13	-
PATIENTS WITH ADVERSE EXPERIENCES :	4	28.6%	4	30.8%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Skin and Appendages	0	0.0	0	0.0
RASH	0	0.0	0	0.0
URTICARIA	0	0.0	0	0.0
Special Senses	0	0.0	0	0.0
OTITIS MEDIA	0	0.0	0	0.0
Urogenital System	0	0.0	0	0.0
ALBUMINURIA	0	0.0	0	0.0

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Table 16.4.2

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Male Specific Adverse Experiences
Intent-to-Treat Population

NO DATA AVAILABLE FOR THIS REPORT

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Table 16.4.3

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	44	--	36	--	27	--	24	--	18	-
PATIENTS WITH ADVERSE EXPERIENCES :	1	2.3%	0	0.0%	1	3.7%	1	4.2%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Urogenital System	1	2.3	0	0.0	1	3.7	1	4.2	0	0.0
DYSMENORRHEA	0	0.0	0	0.0	1	3.7	1	4.2	0	0.0
FEMALE GENITAL DISORDERS	1	2.3	0	0.0	0	0.0	0	0.0	0	0.0

Table 16.4.3

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

DAYS		DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION	:	15	--	14	-
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	1	7.1%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		0	0.0	1	7.1
DYSMENORRHEA		0	0.0	1	7.1
FEMALE GENITAL DISORDERS		0	0.0	0	0.0

Table 16.4.3

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	32	--	22	--	16	--	14	--	9	-
PATIENTS WITH ADVERSE EXPERIENCES :	1	3.1%	1	4.5%	0	0.0%	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Urogenital System	1	3.1	1	4.5	0	0.0	0	0.0	0	0.0
DYSMENORRHEA	1	3.1	0	0.0	0	0.0	0	0.0	0	0.0
UNINTENDED PREGNANCY	0	0.0	1	4.5	0	0.0	0	0.0	0	0.0

Table 16.4.3

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

DAYS		DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION	:	9	--	7	-
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		0	0.0	0	0.0
DYSMENORRHEA		0	0.0	0	0.0
UNINTENDED PREGNANCY		0	0.0	0	0.0

Table 16.4.3

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

DAYS	DAY 56-71		DAY 72-99		DAY 100-127		DAY 128-155		DAY 156-183	
PATIENTS WHO RECEIVED STUDY MEDICATION :	46	--	27	--	18	--	13	--	11	-
PATIENTS WITH ADVERSE EXPERIENCES :	0	0.0%	0	0.0%	1	5.6%	0	0.0%	1	9.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Urogenital System	0	0.0	0	0.0	1	5.6	0	0.0	1	9.1
DYSMENORRHEA	0	0.0	0	0.0	1	5.6	0	0.0	1	9.1
MENSTRUAL DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 16.4.3

Summary of Treatment-Emergent Adverse Experiences by Time of First Occurrence (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

DAYS		DAY 184-211		> DAY 211	
PATIENTS WHO RECEIVED STUDY MEDICATION	:	9	--	9	-
PATIENTS WITH ADVERSE EXPERIENCES	:	1	11.1%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		1	11.1	0	0.0
DYSMENORRHEA		0	0.0	0	0.0
MENSTRUAL DISORDER		1	11.1	0	0.0

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Table 16.5.1

Summary of Treatment-Emergent Adverse Experiences Leading to Dose Reduction Regardless of Attribution
by ADECS Body System and Preferred Term (Continuation Phase) - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	3	5.8%	2	5.0%	0	0.0%	5	4.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Body as a Whole	1	1.9	1	2.5	0	0.0	2	1.6
ABDOMINAL PAIN	0	0.0	1	2.5	0	0.0	1	0.8
HEADACHE	1	1.9	0	0.0	0	0.0	1	0.8
Cardiovascular System	1	1.9	0	0.0	0	0.0	1	0.8
HYPERTENSION	1	1.9	0	0.0	0	0.0	1	0.8
Digestive System	0	0.0	2	5.0	0	0.0	2	1.6
GASTROINTESTINAL DISORDER	0	0.0	1	2.5	0	0.0	1	0.8
NAUSEA	0	0.0	1	2.5	0	0.0	1	0.8
Nervous System	3	5.8	0	0.0	0	0.0	3	2.4
AGITATION	1	1.9	0	0.0	0	0.0	1	0.8
HYPERKINESIA	1	1.9	0	0.0	0	0.0	1	0.8
INSOMNIA	2	3.8	0	0.0	0	0.0	2	1.6

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Table 16.5.2

Summary of Treatment-Emergent Adverse Experiences Leading to Dose Reduction Regardless of Attribution
by ADECS Body System and Preferred Term (Continuation Phase) - Male Specific Adverse Experiences
Intent-to-Treat Population

NO DATA AVAILABLE FOR THIS REPORT

PAROXETINE - PROTOCOL 329

Table 16.5.3

Summary of Treatment-Emergent Adverse Experiences Leading to Dose Reduction Regardless of Attribution
by ADECS Body System and Preferred Term (Continuation Phase) - Female Specific Adverse Experiences
Intent-to-Treat Population

NO DATA AVAILABLE FOR THIS REPORT

PAROXETINE - PROTOCOL 329

Table 16.6.1

Summary of Treatment-Emergent Adverse Experiences Requiring Corrective Therapy Regardless of Attribution
by ADECS Body System and Preferred Term (Continuation Phase) - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	22	42.3%	13	32.5%	15	45.5%	50	40.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Body as a Whole	16	30.8	8	20.0	10	30.3	34	27.2
ABDOMINAL PAIN	1	1.9	1	2.5	0	0.0	2	1.6
FEVER	2	3.8	0	0.0	0	0.0	2	1.6
HEADACHE	12	23.1	6	15.0	3	9.1	21	16.8
INFECTION	2	3.8	1	2.5	4	12.1	7	5.6
PAIN	0	0.0	0	0.0	1	3.0	1	0.8
TRAUMA	1	1.9	0	0.0	3	9.1	4	3.2
Digestive System	5	9.6	5	12.5	3	9.1	13	10.4
CONSTIPATION	1	1.9	1	2.5	0	0.0	2	1.6
DIARRHEA	0	0.0	1	2.5	1	3.0	2	1.6
DYSPEPSIA	0	0.0	2	5.0	0	0.0	2	1.6
GASTROINTESTINAL DISORDER	0	0.0	1	2.5	0	0.0	1	0.8
GINGIVITIS	1	1.9	0	0.0	0	0.0	1	0.8
NAUSEA	3	5.8	0	0.0	0	0.0	3	2.4
PEPTIC ULCER HEMORRHAGE	1	1.9	0	0.0	0	0.0	1	0.8
TOOTH DISORDER	0	0.0	1	2.5	2	6.1	3	2.4
VOMITING	1	1.9	0	0.0	1	3.0	2	1.6
Hemic and Lymphatic System	0	0.0	0	0.0	1	3.0	1	0.8
WBC ABNORMALITY	0	0.0	0	0.0	1	3.0	1	0.8
Metabolic and Nutritional Disorders	1	1.9	1	2.5	0	0.0	2	1.6
DEHYDRATION	0	0.0	1	2.5	0	0.0	1	0.8
WEIGHT GAIN	1	1.9	0	0.0	0	0.0	1	0.8
Musculoskeletal System	1	1.9	2	5.0	0	0.0	3	2.4
MYALGIA	1	1.9	2	5.0	0	0.0	3	2.4
Nervous System	3	5.8	2	5.0	2	6.1	7	5.6
ANXIETY	0	0.0	1	2.5	0	0.0	1	0.8
CONVULSION	0	0.0	1	2.5	0	0.0	1	0.8
EMOTIONAL LABILITY	1	1.9	0	0.0	1	3.0	2	1.6
HYPERTONIA	1	1.9	0	0.0	0	0.0	1	0.8
INSOMNIA	0	0.0	0	0.0	1	3.0	1	0.8
VESTIBULAR DISORDER	1	1.9	0	0.0	0	0.0	1	0.8
Respiratory System	13	25.0	4	10.0	8	24.2	25	20.0
ASTHMA	1	1.9	0	0.0	1	3.0	2	1.6
BRONCHITIS	2	3.8	0	0.0	1	3.0	3	2.4

Table 16.6.1

Summary of Treatment-Emergent Adverse Experiences Requiring Corrective Therapy Regardless of Attribution
by ADECS Body System and Preferred Term (Continuation Phase) - Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	22	42.3%	13	32.5%	15	45.5%	50	40.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
COUGH INCREASED	2	3.8	0	0.0	1	3.0	3	2.4
PHARYNGITIS	4	7.7	0	0.0	3	9.1	7	5.6
RESPIRATORY DISORDER	6	11.5	3	7.5	2	6.1	11	8.8
RHINITIS	2	3.8	0	0.0	1	3.0	3	2.4
SINUSITIS	1	1.9	1	2.5	2	6.1	4	3.2
Skin and Appendages	2	3.8	2	5.0	2	6.1	6	4.8
ACNE	0	0.0	1	2.5	0	0.0	1	0.8
CONTACT DERMATITIS	1	1.9	1	2.5	0	0.0	2	1.6
DRY SKIN	0	0.0	1	2.5	0	0.0	1	0.8
PHOTOSENSITIVITY	1	1.9	0	0.0	0	0.0	1	0.8
RASH	0	0.0	0	0.0	1	3.0	1	0.8
URTICARIA	0	0.0	0	0.0	1	3.0	1	0.8
Special Senses	3	5.8	0	0.0	2	6.1	5	4.0
EAR PAIN	1	1.9	0	0.0	0	0.0	1	0.8
OTITIS EXTERNA	1	1.9	0	0.0	0	0.0	1	0.8
OTITIS MEDIA	1	1.9	0	0.0	2	6.1	3	2.4

PAROXETINE - PROTOCOL 329

Table 16.6.2

Summary of Treatment-Emergent Adverse Experiences Requiring Corrective Therapy Regardless of Attribution
by ADECS Body System and Preferred Term (Continuation Phase) - Male Specific Adverse Experiences
Intent-to-Treat Population

NO DATA AVAILABLE FOR THIS REPORT

PAROXETINE - PROTOCOL 329

Table 16.6.3

Summary of Treatment-Emergent Adverse Experiences Requiring Corrective Therapy Regardless of Attribution
by ADECS Body System and Preferred Term (Continuation Phase) - Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP		PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS	:	33	100.0%	18	100.0%	23	100.0%	74	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	3	9.1%	0	0.0%	2	8.7%	5	6.8%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%	N	%
Urogenital System		3	9.1	0	0.0	2	8.7	5	6.8
DYSMENORRHEA		3	9.1	0	0.0	2	8.7	5	6.8

PAROXETINE - PROTOCOL 329

Table 16.7

Listing of Deaths (Continuation Phase)
by Treatment Group and Patient
Intent-to-Treat Population

NO DATA AVAILABLE FOR THIS REPORT

PAROXETINE - PROTOCOL 329

Table 16.8

Listing of Serious Adverse Experiences by Treatment Group and Patient
Continuation Phase
Intent-to-Treat Population

Treatment Group=PAROXETINE

Patient ID	Preferred Term	Verbatim Term	AE Onset Date	Relative Days *	Duration	Onset Dose (mg)	No. Epi	Inv Int	Act-ion	Inv Rel	Corr Ther	SAE
329.002.00058	Emotional Lability	INTENTIONAL OVERDOSE {TYLENOL OVERDOSE TOOK 80 PILLS}	19JAN95	122, 64	1 Days	40	CON	MOD	STP	PBU	No	Yes
329.003.00250	Emotional Lability	OVERDOSE {INTENTIONAL}	27MAY96	75, 18	01:00 Hrs	30	1	SEV	STP	UNR	No	Yes
329.004.00017	Manic Reaction	HOSPITALIZATION RULE-OUT HYPOMANIA	31AUG95	163, 107	3 Days	30	CON	MIL	NO	UNR	No	Yes
329.005.00011	Emotional Lability	[OVERDOSE{WITH BAYER EXTRA STRENGTH}[INTENTIONAL]	17MAY95	156, 100	1 Days	30	1	SEV	STP	UNR	Yes	Yes
329.005.00109	Peptic Ulcer Hemorrhage	BLEEDING ULCER {PEPTIC}	07MAY95	129, 76	4 Days	20	CON	SEV	NO	UNR	Yes	Yes
329.009.00170	Agitation	AGITATION	09JUL96	246, 189	12:00 Hrs	20	CON	MOD	NO	PSR	No	Yes
	Asthenia	FATIGUE	27JUN96	234, 177	11 Days	20	CON	MOD	NO	PSR	No	Yes
	Nausea	NAUSEA	27JUN96	234, 177	12 Days	20	CON	SEV	NO	REL	Yes	Yes
	Somnolence	DROWSY	27JUN96	234, 177	11 Days	20	CON	MOD	NO	PSR	No	Yes
	Tremor	SHAKY TREMORS	27JUN96	234, 177	2 Days	20	CON	MOD	NO	PSR	No	Yes

* days relative to start of acute phase, days relative to start of continuation phase
Number of Episodes [No. Epi]: CON = Continuous
Investigator Intensity [Inv Int] : MIL = Mild, MOD = Moderate, SEV = Severe
Action Taken on Study Medication [Action] : DCR = Dose Decreased, INC = Dose Increased, NO = None, STP = Drug Stopped
Investigator Relationship [Inv Rel]: PBU = Probably Unrelated, PSR = Possibly Related, REL = Related, UNR = Not Related
Corrective Therapy [Corr Ther]
Serious AE as Judged according to SB Criteria by Investigator [SAE]

PAROXETINE - PROTOCOL 329

Table 16.8

Listing of Serious Adverse Experiences by Treatment Group and Patient
Continuation Phase
Intent-to-Treat Population

Treatment Group=IMIPRAMINE

Patient ID	Preferred Term	Verbatim Term	AE Onset Date	Relative Days *	Duration	Onset Dose (mg)	No. Epi	Inv Int	Act-ion	Inv Rel	Corr Ther	SAE
329.008.00273	Accidental Overdose	TRICYCLIC TOXICITY	09SEP96	116, 53	8 Days	300		SEV	STP	REL	No	Yes
329.012.00221	Emotional Lability	OVERDOSE {INTENTIONAL}	03NOV96	132, 69	19:30 Hrs	200	CON	SEV	STP	UNR	No	Yes

* days relative to start of acute phase, days relative to start of continuation phase
Number of Episodes [No. Epi]: CON = Continuous
Investigator Intensity [Inv Int] : MIL = Mild, MOD = Moderate, SEV = Severe
Action Taken on Study Medication [Action] : DCR = Dose Decreased, INC = Dose Increased, NO = None, STP = Drug Stopped
Investigator Relationship [Inv Rel]: PBU = Probably Unrelated, PSR = Possibly Related, REL = Related, UNR = Not Related
Corrective Therapy [Corr Ther]
Serious AE as Judged according to SB Criteria by Investigator [SAE]

PAROXETINE - PROTOCOL 329

Table 16.8

Listing of Serious Adverse Experiences by Treatment Group and Patient
Continuation Phase
Intent-to-Treat Population

Treatment Group=PLACEBO

Patient ID	Preferred Term	Verbatim Term	AE Onset Date	Relative Days *	Duration	Onset Dose (mg)	No. Epi	Inv Int	Act-ion	Inv Rel	Corr Ther	SAE
329.002.00241	Emotional Lability	PT. HOSPITALIZED FOR SUICIDAL IDEATION	23MAY96	108, 52	Not Stated	0	CON	SEV	STP	PBU	Yes	Yes
	Hostility	PT. HOSPITALIZED FOR HOMICIDAL IDEATION	23MAY96	108, 52	Not Stated	0	CON	SEV	STP	PBU	No	Yes

* days relative to start of acute phase, days relative to start of continuation phase
Number of Episodes [No. Epi]: CON = Continuous
Investigator Intensity [Inv Int] : MIL = Mild, MOD = Moderate, SEV = Severe
Action Taken on Study Medication [Action] : DCR = Dose Decreased, INC = Dose Increased, NO = None, STP = Drug Stopped
Investigator Relationship [Inv Rel]: PBU = Probably Unrelated, PSR = Possibly Related, REL = Related, UNR = Not Related
Corrective Therapy [Corr Ther]
Serious AE as Judged according to SB Criteria by Investigator [SAE]

Table 16.8.1 Narratives for Patients with Serious Non-Fatal Adverse Events

PID 329.002.00058

(95000667-1)

Primary Adverse Event: Preferred Term (Verbatim) Emotional Lability (Intentional Overdose (Tylenol) [Asymptomatic]

Demography: Age: 16 years Date of Birth: 25-May-78 Sex: Female
Height: 63 in. Weight: 203.5 lbs. Race: Caucasian

Country: United States

Medical History: Past: Mental status impaired (ADD)
Current: Headaches

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 20-Sep-94 **End:** 16-Nov-94
Start Continuation Phase: 17-Nov-94 **End:** 16-Jun-95

Adverse Event Remarks:
This 16-year-old Caucasian female patient, weight 203.5 lbs., height 63 in., was a participant in study 29060/329 for major depression. On 20-Sep-94, the patient was randomized to paroxetine and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind paroxetine in the continuation phase on 17-Nov-94.

The patient had recently reported some family difficulties (divorced parents) and an argument involving her 20-year-old boyfriend, who was apparently involved in Satanic activities. At her last clinic visit, there was no evidence of recurrent depression. Her Hamilton Depression scale score was 5. The patient was hospitalized on 19-Jan-95 after taking 80 Tylenol tablets. Her parents reported this event after she had been discharged. The patient reported no sequelae from the overdose. The investigator considered the event to be moderately severe. The patient was withdrawn from the study due to the overdose.

PID 329.002.00058 (continued)

At the time of the overdose, the patient was receiving 40 mg paroxetine per day. In the opinion of the investigator, the overdose was probably unrelated to the study medication.

Concomitant Medications:	**Start**	**End**
Amoxicillin	18-Nov-94	28-Nov-94

Treatment Medications:
None

Laboratory Remarks:
Laboratory results were all within reference range at week 20 visit.

Reporter Attribution for Primary AE: Probably unrelated

Reason for Seriousness: Hospitalization required
Overdose

PID 329.002.00241

(96012125-1)

Primary Adverse Events: Emotional Lability (Suicidal Ideation)
Preferred Term (Verbatim): Hostility (Homicidal Ideation)

Demography: Age: 15 years Date of Birth: 20-June-80 Sex: Male
Height: 69 in. Weight: 202.0 lbs. Race: Portuguese

Country: United States

Medical History: Past: None
Current: Allergies to penicillin, pollen, poultry dust; nasal congestion; atrial extrasystoles

Study Diagnosis: Unipolar Major Depression

Study Medication: Placebo

Start Acute Phase: 06-Feb-96 **End:** 01-Apr-96
Start Continuation Phase: 02-Apr-96 **End:** 23-May-96

Adverse Event Remarks:
This 15-year-old Portuguese male patient, weight 202.0 lbs., height 69 in., was a participant in study 29060/329 for major depression. On 06-Feb-96, the patient was randomized to placebo and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind placebo in the continuation phase on 02-Apr-96.

On 23-May-96 the patient's mother took him to see a physician for a second opinion as she was concerned about her son's anger and irritability. The patient was evaluated and was admitted to the hospital on 23-May-96 due to severe suicidal and homicidal (towards his parents) ideation. His mother had found metal pipes and knives in the patients room just prior to his admission. The admitting physician stated that the patient was extremely depressed and rageful. The patient's study medication was stopped on 23-May-96 and the patient was started on Prozac 10 mg shortly after his admission. The patient was withdrawn from the study due to these events. The admitting physician did not feel down titration of study medication was necessary.

PID 329.002000241 (continued)

At the time of the events, the patient was receiving double-blind placebo. In the opinion of the investigator, the emotional lability and hostility were probably unrelated to the study medication.

Concomitant Medications:
None

Treatment Medications:	**Start**	**End**
Fluoxetine 10 mg	23-May-96	unknown

Laboratory Remarks:
Laboratory results were all within reference range at week 8 visit, except slightly elevated eosinophils (5.4%, reference range 0%-5%).

Reporter Attribution for Primary AE: Probably unrelated

Reason for Seriousness: Involved or prolonged inpatient hospitalization
Significant disability or incapacity
Life threatening

PID 329.003.00250

(96007553-1)

Primary Adverse Event: Preferred Term (Verbatim) Emotional Lability (Overdose, intentional) [Asymptomatic]

Demography: Age: 15 years Date of Birth: 07-Dec-80 Sex: Female
Height: 64 in Weight: 180.0 lbs. Race: Black

Country: United States

Medical History: Past: None
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 14-Mar-96 **End:** 09-May-96
Start Continuation Phase: 10-May-96 **End:** 27-May-96

Adverse Event Remarks:
This 15-year-old Black female patient, weight 180.0 lbs., height 64 in., was a participant in study 29060/329 for major depression. On 19-Mar-96, the patient was randomized to paroxetine and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind paroxetine in the continuation phase on 10-May-96.

On 27-May-96 the patient took a 20-tablet overdose of study medication. She was taken to the emergency room by her sister. Her vital signs were fine, and she was alert. The patient was hospitalized for observation. She did not experience any physical distress. The patient was discharged from the general hospital and admitted to psychiatric unit as she remained suicidal. The investigator considered the event to be severe in intensity. On 28-May-96, the study medication was stopped and the blind broken.

PID 329.003.00250 (continued)

At the time of the overdose, the patient was receiving 30 mg paroxetine per day. In the opinion of the investigator, the overdose was not related to the study medication.

Concomitant Medications:	**Start**	**End**
Benadryl	29-Apr-96	29-Apr-96

Treatment Medications:
None

Laboratory Remarks:
No laboratory results were available after the screening visit.

Reporter Attribution for Primary AE: Not related

Reason for Seriousness: Hospitalization required
Overdose

PID 329.004.00017

(95009265-1)

Primary Adverse Event: Preferred Term (Verbatim) Manic Reaction (Rule out Hypomania)

Demography: Age: 16 years Date of Birth: 05-Dec-78 Sex: Female
Height: 63 in. Weight: 137.2 lbs. Race: East Indian

Country: Canada

Medical History: Past: None
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 22-Mar-95 **End:** 16-May-95
Start Continuation Phase: 17-May-95 **End:** 14-Nov-95

Adverse Event Remarks:
This 16-year-old East Indian female patient, weight 137.2 lbs., height 63 in., was a participant in study 29060/329 for major depression. On 22-Mar-95, the patient was randomized to paroxetine and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind paroxetine in the continuation phase on 17-May-95.

On 24-August-95 the patient came to the center with her mother for an extra visit. Her mother was concerned about hypomania because the patient had left home at midnight to meet men with a friend. The patient denied any hypomanic symptoms, describing the event as "acting-out behavior."

The patient was hospitalized from 31-Aug-95 to 2-Sep-95 to assess possible hypomanic symptoms. No such symptoms were observed during this period and the patient was discharged and continued on study medication. The investigator considered the event to be mild in intensity.

At the time of the hospitalization, the patient was receiving 30 mg paroxetine per day. In the opinion of the investigator, the manic reaction was not related to the study medication.

PID 329.004.00017 (continued)

Concomitant Medications:	**Start**	**End**
Maalox	08-Nov-95	08-Nov-95
Vitamin B Complex	08-May-95	Ongoing
Tylenol	29-Aug-95	30-Aug-95
Benylin	14-Sep-95	16-Sep-95

Treatment Medications:
None known

Laboratory Remarks:
Laboratory results were all within reference range at the week 32 visit.

Reporter Attribution for Primary AE: Not related

Reason for Seriousness: Hospitalization required

PID 329.005.00011

(95004620-1)

Primary Adverse Event: Preferred Term (Verbatim) Emotional lability (Overdose, intentional)

Demography: Age: 17 years Date of Birth: 09-Dec-77 Sex: Female
Height: 69 in. Weight: 122.0 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 13-Dec-94 **End:** 06-Feb-95
Start Continuation Phase: 07-Feb-95 **End:** 17-May-95

Adverse Event Remarks:
This 17-year-old Caucasian female patient, weight 122.0 lbs., height 69 in., was a participant in study 29060/329 for major depression. On 13-Dec-94, the patient was randomized to paroxetine and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind paroxetine in the continuation phase on 07-Feb-95.

On 17-May-95, day 156 of the study, the patient was reported by her mother to have been experiencing several stressors recently, including being taunted by classmates about being depressed, getting a bad report card (failing 5 subjects), and being told to study before going to a church meeting (because of failing grades). The patient disobeyed her mother and instead invited her boyfriend over the house. When mother arrived home she confronted the patient, who became angry, began swearing and kicking, and continued in a tantrum. Boyfriend and mother attempted to talk to patient but to no avail.

PID 329.005.00011 (continued)

When boyfriend left, patient was crying and sobbing to mother, stating, "I just want to die." Patient then began to bang her head on the wall, ran upstairs and locked herself in the bathroom. Mother tried to follow but could not get in the bathroom. Patient ran water while in bathroom while asking her mother over and over to tell her how much she loved her. When she finally opened the door there was an empty bottle of Bayer Extra Strength for Menstrual Cramps on the floor. When mother questioned patient, she refused to tell her if she took anything. Mother called Poison Control Center, which recommended she take patient to closest medical hospital, where they pumped her stomach and found 20 pills. She was treated with IV fluids. Patient was admitted to intensive care and remained there at time of report. Reporter added that two weeks previously, when patient reported for her scheduled visit, HAM-D was a 2 and she did not fulfill criteria for major depressive disorder. The patient was withdrawn from the study due to this event, which was considered to be severe in intensity.

At the time of the overdose, the patient was receiving 30 mg paroxetine per day. In the opinion of the investigator, the emotional lability was not related to the study medication.

Concomitant Medications:	**Start**	**End**
Tylenol	20-Dec-94	03-Jan-95

Treatment Medications:	**Start**	**End**
Normal Saline	17-May-95	19-May-95
Charcoal	17-May-95	17-May-95

Laboratory Remarks:
Laboratory results were all within reference range at week 20 visit, except for slightly decreased creatinine (0.6 mg/dL, reference range 0.8-1.5 mg/dL).

Reporter Attribution for Primary AE: Not related

Reason for Seriousness: Hospitalization required

PID 329.005.00109

(95004714-1)

Primary Adverse Event: Preferred Term (Verbatim) Peptic Ulcer Hemorrhage (Bleeding Ulcer)

Demography: Age: 17 years Date of Birth: 05-Aug-77 Sex: Female
Height: 67 in. Weight: 137.0 lbs. Race: Black

Country: United States

Medical History: Past: Asthma, bleeding ulcer (NOS)
Current: Postpartum care

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 30-Dec-94 **End:** 20-Feb-95
Start Continuation Phase: 21-Feb-95 **End:** 16-May-95

Adverse Event Remarks:
This 17-year-old black female patient, weight 137.0 lbs., height 67 in., was a participant in study 29060/329 for major depression. On 30-Dec-94, the patient was randomized to paroxetine and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind paroxetine in the continuation phase on 21-Feb-95.

On 07-May-95, after complaints of nausea, stomach ache, bloating, dizziness and fainting, the patient was admitted to the hospital, where she was diagnosed with bleeding ulcers Patient was hospitalized for three days receiving IV fluids. At the same time, the hospital refused to allow her to continue taking her study medication because it was not prescribed by a doctor at their hospital.

PID 329.005.00109 (continued)

After patient's symptoms resolved, she was discharged and returned home, where she again started taking study medication. After resuming medication, patient became nauseated and vomited to the point that she stopped taking study medication. Patient did this without consulting study coordinator or primary investigator. When she arrived for week 20 scheduled appointment she informed study coordinator of incident and that she had not taken study medication for 9 days. Current HAM-D was 0 and she did not meet criteria for major depressive disorder at this time. Events were reported by patient. The investigator site made numerous unsuccessful attempts at contacting the patient and was unable to verify this report. The hospital where the patient claimed to have been hospitalized has no record of these events.

At the time of the peptic ulcer hemorrhage, the patient was receiving 20 mg paroxetine per day. In the opinion of the investigator, the peptic ulcer hemorrhage was severe in intensity and was not related to the study medication. The patient subsequently was discontinued from the study due to non-compliance.

Concomitant Medications:	**Start**	**End**
Prenatal Vitamin	30-Nov-93	Ongoing
Ferrous Sulfate	19-Aug-94	Ongoing
Tylenol	20-Mar-95	22-Mar-95
Desogen 28	12-Jan-95	Ongoing
Zantac	01-May-95	08-May-95

Treatment Medications:	**Start**	**End**
IV Fluids	07-May-95	10-May-95

Laboratory Remarks:
Laboratory results were all within reference range at week 20 visit.

Reporter Attribution for Primary AE: Not related

Reason for Seriousness: Involved or prolonged inpatient hospitalization
Significant disability or incapacity
Significant side effect

PID 329.008.00273

(96014019-1)

Primary Adverse Event: Preferred Term (Verbatim) Accidental Overdose (Tricyclic Toxicity)

Demography: Age: 12 years Date of Birth: 28-Feb-84 Sex: Female
Height: 72 in. Weight: 152.0 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: Temporomandibular joint pain

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 17-May-96 **End:** 18-Jul-96
Start Continuation Phase: 19-Jul-96 **End:** 09-Sep-96

Adverse Event Remarks:
This 12-year-old Caucasian female patient, weight 152.0 lbs., height 72.0 in., was a participant in study 29060/329 for major depression. On 17-May-96, the patient was randomized to imipramine and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind imipramine in the continuation phase on 19-Jul-96.

Patient experienced severe tricyclic toxicity on 09-Sep-96. Study medication was stopped on 09-Sep-96. Patient was hospitalized for the event. Investigator attempted to obtain medical records from the hospital (ICU), in order to review specific presenting signs and symptoms (and duration) as well as objective testing (including toxicology screen results, imipramine and desipramine levels, and EKG findings). Initial imipramine and desipramine levels on 09-Sep-96 were reported over the phone as 800 ng/mL.

PID 329.008.00273 (continued)

Patient also had near syncope, hypotension and cerebellar findings during the initial exam after first presenting in the emergency room. She reportedly had electrocardiogram abnormalities, including QRS widening and increased QTC interval. The investigator considered the event to be life-threatening. There was no evidence suggesting the patient took an overdose (i.e. no history of suicidal ideation or behavior; previous medication compliance excellent; her medication cards were reviewed and only the expected number of pills were missing). The investigator planned to interview the patient to assess whether other factors not yet identified may have been involved. Patient was discharged on 12-Sept-96 and the condition ultimately cleared on 16-Sep-96.

At the time of the overdose, the patient was receiving 300 mg imipramine per day. In the opinion of the investigator, the tricyclic toxicity was related to the study medication.

Concomitant Medications:	**Start**	**End**
Tylenol	10-Apr-96	Ongoing
Ansaid	20-Mar-96	10-Apr-96

Treatment Medications:
None known

Laboratory Remarks:
Laboratory results were all within reference range at week 4 visit.

Reporter Attribution for Primary AE: Related

Reason for Seriousness: Involved or prolonged inpatient hospitalization
Life threatening

PID 329.009.00170

(96010009-1)

Primary Adverse Event:	Nausea (Nausea)
Preferred Term (Verbatim)	Agitation (Agitation) Asthenia (Fatigue) Somnolence (Drowsy) Tremor (Shaky tremors)

Demography: Age: 14 years Date of Birth: 20-Mar-1981 Sex: Female
Height: 66 in. Weight: 101.6 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: Myalgia, headache, scoliosis

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 07-Nov-95 **End:** 02-Jan-96
Start Continuation Phase: 03-Jan-96 **End:** 08-Jul-96

Adverse Event Remarks:
This 14-year-old Caucasian female patient, weight 101.6 lbs., height 66 in., was a participant in study 29060/329 for major depression. On 07-Nov-95, the patient was randomized to paroxetine and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind paroxetine in the continuation phase on 29-Jan-96.

PID 329.009.00170 (continued)

Patient was tapering medication and missed a dose on 27-Jun-96. The following day after eating, she became nauseated and shaky. On 28-Jun-96 she missed the second taper dose and experienced drowsiness, fatigue, and worsening nausea. However, the shakiness abated. On 30-Jun-96, when the taper dose was restarted, the patient experienced extreme irritability, nihilistic thoughts, negative attitude, increased appetite, and worsening nausea. On 01-Jul-96, severe vomiting began, and the patient was unable to keep food down. Maalox and Dramamine were begun without effect and were discontinued. The symptoms continued, and the nausea progressively worsened. The patient wanted to die and planned her funeral. By 06-Jul-96 the vomiting resolved and the nausea decreased in severity. She was less drowsy and back to baseline on 08-Jul-96.

On 09-Jul-96 the patient's menses began, and she had cramps, constipation, and an exaggerated response to discomfort, with crying, agitation, scratching her leg with her nails, and continued nihilistic thoughts. Motrin 400 mg was given. 10-Jul-96 she felt much better, without dysmenorrhea and vomiting, but was irritable and still had negative attitude. She expressed a desire to restart medication. The physician said the patient had an excellent response to therapy after 8 months on study medication but experienced severe withdrawal symptoms. The investigator reported that the nausea and vomiting were severe and related to study medication. Tremors, fatigue, and agitation were moderately severe. At hospitalization, the following laboratory values were noted:

Laboratory Parameter	Laboratory Value	Unit	Reference Range
Hematocrit	35.3	%	36%-49%
SGOT	45	U/L	0-41 U/L
SGPT	61	U/L	0-48 U/L

At the time of the events, the patient was receiving 20 mg paroxetine per day. In the opinion of the investigator, nausea was related to study medication and the other adverse events were possibly related to the study medication.

Concomitant Medications:
None

Treatment Medications:	Start	End
Maalox	01-Jul-96	Not known
Motrin	09-Jul-96	Ongoing
Dramamine	01-Jul-96	Not known

PID 329.009.00170 (continued)

Laboratory Remarks:
At the final visit on day 247, all laboratory values were within reference range except for slightly decreased glucose (62 mg/dL, reference range 70-115 mg/dL).

Vital Sign Remarks:
The patient entered the study on 07-Nov-95 with a baseline weight of 101.6 lbs. On days 3 and 45, adverse events of loss of appetite were reported (mild and moderate in intensity, respectively) as well as mild weight loss. At day 45, the patient's weight had decreased to 98.8 lb. The events of loss of appetite were considered possibly related to study medication, and the weight loss was considered probably unrelated to study medication. At week 24, the patient's weight increased to 109.0, an increase ≥7% and of potential clinical concern. Adverse events of increased appetite were reported on days 147 and 237 that were considered mild and moderately severe, respectively.

Reporter Attribution for Primary AE:	Nausea	Related
	Agitation	Possibly related
	Asthenia	Possibly related
	Somnolence	Possibly related
	Agitation	Possibly related

Reason for Seriousness: Involved significant disability or incapacity

PID 329.012.00221

(96016246-1)

Primary Adverse Event: Preferred Term (Verbatim) Emotional lability (Overdose, intentional)

Demography: Age: 17 years Date of Birth: 28-Nov-78 Sex: Male
Height: 69 in. Weight: 148.2 lbs. Race: Caucasian

Country: Canada

Medical History: Past: None
Current: Headache

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 25-Jun-96 **End:** 26-Aug-96
Start Continuation Phase: 27-Aug-96 **End:** 03-Nov-96

Adverse Event Remarks:
This 17-year-old Caucasian male patient, weight 148.2 lbs., height 69 in., was a participant in study 29060/329 for major depression. On 25-Jun-96, the patient was randomized to imipramine and received the first dose of double-blind study medication. The patient completed the acute phase of the study and took the first dose of double-blind imipramine in the continuation phase on 27-Aug-96.

At hour 00:30 on 03-Nov-96, following an argument with his girlfriend, the patient took 8 mg of oral lorazepam (which had been prescribed to his father). The patient presented to the emergency room with ataxia and drowsiness, noted as severe in intensity as a result of the overdose. The events were well resolved when the patient was discharged from the emergency room at hour 19:30 the same day. The patient indicated that the overdose was an impulsive act, that he did not intend to die, and that he was not actively suicidal. He was dysphoric, apathetic, and mildly withdrawn. The patient gave assurance that he would not harm himself before his next visit, scheduled the following day (04-Nov-96). The patient did not wish to continue in the study, stating "I may be on placebo, that's why I may be getting worse again." The investigator considered the event to be severe in intensity. The patient was withdrawn from the study.

PID 329.012.00221 (continued)

At the time of the overdose, the patient was receiving 200 mg imipramine per day. In the opinion of the investigator, the emotional lability was not related to the study medication.

Concomitant Medications:	**Start**	**End**
Laxative (Unknown Name)	14-Oct-96	01-Nov-96
Aspirin	10-Sep-96	10-Sep-96
Chloral Hydrate	19-Aug-96	22-Sep-96
Tylenol	01-Jan-94	Ongoing

Treatment Medications:	**Start**	**End**
None known		

Laboratory Remarks:
Laboratory results were all within reference range at week 8 visit, except for elevated eosinophils (8.3%, reference range 0%-5%), slightly decreased uric acid (3.9 mg/dL, reference range 4-8 mg/dL), and findings of squamous epithelial cells in the urine.

Reporter Attribution for Primary AE: Not related

Reason for Seriousness: Overdose

PAROXETINE - PROTOCOL 329

Table 16.9.1

Summary of Adverse Experiences Leading to Withdrawal during Continuation Phase by ADECS Body System and Preferred Term
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	52	100.0%	40	100.0%	33	100.0%	125	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	4	7.7%	6	15.0%	3	9.1%	13	10.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Body as a Whole	0	0.0	3	7.5	1	3.0	4	3.2
ABNORMAL LABORATORY VALUE	0	0.0	1	2.5	0	0.0	1	0.8
ACCIDENTAL OVERDOSE	0	0.0	1	2.5	0	0.0	1	0.8
ASTHENIA	0	0.0	1	2.5	0	0.0	1	0.8
INFECTION	0	0.0	0	0.0	1	3.0	1	0.8
Metabolic and Nutritional Disorders	0	0.0	1	2.5	0	0.0	1	0.8
DEHYDRATION	0	0.0	1	2.5	0	0.0	1	0.8
Nervous System	3	5.8	3	7.5	1	3.0	7	5.6
CONVULSION	0	0.0	1	2.5	0	0.0	1	0.8
EMOTIONAL LABILITY	3	5.8	1	2.5	1	3.0	5	4.0
HOSTILITY	0	0.0	0	0.0	1	3.0	1	0.8
NEUROSIS	0	0.0	1	2.5	0	0.0	1	0.8
Respiratory System	0	0.0	0	0.0	1	3.0	1	0.8
SINUSITIS	0	0.0	0	0.0	1	3.0	1	0.8
Skin and Appendages	1	1.9	0	0.0	0	0.0	1	0.8
CONTACT DERMATITIS	1	1.9	0	0.0	0	0.0	1	0.8

PAROXETINE - PROTOCOL 329

Table 16.9.2

Summary of Adverse Experiences Leading to Withdrawal during Continuation Phase by ADECS Body System and Preferred Term
Male Specific Adverse Experiences
Intent-to-Treat Population

NO DATA AVAILABLE FOR THIS REPORT

PAROXETINE - PROTOCOL 329

Table 16.9.3

Summary of Adverse Experiences Leading to Withdrawal during Continuation Phase by ADECS Body System and Preferred Term
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP		PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS	:	33	100.0%	18	100.0%	23	100.0%	74	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	1	5.6%	0	0.0%	1	1.4%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%	N	%
Urogenital System		0	0.0	1	5.6	0	0.0	1	1.4
UNINTENDED PREGNANCY		0	0.0	1	5.6	0	0.0	1	1.4

Table 16.9.4 Narratives for Patients with Non-Serious Adverse Events Leading to Withdrawal

PID 329.002.00057

Primary Adverse Experience: Unintended pregnancy (Pregnancy)
Preferred term (Verbatim term)
Other Adverse Experience: Nausea (Nausea)
Vomiting (Vomiting)

Demography: Age: 15 years Date of Birth: 30-may-79 Sex: Female
Height: 67 in. Weight: 162.5 lbs. Race: Caucasian

Country: United States

Medical History: Past: Childhood migraine, concussion, hernia operation, tonsillectomy, tubes in ears
Current: Heartburn, headaches, Scheuermann's kyphosis, stomach problems

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 08-Sep-94 **End:** 03-Nov-94
Start Continuation Phase: 04-Nov-94 **End:** 29-Dec-94

AE Remarks:

This 15-year-old Caucasian female was randomized to imipramine and completed the 8-week acute phase of the study. At the completion of the acute phase the patient was taking 300 mg of imipramine per day. On day 94 of the study the patient was withdrawn from the study after it was determined that she was pregnant. The investigator reported the event as moderate in intensity and unrelated to the study medication.

Concomitant Medications:	**Start**	**End**
Acetaminophen	01-Aug-94	Ongoing
Acetylsalicylic Acid	29-Nov-94	29-Nov-94
Cannabis	Unknown	Unknown

PID 329.002.00057 (continued)

Other Safety Parameters:
At week 12 ALT was 75 U/L (reference range 0-48 U/L). ALT was 8 U/L at screening.

Vital signs: Pulse was high at week 12 (128 bpm).

PID 329.005.00006

Primary Adverse Experience: Neurosis (Obsessive thoughts)
Preferred term (Verbatim term)

Demography: Age: 17 years Date of Birth: 28-Aug-77 Sex: Male
Height: 68 in. Weight: 145.0 lbs. Race: Caucasian

Country: United States

Medical History: Past: Allergic to dust and pollen; recurrent tonsillitis, mononucleosis
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 04-Nov-94 **End**: 02-Jan-95
Start Continuation Phase: 03-Jan-95 **End**: 11-Apr-95

AE Remarks:

This 17-year-old Caucasian male was randomized to imipramine and completed the 8-week acute phase of the study. At the completion of the acute phase the patient was taking 300 mg of imipramine per day. On day 116 of the study the patient developed neurosis (obsessive thoughts) and was withdrawn from the study on day 175. The duration of the event was not reported. The investigator indicated that the event was of moderate intensity and probably unrelated to the study medication.

Concomitant Medications:
None

Other Safety Parameters:
RBCs were 5.5 mill/mcL (reference range 4.1–5.3 mill/mcL) at final visit.

PID 329.005.00007

Primary Adverse Experience: Convulsion (seizure)
Preferred term (Verbatim term) Dehydration (dehydration)
Rash (rash-bilateral forearms)

Demography: Age: 15 yrs Date of Birth: 15-Mar-79 Sex: Female
Height: 64.0 in. Weight: 135.0 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: Questionable ovarian cyst

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 09-Nov-94 **End**: 10-Jan-95
Start Continuation Phase: 11-Jan-95 **End**: 19-May-95

AE Remarks:

This 15-year-old Caucasian female was randomized to imipramine and completed the 8-week acute phase of the study. On day 2 of the acute phase, when the patient was receiving 50 mg imipramine per day, the patient developed a moderately severe rash on her forearms that was treated with Caladryl and resolved in 5 days. On day 42 of the acute phase, the patient experienced hand tremors; the dose was reduced from 300 to 250 mg imipramine per day, but the tremors continued. At the completion of the acute phase the patient was taking 250 of imipramine per day. On day 191 of the study the patient developed dehydration and on day 197 had a convulsion. The patient was withdrawn from the study for these two events and also for the rash that had been seen during the acute phase. The dehydration was treated with Compazine and resolved in 8 days; the seizure was treated with Benadryl. The investigator reported that the seizure and dehydration were severe in intensity. The dehydration and rash were considered probably unrelated to study medication and the seizure was considered unrelated.

PID 329.005.00007 (continued)

Concomitant Medications:	**Start**	**End**
Birth Control Pills	04-Apr-94	Ongoing
Caladryl Lotion	10-Nov-94	14-Nov-94
Tylenol	28-Jan-95	Ongoing
Compazine	22-May-95	22-May-95
Compazine Suppositories	23-May-95	24-May-95
Benadryl	24-May-95	24-May-95

Other Safety Parameters:
All vital signs were within reference range at all visits and all laboratory results were within reference range at week 28.

PID 329.005.00012

Primary Adverse Experience: Infection (toxoplasmosis)
Preferred term (Verbatim term)

Demography: Age: 14 years Date of Birth: 02-May-80 Sex: Female
Height: 69 in. Weight: 145.5 lbs. Race: Caucasian

Country: United States

Medical History: Past: Toxoplasmosis (right eye)
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Placebo

Start Acute Phase: 19-Dec-94 **End**: 15-Feb-95
Start Continuation Phase: 16-Feb-95 **End**: 01-Jun-95

AE Remarks:

This 14-year-old Caucasian female was randomized to placebo and completed the 8-week acute phase of the study. On day 165 of the study the patient developed an eye infection (toxoplasmosis) and was withdrawn from the study. The patient had a past history of the same infection. The infection was treated with steroid eye drops. The investigator considered the event to be moderate in intensity and unrelated to the study medication.

Concomitant Medications:	**Start**	**End**
Tylenol	24-Jan-95	24-Jan-95
Steroid eye drops NOS	01-Jun-95	Ongoing

Other Safety Parameters:
Laboratory results were all within reference range at week 20 visit, except for slightly decreased alkaline phosphatase, which was 36 U/L (reference range 44-280 U/L)

PID 329.005.00111

Primary Adverse Experience: Sinusitis (sinus infection)
Preferred term (Verbatim term)

Demography: Age: 16 yrs Date of Birth: 28-Dec-78 Sex: Female
Height: 65 in. Weight: 132.5 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Placebo

Start Acute Phase: 11-Jan-95 **End**: 04-Apr-95
Start Continuation Phase: 05-Apr-95 **End**: 18-Apr-95

AE Remarks:

This 16-year-old Caucasian female was randomized to placebo and completed the 8-week acute phase of the study. On day 97 of the study the patient developed sinusitis (sinus infection) and was withdrawn from the study. The event was treated with Augmentin, Tylenol, Tylenol #3, and steroidal nasal preparations NOS. The event was considered by the investigator to be severe in intensity and unrelated to the study medication.

Concomitant Medications:	**Start**	**End**
Tylenol	07-Jan-95	20-Feb-95
Amoxicillin	16-Feb-95	20-Feb-95
Nasalcrom	16-Feb-95	Ongoing
Vancenase	16-Feb-95	Ongoing
Tylenol	16-Mar-95	17-Mar-95
Beconase nasal spray	05-Apr-95	Ongoing
Proventil	05-Apr-95	07-Apr-95

Other Safety Parameters:
Laboratory results were all within reference range at week 16 visit.

PID 329.005.00116

Primary Adverse Experience: Contact dermatitis (Poison ivy)
Preferred term (Verbatim term)

Demography: Age: 16 years Date of Birth: 23-May-78 Sex: Female
Height: 71 in. Weight: 206.8 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 07-Feb-95 **End**: 05-Apr-95
Start Continuation Phase: 06-Apr-95 **End**: 27-Jun-95

AE Remarks:

This 16-year-old Caucasian female was randomized to paroxetine and completed the 8-week acute phase of the study. At the completion of the acute phase the patient was taking 20 mg of paroxetine per day. The patient entered the continuation phase of the study and developed contact dermatitis (poison ivy) on day 131 of the study. The event lasted 26 days and the patient was withdrawn from the study 8 days later due to this event. The investigator considered the poison ivy to be moderate in intensity and unrelated to the study medication.

PID 329.005.00116 (continued)

Concomitant Medications:	**Start**	**End**
Augmentin	03-Mar-95	13-Mar-95
Tylenol	03-Mar-95	04-Apr-95
Ear Drops NOS	03-Mar-95	04-Apr-95
Amoxicillin	04-Mar-95	14-Mar-95
Ventolin Inhaler	04-Mar-95	14-Mar-95
Advil	12-Apr-95	12-Apr-95
Robitussin	22-Apr-95	07-May-95
Smith Brothers Cough Drop	22-Apr-95	07-May-95
Advil	28-May-95	30-May-95
Prednisone	21-Jun-95	12-Jul-95
Ceftin	27-Jun-95	07-Jul-95

Other Safety Parameters:
All laboratory results were within reference range at the last scheduled visit.
All vital signs were within reference range at all visits.

PID 329.009.00169

Primary Adverse Experience: Manic reaction (Hypomania)
Preferred term (Verbatim term)

Demography: Age: 13 yrs Date of Birth: 27-Aug-82 Sex: Male
Height: 56 in. Weight: 80.2 lbs. Race: Hispanic

Country: United States

Medical History: Past: None
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Placebo

Start Acute Phase: 31-Oct-95 **End**: 27-Dec-95
Start Continuation Phase: 04-Jan-96 **End**: 22-Jan-96

AE Remarks:

This 13-year-old Hispanic male was randomized to placebo and completed the 8-week acute phase of the study. On day 64 of the study the patient experienced a manic reaction and was withdrawn from the study. The investigator considered the event to be severe in intensity and related to the study medication. It was not stated how long the event lasted.

Concomitant Medications:	**Start**	**End**
Elimite	05-Dec-95	05-Dec-95

PID 329.009.00169 (continued)

Other Safety Parameters:
At the week 8 visit, the last visit at which laboratory testing was performed, the following parameters were below reference range: Hemoglobin (13.7 g/dL, reference range 13.8-17.2 g/dL); Hematocrit (39.6%, reference range 41%-50%), Creatinine (0.6 mg/dL, reference range 0.8-1.5 mg/dL), and Uric Acid (2.7 mg/dL, reference range 4-8 mg/dL). All four parameters had also been low at baseline.

All vital signs were within reference range at all visits except at visit 12, when weight was 86.2 lbs. and increase ≥7% from baseline (80.9 lbs.). The weight gain and the out-of-range laboratory values were not considered adverse events by the investigator.

PID 329.009.00194

Primary Adverse Experience: Nausea (Nausea)
Preferred term (Verbatim term)

Demography: Age: 12 yrs Date of Birth: 18-Aug-83 Sex: Male
Height: 56 in. Weight: 90.4 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: Allergies to milk, ankle pain (secondary to surgical correction right foot [club]), headache (occasional), myalgia (unspecified)

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 05-Dec-95 **End**: 29-Jan-96
Start Continuation Phase: 30-Jan-96 **End**: 05-Jun-96

AE Remarks:

This 12-year-old Caucasian male was randomized to imipramine and completed the 8-week acute phase of the study. At the completion of the acute phase the patient was taking 200 mg of imipramine per day. While in the acute phase (day 43) the patient developed nausea, which remained ongoing. The patient continued in the study and entered the continuation phase. On day 184 of the study the patient was withdrawn for this event. The investigator considered the event to be moderate in severity and possibly related to the study medication.

Concomitant Medications:	**Start**	**End**
Tylenol	01-Jan-94	Ongoing
Tagamet	01-Jan-96	Ongoing
Tylenol Sinus	02-Jan-96	16-Jan-96
Cough Syrup (NOS)	02-Jan-96	16-Jan-96
Tylenol Sinus	02-Jan-96	16-Jan-96

PID 329. 009.00194 (continued)

Other Safety Parameters:
All laboratory results were within reference range at the last scheduled visit, except for hemoglobin (12.8 g/dL, reference range 13.8-17.2g/dL) and hematocrit (37.1%, reference range 41%-50%). Both parameters had been low at baseline.

All vital signs were within reference range at all visits.

PID 329.010.00281

Primary Adverse Experience: Asthenia (Fatigue)
Preferred term (Verbatim term)

Demography: Age: 13 yrs Date of Birth: 22-Dec-82 Sex: Male
Height: 67 in. Weight: 138.2 lbs. Race: Caucasian

Country: United States

Medical History: Past: bilateral tube placement, chicken pox, jaundice (complication of medical care), removal of Baker's cyst from right leg
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 26-Jul-96 **End:** 24-Sep-96
Start Continuation Phase: 25-Sep-96 **End:** 03-Jan-97

AE Remarks:

This 13-year-old Caucasian male was randomized to imipramine and completed the 8-week acute phase of the study. At completion of the acute phase the patient was taking 300 mg of imipramine per day. On day 133 of the study the patient developed moderately severe asthenia. It persisted until day 152 of the study, when it became severe, and the patient was withdrawn from the study. The investigator considered the event to be possibly related to study medication. The severe asthenia lasted 30 days.

Concomitant Medications:	**Start**	**End**
Tylenol	03-Sep-96	03-Sep-96
Tylenol	18-Dec-96	19-Dec-96

PID 329.010.00281 (continued)

Other Safety Parameters:
All laboratory results were within reference range at the last scheduled visit (week 24) except that Hemoglobin was decreased (13.3 g/dL, reference range 13.8-17.2), hematocrit was decreased (39.3%, reference range 41%-50%), and Monocytes were elevated (10.6%, reference range 0%-10%). Hemoglobin and hematocrit had also been below reference range at baseline.

All vital signs were within reference range at all visits.

PID 329.011.00208

Primary Adverse Experience: Abnormal laboratory value (Toxic imipramine level)
Preferred term (Verbatim term)

Demography: Age: 13 yrs Date of Birth: 30-Jun-83 Sex: Male
Height: 58 in. Weight: 84.5 lbs. Race: Caucasian

Country: United States

Medical History: Past: Adenoidectomy, tonsillectomy
Current: Headaches

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 06-Sep-96 **End**: 03-Nov-96
Start Continuation Phase: 04-Nov-96 **End**: 07-Nov-96

AE Remarks:

This 13-year-old Caucasian male was randomized to imipramine and completed the 8-week acute phase of the study. On day 63 of the study, it was discovered that the patient had a toxic imipramine level and the patient was withdrawn from the study. At the time of the event the patient was taking 300 mg of imipramine per day. The investigator considered this event to be mild in intensity and related to the study medication.

Concomitant Medications:	**Start**	**End**
Tylenol	01-Jan-93	Ongoing
Aleve	01-Jan-96	Ongoing

Other Safety Parameters:
All laboratory results were within reference range at the last scheduled visit (week 8) except for low white blood cell count (4.4 thou/mcL, reference range 4.5-13 thou/mcL) and low uric acid (2.3 mg/dL, reference range 4-8 mg/dL). Uric acid values had been low at baseline.

All vital signs were within reference range at all visits.

PAROXETINE - PROTOCOL 329

Table 16.10.1

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	18	100.0%	34	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	10	55.6%	27	79.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	7	38.9	16	47.1
ABDOMINAL PAIN	1	5.6	5	14.7
ALLERGIC REACTION	0	0.0	1	2.9
ASTHENIA	1	5.6	1	2.9
CHEST PAIN	0	0.0	1	2.9
FEVER	0	0.0	2	5.9
HEADACHE	4	22.2	10	29.4
INFECTION	0	0.0	5	14.7
TRAUMA	1	5.6	1	2.9
Cardiovascular System	2	11.1	3	8.8
ARRHYTHMIA	1	5.6	0	0.0
HYPERTENSION	0	0.0	1	2.9
PALPITATION	0	0.0	1	2.9
SYNCOPE	1	5.6	0	0.0
TACHYCARDIA	0	0.0	1	2.9
Digestive System	4	22.2	8	23.5
CONSTIPATION	2	11.1	0	0.0
DECREASED APPETITE	0	0.0	1	2.9
DRY MOUTH	1	5.6	0	0.0
GINGIVITIS	0	0.0	1	2.9
INCREASED APPETITE	1	5.6	0	0.0
NAUSEA	2	11.1	7	20.6
PEPTIC ULCER HEMORRHAGE	0	0.0	1	2.9
VOMITING	2	11.1	2	5.9
Hemic and Lymphatic System	0	0.0	2	5.9
THROMBOCYTHEMIA	0	0.0	1	2.9
THROMBOCYTOPENIA	0	0.0	1	2.9
Metabolic and Nutritional Disorders	3	16.7	1	2.9
WEIGHT GAIN	3	16.7	1	2.9
Musculoskeletal System	1	5.6	0	0.0
MYALGIA	1	5.6	0	0.0
Nervous System	7	38.9	14	41.2
AGITATION	2	11.1	0	0.0
AMNESIA	0	0.0	1	2.9

Table 16.10.1

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	18	100.0%	34	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	10	55.6%	27	79.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
DIZZINESS	2	11.1	7	20.6
DRUG DEPENDENCE	0	0.0	1	2.9
EMOTIONAL LABILITY	0	0.0	4	11.8
HYPERKINESIA	0	0.0	2	5.9
HYPERTONIA	0	0.0	1	2.9
INSOMNIA	1	5.6	3	8.8
MANIC REACTION	0	0.0	1	2.9
NERVOUSNESS	1	5.6	0	0.0
PERSONALITY DISORDER	1	5.6	0	0.0
SOMNOLENCE	1	5.6	0	0.0
TREMOR	2	11.1	1	2.9
VESTIBULAR DISORDER	1	5.6	0	0.0
Respiratory System	3	16.7	11	32.4
ASTHMA	1	5.6	0	0.0
BRONCHITIS	0	0.0	2	5.9
COUGH INCREASED	0	0.0	2	5.9
EPISTAXIS	1	5.6	0	0.0
PHARYNGITIS	0	0.0	6	17.6
RESPIRATORY DISORDER	2	11.1	4	11.8
RHINITIS	0	0.0	3	8.8
SINUSITIS	0	0.0	1	2.9
Skin and Appendages	0	0.0	2	5.9
CONTACT DERMATITIS	0	0.0	1	2.9
PHOTOSENSITIVITY	0	0.0	1	2.9
Special Senses	3	16.7	1	2.9
ABNORMAL VISION	1	5.6	0	0.0
EAR PAIN	0	0.0	1	2.9
OTITIS EXTERNA	1	5.6	0	0.0
OTITIS MEDIA	1	5.6	0	0.0
Urogenital System	2	11.1	0	0.0
ALBUMINURIA	1	5.6	0	0.0
HAEMATURIA	1	5.6	0	0.0
URINARY CASTS	1	5.6	0	0.0
URINARY TRACT INFECTION	1	5.6	0	0.0

Table 16.10.1

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	15	100.0%	25	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	12	80.0%	15	60.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	7	46.7	7	28.0
ABDOMINAL PAIN	4	26.7	0	0.0
ABNORMAL LABORATORY VALUE	1	6.7	0	0.0
ACCIDENTAL OVERDOSE	1	6.7	0	0.0
ASTHENIA	1	6.7	1	4.0
HEADACHE	1	6.7	6	24.0
INFECTION	1	6.7	0	0.0
Cardiovascular System	1	6.7	3	12.0
ELECTROCARDIOGRAM ABNORMAL	1	6.7	0	0.0
HYPERTENSION	0	0.0	1	4.0
SYNCOPE	0	0.0	1	4.0
TACHYCARDIA	0	0.0	2	8.0
Digestive System	6	40.0	7	28.0
CONSTIPATION	0	0.0	1	4.0
DIARRHEA	1	6.7	2	8.0
DRY MOUTH	1	6.7	2	8.0
DYSPEPSIA	0	0.0	2	8.0
GASTROINTESTINAL DISORDER	1	6.7	0	0.0
INCREASED APPETITE	0	0.0	1	4.0
NAUSEA	3	20.0	0	0.0
TOOTH DISORDER	1	6.7	0	0.0
ULCERATIVE STOMATITIS	1	6.7	0	0.0
VOMITING	1	6.7	1	4.0
Hemic and Lymphatic System	0	0.0	1	4.0
ANEMIA	0	0.0	1	4.0
Metabolic and Nutritional Disorders	0	0.0	2	8.0
DEHYDRATION	0	0.0	1	4.0
WEIGHT GAIN	0	0.0	1	4.0
Musculoskeletal System	0	0.0	3	12.0
MYALGIA	0	0.0	3	12.0
Nervous System	5	33.3	6	24.0
ABNORMAL DREAMS	0	0.0	1	4.0
ANXIETY	0	0.0	1	4.0
CONVULSION	0	0.0	1	4.0

Table 16.10.1

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	15	100.0%	25	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	12	80.0%	15	60.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
DIZZINESS	2	13.3	1	4.0
EMOTIONAL LABILITY	0	0.0	1	4.0
INSOMNIA	2	13.3	1	4.0
NEUROSIS	0	0.0	1	4.0
SOMNOLENCE	1	6.7	0	0.0
Respiratory System	0	0.0	5	20.0
RESPIRATORY DISORDER	0	0.0	3	12.0
RHINITIS	0	0.0	1	4.0
SINUSITIS	0	0.0	1	4.0
Skin and Appendages	2	13.3	1	4.0
ACNE	1	6.7	0	0.0
CONTACT DERMATITIS	1	6.7	0	0.0
DRY SKIN	0	0.0	1	4.0
SWEATING	1	6.7	0	0.0
Special Senses	1	6.7	0	0.0
ABNORMAL VISION	1	6.7	0	0.0
Urogenital System	1	6.7	2	8.0
DYSURIA	0	0.0	1	4.0
PYURIA	0	0.0	1	4.0
URINARY RETENTION	1	6.7	0	0.0
URINATION IMPAIRED	1	6.7	0	0.0

Table 16.10.1

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	15	100.0%	18	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	9	60.0%	12	66.7%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	8	53.3	7	38.9
ABDOMINAL PAIN	1	6.7	0	0.0
ASTHENIA	0	0.0	1	5.6
BACK PAIN	2	13.3	0	0.0
HEADACHE	2	13.3	4	22.2
INFECTION	2	13.3	2	11.1
PAIN	0	0.0	1	5.6
TRAUMA	4	26.7	1	5.6
Cardiovascular System	0	0.0	2	11.1
ARRHYTHMIA	0	0.0	1	5.6
PALPITATION	0	0.0	1	5.6
Digestive System	2	13.3	4	22.2
DIARRHEA	1	6.7	2	11.1
NAUSEA	2	13.3	1	5.6
TOOTH DISORDER	0	0.0	2	11.1
VOMITING	1	6.7	2	11.1
Hemic and Lymphatic System	1	6.7	2	11.1
LYMPHADENOPATHY	1	6.7	0	0.0
WBC ABNORMALITY	0	0.0	2	11.1
Nervous System	5	33.3	3	16.7
DIZZINESS	3	20.0	1	5.6
DRUG DEPENDENCE	0	0.0	1	5.6
EMOTIONAL LABILITY	0	0.0	1	5.6
HOSTILITY	0	0.0	1	5.6
HYPESTHESIA	1	6.7	0	0.0
INSOMNIA	1	6.7	0	0.0
Respiratory System	3	20.0	5	27.8
ASTHMA	1	6.7	0	0.0
BRONCHITIS	0	0.0	1	5.6
COUGH INCREASED	0	0.0	1	5.6
EPISTAXIS	1	6.7	0	0.0
PHARYNGITIS	0	0.0	3	16.7
RESPIRATORY DISORDER	2	13.3	0	0.0
RHINITIS	0	0.0	1	5.6
SINUSITIS	1	6.7	2	11.1

PAROXETINE - PROTOCOL 329

Table 16.10.1

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Non-gender Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	15	100.0%	18	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	9	60.0%	12	66.7%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Skin and Appendages		1	6.7	2	11.1
RASH		1	6.7	1	5.6
URTICARIA		0	0.0	1	5.6
Special Senses		2	13.3	0	0.0
OTITIS MEDIA		2	13.3	0	0.0
Urogenital System		1	6.7	0	0.0
ALBUMINURIA		1	6.7	0	0.0

PAROXETINE - PROTOCOL 329

Table 16.10.2

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Male Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	6	100.0%	13	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%

PAROXETINE - PROTOCOL 329

Table 16.10.2

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Male Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	10	100.0%	12	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%

PAROXETINE - PROTOCOL 329

Table 16.10.2

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Male Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	5	100.0%	5	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%

PAROXETINE - PROTOCOL 329

Table 16.10.3

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PAROXETINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	12	100.0%	21	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	1	8.3%	3	14.3%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		1	8.3	3	14.3
DYSMENORRHEA		1	8.3	2	9.5
FEMALE GENITAL DISORDERS		0	0.0	1	4.8

Table 16.10.3

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: IMIPRAMINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	5	100.0%	13	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	2	15.4%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		0	0.0	2	15.4
DYSMENORRHEA		0	0.0	1	7.7
UNINTENDED PREGNANCY		0	0.0	1	7.7

Table 16.10.3

Summary of Treatment-Emergent Adverse Experiences by Age Group (Continuation Phase)
Female Specific Adverse Experiences
Intent-to-Treat Population

TREATMENT GROUP: PLACEBO

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	10	100.0%	13	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	1	10.0%	2	15.4%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		1	10.0	2	15.4
DYSMENORRHEA		1	10.0	1	7.7
MENSTRUAL DISORDER		0	0.0	1	7.7

PAROXETINE - PROTOCOL 329

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PAROXETINE

N = 52

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Diastolic B.P. - Sitting (mmHg)	Baseline	49	68.86	7.64	56.00	86.00
	Week 12	48	68.31	7.78	50.00	80.00
	Week 16	37	68.57	10.62	44.00	88.00
	Week 20	34	68.56	9.08	52.00	92.00
	Week 24	24	66.54	9.35	50.00	80.00
	Week 28	19	67.37	12.43	51.00	96.00
	Week 32	18	67.50	8.43	54.00	82.00
	Endpoint	49	67.76	9.61	44.00	82.00
	Endpoint - Change from Baseline	49	-1.10	10.33	-30.00	20.00
Systolic B.P. - Sitting (mmHg)	Baseline	49	111.08	12.93	88.00	138.00
	Week 12	48	110.27	11.52	90.00	138.00
	Week 16	37	110.84	11.17	90.00	145.00
	Week 20	34	109.32	12.95	84.00	137.00
	Week 24	24	105.96	17.23	60.00	139.00
	Week 28	19	108.84	13.36	90.00	140.00
	Week 32	18	107.28	13.07	84.00	128.00
	Endpoint	49	110.76	13.82	84.00	145.00
	Endpoint - Change from Baseline	49	-0.33	14.62	-38.00	33.00
Diastolic B.P. - Standing (mmHg)	Baseline	49	69.31	7.36	51.00	86.00
	Week 12	48	70.21	9.19	48.00	88.00
	Week 16	38	69.05	10.12	49.00	86.00
	Week 20	34	67.53	7.94	50.00	80.00
	Week 24	24	66.25	5.68	56.00	76.00
	Week 28	19	68.16	9.23	54.00	85.00
	Week 32	18	69.22	10.51	54.00	92.00
	Endpoint	49	68.27	9.40	50.00	92.00
	Endpoint - Change from Baseline	49	-1.04	9.59	-30.00	20.00

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PAROXETINE

N = 52

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Systolic B.P. - Standing (mmHg)	Baseline	49	110.22	13.65	90.00	144.00
	Week 12	48	108.69	11.44	90.00	133.00
	Week 16	38	109.26	13.96	84.00	140.00
	Week 20	34	107.59	14.43	86.00	142.00
	Week 24	24	103.42	12.79	84.00	128.00
	Week 28	19	106.53	13.24	88.00	139.00
	Week 32	18	104.28	14.33	80.00	131.00
	Endpoint	49	107.55	14.49	80.00	139.00
	Endpoint - Change from Baseline	49	-2.67	14.62	-30.00	37.00
Pulse - Sitting (bpm)	Baseline	49	77.59	11.38	60.00	112.00
	Week 12	48	78.83	9.85	58.00	106.00
	Week 16	37	78.81	11.05	60.00	106.00
	Week 20	34	75.88	9.20	60.00	94.00
	Week 24	24	78.17	11.22	59.00	100.00
	Week 28	19	74.79	10.07	58.00	100.00
	Week 32	18	79.17	9.33	64.00	99.00
	Endpoint	49	78.10	9.15	59.00	99.00
	Endpoint - Change from Baseline	49	0.51	10.65	-24.00	24.00
Pulse - Standing (bpm)	Baseline	49	83.43	13.74	64.00	119.00
	Week 12	48	86.40	13.07	60.00	114.00
	Week 16	38	87.55	11.64	68.00	115.00
	Week 20	34	83.21	12.20	64.00	112.00
	Week 24	24	84.54	11.85	64.00	106.00
	Week 28	19	82.42	12.22	58.00	99.00
	Week 32	18	84.11	11.84	68.00	112.00
	Endpoint	49	83.86	11.53	64.00	115.00
	Endpoint - Change from Baseline	49	0.43	13.48	-23.00	36.00

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PAROXETINE

N = 52

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Weight (lbs)	Baseline	49	146.33	37.93	74.00	277.00
	Week 12	48	146.47	38.07	74.00	278.00
	Week 16	38	151.17	39.85	98.20	281.00
	Week 20	34	152.05	40.74	103.64	280.00
	Week 24	24	152.39	44.86	105.84	280.00
	Week 28	19	140.80	32.09	106.94	210.30
	Week 32	18	146.88	37.31	108.00	243.00
	Endpoint	49	149.68	38.59	74.00	280.00
	Endpoint - Change from Baseline	49	3.35	7.57	-13.50	20.73

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=IMIPRAMINE

N = 40

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Diastolic B.P. - Sitting (mmHg)	Baseline	36	68.08	10.40	45.00	88.00
	Week 12	32	68.28	11.25	40.00	86.00
	Week 16	30	70.60	11.19	52.00	96.00
	Week 20	25	70.48	8.72	53.00	88.00
	Week 24	16	73.31	8.81	56.00	90.00
	Week 28	15	73.93	10.42	58.00	92.00
	Week 32	13	71.15	13.54	52.00	98.00
	Endpoint	36	70.25	10.92	52.00	98.00
	Endpoint - Change from Baseline	36	2.17	10.26	-24.00	22.00
Systolic B.P. - Sitting (mmHg)	Baseline	36	113.08	15.75	93.00	170.00
	Week 12	32	111.88	12.49	80.00	146.00
	Week 16	30	109.40	11.22	90.00	136.00
	Week 20	25	114.24	12.42	94.00	152.00
	Week 24	16	117.19	19.27	80.00	168.00
	Week 28	15	113.20	13.15	90.00	140.00
	Week 32	13	113.92	10.48	88.00	126.00
	Endpoint	36	114.47	14.96	88.00	168.00
	Endpoint - Change from Baseline	36	1.39	17.93	-56.00	66.00
Diastolic B.P. - Standing (mmHg)	Baseline	36	69.56	10.22	53.00	90.00
	Week 12	32	67.75	11.98	37.00	86.00
	Week 16	30	68.97	11.55	47.00	92.00
	Week 20	25	70.08	11.43	41.00	90.00
	Week 24	16	70.06	11.13	50.00	92.00
	Week 28	15	75.00	9.43	58.00	90.00
	Week 32	13	70.77	15.03	41.00	99.00
	Endpoint	36	68.47	11.92	41.00	99.00
	Endpoint - Change from Baseline	36	-1.08	12.24	-32.00	22.00

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=IMIPRAMINE

N = 40

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Systolic B.P. - Standing (mmHg)	Baseline	36	108.17	14.70	90.00	158.00
	Week 12	32	104.31	12.08	80.00	132.00
	Week 16	30	105.30	12.22	80.00	134.00
	Week 20	25	108.96	15.07	80.00	152.00
	Week 24	16	110.44	13.22	84.00	134.00
	Week 28	15	107.40	14.42	82.00	138.00
	Week 32	13	111.46	13.64	86.00	130.00
	Endpoint	36	107.61	13.03	80.00	130.00
	Endpoint - Change from Baseline	36	-0.56	18.22	-73.00	22.00
Pulse - Sitting (bpm)	Baseline	36	75.44	10.90	53.00	96.00
	Week 12	32	90.63	10.85	66.00	112.00
	Week 16	30	89.57	8.35	65.00	109.00
	Week 20	25	89.96	12.27	64.00	120.00
	Week 24	16	89.31	11.62	72.00	108.00
	Week 28	15	93.27	10.76	78.00	112.00
	Week 32	13	92.00	14.81	64.00	114.00
	Endpoint	36	90.19	13.40	64.00	114.00
	Endpoint - Change from Baseline	36	14.75	13.04	-9.00	36.00
Pulse - Standing (bpm)	Baseline	36	82.36	12.07	62.00	109.00
	Week 12	32	99.56	14.66	78.00	128.00
	Week 16	30	98.67	14.82	72.00	131.00
	Week 20	25	96.60	16.28	65.00	138.00
	Week 24	16	101.88	12.68	74.00	126.00
	Week 28	15	96.40	12.93	76.00	121.00
	Week 32	13	96.85	17.31	70.00	126.00
	Endpoint	36	97.56	16.63	65.00	131.00
	Endpoint - Change from Baseline	36	15.19	15.63	-19.00	46.00

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=IMIPRAMINE

N = 40

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Weight (lbs)	Baseline	36	141.60	30.74	91.40	227.70
	Week 12	32	141.88	32.70	89.90	235.00
	Week 16	31	144.34	33.69	87.00	234.00
	Week 20	24	146.37	34.23	86.70	232.00
	Week 24	16	149.79	35.41	87.40	234.00
	Week 28	15	152.52	37.76	98.00	237.00
	Week 32	12	152.84	41.17	102.00	235.00
	Endpoint	36	143.45	33.22	87.40	235.00
	Endpoint - Change from Baseline	36	1.86	10.07	-16.60	23.00

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PLACEBO

N = 33

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Diastolic B.P. - Sitting (mmHg)	Baseline	31	69.58	10.17	49.00	90.00
	Week 12	28	68.36	9.63	49.00	90.00
	Week 16	23	68.57	9.67	53.00	95.00
	Week 20	15	66.47	8.11	54.00	90.00
	Week 24	14	67.71	8.83	58.00	85.00
	Week 28	9	67.67	12.49	50.00	90.00
	Week 32	13	64.08	10.80	44.00	85.00
	Endpoint	31	67.39	9.26	44.00	90.00
	Endpoint - Change from Baseline	31	-2.19	9.74	-20.00	16.00
Systolic B.P. - Sitting (mmHg)	Baseline	31	107.16	14.25	78.00	132.00
	Week 12	28	107.82	11.16	84.00	130.00
	Week 16	23	106.17	11.59	86.00	132.00
	Week 20	15	104.33	12.78	84.00	130.00
	Week 24	14	107.86	9.06	90.00	120.00
	Week 28	9	105.78	12.51	80.00	120.00
	Week 32	13	101.92	14.58	80.00	128.00
	Endpoint	31	105.00	12.23	80.00	132.00
	Endpoint - Change from Baseline	31	-2.16	13.28	-26.00	26.00
Diastolic B.P. - Standing (mmHg)	Baseline	30	68.53	9.76	50.00	95.00
	Week 12	28	65.93	10.51	42.00	90.00
	Week 16	23	68.57	11.48	50.00	96.00
	Week 20	15	67.87	9.01	54.00	90.00
	Week 24	14	66.86	10.04	50.00	85.00
	Week 28	9	66.89	13.20	50.00	90.00
	Week 32	13	65.85	8.84	52.00	80.00
	Endpoint	30	67.60	10.62	44.00	96.00
	Endpoint - Change from Baseline	30	-0.93	12.12	-20.00	26.00

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PLACEBO

N = 33

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Systolic B.P. - Standing (mmHg)	Baseline	30	105.30	14.80	70.00	126.00
	Week 12	28	105.00	9.48	84.00	122.00
	Week 16	23	103.65	13.83	80.00	135.00
	Week 20	15	101.73	12.83	83.00	120.00
	Week 24	14	105.14	9.85	88.00	120.00
	Week 28	9	104.33	12.02	80.00	120.00
	Week 32	13	101.62	16.16	80.00	138.00
	Endpoint	30	102.47	11.99	80.00	135.00
	Endpoint - Change from Baseline	30	-2.83	13.92	-30.00	30.00
Pulse - Sitting (bpm)	Baseline	31	79.84	10.27	64.00	100.00
	Week 12	28	79.18	13.26	60.00	120.00
	Week 16	23	75.83	8.92	54.00	90.00
	Week 20	15	73.13	12.92	48.00	100.00
	Week 24	14	75.29	11.74	60.00	98.00
	Week 28	9	77.67	10.32	64.00	93.00
	Week 32	13	73.92	11.23	60.00	96.00
	Endpoint	31	76.39	12.34	60.00	108.00
	Endpoint - Change from Baseline	31	-3.45	12.09	-28.00	24.00
Pulse - Standing (bpm)	Baseline	30	86.60	12.74	64.00	115.00
	Week 12	28	86.11	13.10	61.00	120.00
	Week 16	23	83.91	9.02	64.00	100.00
	Week 20	15	84.13	15.22	60.00	120.00
	Week 24	14	82.00	16.34	60.00	112.00
	Week 28	9	84.00	12.49	64.00	100.00
	Week 32	13	79.85	8.96	64.00	100.00
	Endpoint	30	82.87	11.82	61.00	111.00
	Endpoint - Change from Baseline	30	-3.73	12.81	-29.00	20.00

Table 16.11

Summary of Mean Vital Signs and Body Weight at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PLACEBO

N = 33

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Weight (lbs)	Baseline	31	140.63	37.00	80.20	226.01
	Week 12	28	142.74	39.90	86.20	236.50
	Week 16	23	141.59	36.88	98.34	240.00
	Week 20	15	141.90	38.01	97.46	238.00
	Week 24	14	142.41	37.63	101.65	242.00
	Week 28	9	145.68	48.19	100.50	250.00
	Week 32	13	139.79	41.64	95.00	248.00
	Endpoint	31	143.65	38.42	86.20	248.00
	Endpoint - Change from Baseline	31	3.01	5.89	-11.00	21.99

PAROXETINE - PROTOCOL 329

Table 16.12

Summary of Clinically Significant Abnormal Vital Signs by Treatment Group
Continuation Phase
Intent-to-Treat Population

Parameter		PAROXETINE N = 52 n	%	IMIPRAMINE N = 40 n	%	PLACEBO N = 33 n	%
Diastolic B.P. - Sitting (mmHg)	H	0	0.0	0	0.0	0	0.0
	L	0	0.0	1	2.5	0	0.0
Systolic B.P. - Sitting (mmHg)	H	0	0.0	0	0.0	0	0.0
	L	1	1.9	1	2.5	0	0.0
Diastolic B.P. - Standing (mmHg)	H	0	0.0	0	0.0	0	0.0
	L	1	1.9	2	5.0	0	0.0
Systolic B.P. - Standing (mmHg)	H	0	0.0	0	0.0	0	0.0
	L	1	1.9	1	2.5	2	6.1
Pulse - Sitting (bpm)	H	0	0.0	0	0.0	0	0.0
	L	0	0.0	0	0.0	0	0.0
Pulse - Standing (bpm)	H	0	0.0	7	17.5	0	0.0
	L	0	0.0	0	0.0	0	0.0
Weight (lbs)	H	13	25.0	6	15.0	6	18.2
	L	2	3.8	5	12.5	0	0.0

Vital Sign Abnormality Criteria: Systolic: L = <90,dec>=30 H = >180,inc>=40; Diastolic: L = <50,dec>=20 H = >105,inc>=30;
Pulse: L = <50,dec>=30 H = >120,inc>=30; Weight: L = dec>=7% H = inc>=7%.

Table 16.12.1 Narratives for Patients with Vital Signs of Potential Clinical Concern

PID 329.001.00122

Vital Sign of Concern: Weight

Primary Adverse Event: Preferred Term (Verbatim term): Weight Gain (Weight gain)
Increased Appetite (Increased appetite)

Demography: Age: 15 yrs Date of Birth: 09-May-80 Sex: Male
Height: 69 in. Weight: 166.0 lbs. Race: Caucasian

Country: United States

Medical History: Past: Hernia repair, right foot infection
Current: Acne, heavy perspiration

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 20-Jun-95 **End:** 15-Aug-95
Start Continuation Phase: 16-Aug-95 **End:** 18-Dec-95

Vital Sign Remarks:
The patient entered the study on 20-Jun-95 with a baseline weight of 166.0 lbs. At week 20, the weight had increased to 179.0 lbs. (increase ≥7%), which was considered to be of potential clinical concern. Adverse events of moderately severe weight gain and increased appetite had been reported by the investigator on day 114, and were considered related to study medication. The patient withdrew from the study on day 182 due to lack of efficacy. At week 24, the weight was 180.5 lbs.

Vital Sign	Week	Value
Weight (lbs.)	Baseline	166.0
	4	164.0
	8	171.0
	12	171.0
	16	171.0
	20	179.0
	24	180.5

PID 329.001.00122 (continued)

Relevant Adverse Events:	**Onset (Days into Study)**	**Duration**
Increased Appetite	Day 114	Not stated
Weight Gain	Day 114	Not stated

Concomitant Medications:	**Start**	**End**
Bactrim DS	01-Feb-95	Ongoing
Centrum	01-Apr-95	20-Jun-95

PID 329.005.00151

Vital Sign of Concern: Weight

Primary Adverse Event: Preferred Term (Verbatim term): Weight Gain (Weight gain)

Demography: Age: 14 yrs Date of Birth: 28-Nov-80 Sex: Female
Height: 63 in. Weight: 112.5 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: Back pain, headaches

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 06-Sep-95 **End:** 01-Nov-95
Start Continuation Phase: 02-Nov-95 **End:** 30-Apr-96

Vital Sign Remarks:
The patient entered the study on 06-Sep-95 with a baseline weight of 112.5 lbs. At week 32, the weight had increased to 119.8 lbs. (increase ≥7%), which was considered to be of potential clinical concern. An adverse event of moderately severe weight gain had been reported by the investigator on day 84 and was considered possibly related to study medication. The patient completed the study as planned.

Vital Sign	Week	Value
Weight (lbs.)	Baseline	110.9
	4	105.2
	8	109.8
	12	111.0
	16	114.0
	20	114.0
	24	116.7
	28	118.4
	32	119.8

PID 329.005.00151 (continued)

Relevant Adverse Events:	**Onset (Days into Study)**	**Duration**
Weight Gain	84	156 days

Concomitant Medications:	**Start**	**End**
Extra Strength Tylenol	06-Sep-95	06-Sep-95
Erythromycin	23-Oct-95	07-Nov-95
Tylenol	15-Oct-95	17-Oct-95
Amoxicillin	16-Oct-95	02-Nov-95
Tylenol	19-Oct-95	19-Oct-95
Refresh	08-Feb-96	08-Mar-96

PID 329.005.00257

Vital Sign of Concern: Weight

Associated Adverse Event: Weight Gain (Weight gain)

Demography: Age: 12 yrs Date of Birth: 03-Feb-84 Sex: Female
Height: 63 in. Weight: 112.0 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: Acne

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 11-Mar-96 **End:** 05-May-96
Start Continuation Phase: 06-May-96 **End:** 04-Nov-96

Vital Sign Remarks:
The patient entered the study on 11-Mar-96 with a baseline weight of 112.5 lbs. At week 16, the weight had increased to 122.3 lbs. (increase ≥7%), which was considered to be of potential clinical concern. An adverse event of moderately severe weight gain was reported by the investigator on day 85, and was considered possibly related to study medication. The patient completed the study as planned. At week 32, the patient's weight was 123.0 lbs.

Vital Sign	Week	Value
Weight (lbs.)	Baseline	112.5
	4	112.0
	8	112.0
	12	117.3
	16	122.3
	20	124.5
	24	122.0
	28	123.0
	32	123.0

PID 329.005.00257 (continued)

Relevant Adverse Events:	Onset (Days into Study)	Duration
Weight Gain	Day 85	Not stated

Concomitant Medications:	Start	End
Accutane	11-Nov-95	Ongoing
Vitamin C	13-Mar-96	Ongoing
Semprex-D	24-Mar-96	24-Mar-96
Ceclor	25-Mar-96	05-Apr-96
Rynatan	25-Mar-96	27-Mar-96
Ceclor	22-Apr-96	06-May-96
Flonase	22-Apr-96	28-Apr-96
Albuterol	22-Apr-96	06-May-96
Slo-Bid	03-May-96	10-May-96
Amoxicillin	02-Aug-96	09-Aug-96
Antibiotics Ear Drops NOS	02-Aug-96	09-Aug-96
Advil	14-Aug-96	21-Aug-96
Marax	28-Sep-96	Ongoing
Monistat	07-Nov-96	14-Nov-96

PID 329.007.00268

Vital Sign of Concern: Weight

Primary Adverse Event: Preferred Term (Verbatim term): Weight Gain (Weight gain)

Demography: Age: 13 years Date of Birth: 15-Mar-83 Sex: Female
Height: 64 in. Weight: 225.0 lbs. Race: Caucasian

Country: United States

Medical History: Past: Lymph node infection (bilateral groin nodes)
Current: Headaches (occasional), menstrual cramps

Study Diagnosis: Unipolar Major Depression

Study Medication: Paroxetine

Start Acute Phase: 01-Apr-96 **End:** 29-May-96
Start Continuation Phase: 30-May-96 **End:** 18-Dec-96

Vital Sign Remarks:
The patient entered the study on 01-Apr-96 with a baseline weight of 225.0. At week 32, the weight had increased to 244.0 lbs. (increase ≥7%), which was considered to be of potential clinical concern. An adverse event of moderately severe weight gain was reported by the investigator on day 183, and was considered possibly related to study medication. The weight gain was treated with T-Lite (Dietary Supplement). The patient completed the study as planned.

Vital Sign	Week	Value
Weight (lbs.)	Baseline	225.0
	4	223.0
	8	222.0
	12	221.0
	16	227.0
	20	231.0
	24	234.0
	32	244.0

PID 329.007.00268 (continued)

Relevant Adverse Events:	Onset (Days into Study)	Duration
Weight Gain	183	95 Days

Concomitant Medications:	Start	End
Dulcolax	19-Nov-96	19-Nov-96
Neomycin	27-Jun-96	29-Jun-96
Polymyxin	27-Jun-96	29-Jun-96
Cephalexin	21-Jun-96	23-Jun-96
Cephalexin	26-Jun-96	29-Jun-96
Cephalexin	01-Jul-96	10-Jul-96
Keflex	10-Apr-96	14-Apr-96
Aspirin	29-Apr-96	29-Apr-96
Compazine	04-Nov-96	04-Nov-96
Ibuprofen	10-Apr-96	10-Apr-96
Ibuprofen	27-May-96	30-May-96
Motrin	01-Jan-94	Ongoing
T-Lite (Dietary Supplement)	01-Sep-96	02-Oct-96

PID 329.009.00305

Vital Sign of Concern: Standing Pulse

Primary Adverse Event: Preferred Term (Verbatim term): Electrocardiogram Abnormal (Positive/negative right axis deviation)

Demography: Age: 14 yrs Date of Birth: 25-Dec-81 Sex: Male
Height: 72 in. Weight: 136.5 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: None

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 07-May-96 **End:** 02-Jul-96
Start Continuation Phase: 03-Jul-96 **End:** 22-Jan-97

Vital Sign Remarks:
The patient entered the study on 07-May-96 with a baseline standing pulse of 89 bpm, which was within the reference range of 50-120 bpm. At week 4, the standing pulse had increased to 132 bpm (an increase ≥30 bpm), which was considered to be of potential clinical concern. The out-of-range pulse rate continued at weeks 4, 7, 8, 16, 24, 28 and 32. Tachycardia was not reported as an adverse event. The patient completed the study as planned. At the end of the study (day 249), right axis deviation of mild intensity on electrocardiogram was reported as an adverse event, and was considered probably unrelated to study medication.

PID 329.009.00305 (continued)

Vital Sign	Week	Value	Reference Range
Pulse (bpm)	BL	89	50-120
	4	132	
	8	140	
	12	120	
	16	123	
	20	117	
	24	126	
	28	121	
	32	125	

Concomitant Medications:	Start	End
Imodium A-D	02-Jul-96	02-Jul-96

PID 329.009.00325

Vital Sign of Concern: Standing Pulse

Primary Adverse Event: Preferred Term (Verbatim term): Tachycardia (Tachycardia)

Demography: Age: 15 yrs Date of Birth: 22-Oct-80 Sex: Female
Height: 67 in. Weight: 116.0 lbs. Race: Caucasian

Country: United States

Medical History: Past: None
Current: Asthma, headache (occasional), menstrual cramps, nausea

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 27-Aug-96 **End:** 20-Oct-96
Start Continuation Phase: 21-Oct-96 **End:** 28-Dec-96

Vital Sign Remarks:
The patient entered the study on 27-Aug-96 with a baseline standing pulse of 97 bpm, which was within the reference range of 50-120 bpm. At week 4, the standing pulse had increased to 131 bpm (an increase ≥30 bpm), which was considered to be of potential clinical concern. An adverse event of moderately severe tachycardia was reported by the investigator, and was considered possibly related to study medication. The patient withdrew from the study on day 124 due to lack of efficacy. At week 16, the standing pulse was 131 bpm.

PID 329.009.00325 (continued)

Vital Sign	Week	Value	Reference Range
Pulse (bpm)	BL	97	50-120
	4	131	
	8	119	
	12	125	
	16	131	

Relevant Adverse Events:	Onset (Days into Study)	Duration
Tachycardia (tachycardia)	58	27 days

Concomitant Medications:	Start	End
Orudis KT	01-Jan-90	Ongoing
Ventolin Inhaler	01-Jan-90	Ongoing
Zantac	01-Jan-95	Ongoing
Tylenol Extra Strength	01-Jan-95	Ongoing
Desogen	22-Sep-96	Ongoing
Benadryl	10-Oct-96	Ongoing

PAROXETINE - PROTOCOL 329

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PAROXETINE

N = 52

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Alanine Aminotransferase (U/L)	Baseline	7	11.57	6.02	4.00	20.00
	Week 12	4	13.50	9.11	7.00	27.00
	Week 16	1	9.00	.	9.00	9.00
	Week 20	31	14.74	7.43	5.00	42.00
	Week 24	6	15.17	4.71	10.00	23.00
	Week 32	17	19.59	13.81	7.00	59.00
Alkaline Phosphatase (U/L)	Baseline	7	125.43	62.97	58.00	230.00
	Week 12	4	88.75	42.11	62.00	151.00
	Week 16	1	128.00	.	128.00	128.00
	Week 20	31	116.23	69.86	32.00	329.00
	Week 24	6	90.50	25.59	49.00	123.00
	Week 32	17	94.47	41.85	59.00	240.00
Aspartate Aminotransferase (U/L)	Baseline	7	20.00	6.56	14.00	34.00
	Week 12	4	17.25	1.89	16.00	20.00
	Week 16	1	16.00	.	16.00	16.00
	Week 20	31	17.45	3.85	12.00	26.00
	Week 24	6	18.00	2.00	16.00	21.00
	Week 32	17	18.65	5.59	12.00	38.00
Total Bilirubin (mg/dL)	Baseline	7	0.80	0.33	0.60	1.50
	Week 12	4	0.63	0.13	0.50	0.80
	Week 16	1	0.70	.	0.70	0.70
	Week 20	31	0.61	0.12	0.40	1.00
	Week 24	6	0.68	0.15	0.50	0.90
	Week 32	17	0.65	0.15	0.50	1.00
Blood Urea Nitrogen (mg/dL)	Baseline	7	12.29	2.50	9.00	15.00
	Week 12	4	10.50	3.70	6.00	14.00
	Week 16	1	10.00	.	10.00	10.00
	Week 20	31	11.48	2.20	6.00	15.00
	Week 24	6	11.83	2.32	9.00	15.00
	Week 32	17	11.18	3.11	7.00	17.00
Creatinine (mg/dL)	Baseline	7	0.89	0.18	0.70	1.10
	Week 12	4	0.90	0.14	0.80	1.10
	Week 16	1	1.00	.	1.00	1.00
	Week 20	31	0.93	0.15	0.60	1.20
	Week 24	6	0.90	0.13	0.70	1.00
	Week 32	17	0.90	0.10	0.80	1.10

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PAROXETINE

N = 52

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Basophils (%)	Baseline	14	0.91	0.54	0.10	1.70
	Week 12	6	0.93	0.34	0.30	1.20
	Week 16	1	0.70	.	0.70	0.70
	Week 20	31	0.60	0.48	0.00	2.00
	Week 24	8	0.56	0.53	0.20	1.80
	Week 32	17	0.68	0.29	0.00	1.10
Eosinophils (%)	Baseline	14	3.06	1.88	0.60	6.80
	Week 12	6	3.82	2.11	1.00	7.40
	Week 16	1	5.50	.	5.50	5.50
	Week 20	31	4.01	2.19	0.00	9.90
	Week 24	8	5.30	3.72	1.60	12.40
	Week 32	17	4.29	2.75	0.90	9.80

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PAROXETINE

N = 52

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Hematocrit (vol%)	Baseline	14	39.25	3.59	30.90	44.00
	Week 12	6	39.00	1.56	37.60	41.90
	Week 16	1	43.30	.	43.30	43.30
	Week 20	29	40.85	3.14	36.80	47.90
	Week 24	8	39.61	2.96	35.50	44.50
	Week 32	17	40.16	2.69	35.00	47.20
Hemoglobin (g%)	Baseline	14	13.30	1.30	10.00	15.10
	Week 12	6	13.40	0.42	13.00	14.10
	Week 16	1	15.40	.	15.40	15.40
	Week 20	29	13.98	1.11	12.30	16.60
	Week 24	8	13.43	0.91	12.00	15.10
	Week 32	17	13.71	0.91	12.30	16.30
Lymphocytes (%)	Baseline	14	28.75	7.14	18.50	43.00
	Week 12	6	30.17	9.63	15.60	41.10
	Week 16	1	36.70	.	36.70	36.70
	Week 20	31	33.15	8.79	15.10	51.00
	Week 24	8	31.86	7.15	21.00	42.40
	Week 32	17	32.02	8.16	16.80	46.60
Monocytes (%)	Baseline	14	6.55	1.82	4.40	11.10
	Week 12	6	6.47	3.03	3.30	11.30
	Week 16	1	7.50	.	7.50	7.50
	Week 20	31	6.52	2.48	1.00	11.00
	Week 24	8	6.29	1.66	3.80	9.20
	Week 32	17	6.64	2.96	1.20	12.00
Neutrophil Bands (%)	Baseline	1	0.00	.	0.00	0.00
	Week 20	1	0.00	.	0.00	0.00
	Week 32	1	1.00	.	1.00	1.00
Segmented Neutrophils (%)	Baseline	14	60.74	6.96	48.00	70.00
	Week 12	6	58.65	11.33	46.90	78.90
	Week 16	1	49.60	.	49.60	49.60
	Week 20	31	55.73	9.60	34.00	73.50
	Week 24	8	56.01	8.88	40.10	65.60
	Week 32	17	56.09	8.44	40.10	72.80
Platelets (k/mm**3)	Baseline	14	256000	32270.5	183000	309000
	Week 12	6	305167	66022.5	226000	381000

PAROXETINE - PROTOCOL 329

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PAROXETINE

N = 52

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Platelets (k/mm**3)	Week 16	1	388000	.	388000	388000
	Week 20	29	241483	69496.5	28000.0	380000
	Week 24	9	261556	59213.8	202000	382000
	Week 32	17	245882	51171.1	162000	361000
White Blood Cell Count (k/mm**3)	Baseline	14	7.01	2.28	3.60	10.20
	Week 12	6	9.17	4.44	4.50	16.80
	Week 16	1	9.60	.	9.60	9.60
	Week 20	29	6.94	1.84	4.40	11.00
	Week 24	8	8.30	2.96	4.70	13.00
	Week 32	17	6.66	1.31	4.50	9.30

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=IMIPRAMINE

N = 40

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Alanine Aminotransferase (U/L)	Baseline	8	11.63	2.83	8.00	15.00
	Week 16	4	31.50	29.83	9.00	75.00
	Week 20	19	18.84	13.19	7.00	54.00
	Week 24	5	13.00	5.70	7.00	20.00
	Week 32	13	22.69	14.48	13.00	67.00
Alkaline Phosphatase (U/L)	Baseline	8	125.75	90.76	42.00	293.00
	Week 16	4	89.25	30.85	64.00	134.00
	Week 20	19	151.32	80.64	37.00	285.00
	Week 24	5	99.40	65.22	49.00	211.00
	Week 32	13	115.46	55.74	47.00	225.00
Aspartate Aminotransferase (U/L)	Baseline	8	17.63	2.26	13.00	20.00
	Week 16	4	22.25	10.87	15.00	38.00
	Week 20	19	19.89	6.04	14.00	38.00
	Week 24	5	14.00	1.73	13.00	17.00
	Week 32	13	20.46	4.41	13.00	28.00
Total Bilirubin (mg/dL)	Baseline	8	0.78	0.24	0.50	1.30
	Week 16	4	0.65	0.13	0.50	0.80
	Week 20	19	0.65	0.25	0.10	1.40
	Week 24	5	0.70	0.35	0.50	1.30
	Week 32	13	0.76	0.35	0.40	1.50
Blood Urea Nitrogen (mg/dL)	Baseline	8	11.25	2.96	8.00	17.00
	Week 16	4	10.75	2.06	8.00	13.00
	Week 20	19	11.37	3.25	5.00	16.00
	Week 24	5	11.60	5.13	7.00	20.00
	Week 32	13	11.85	3.18	7.00	19.00
Creatinine (mg/dL)	Baseline	8	0.95	0.12	0.70	1.10
	Week 16	4	0.93	0.10	0.80	1.00
	Week 20	19	0.97	0.11	0.80	1.10
	Week 24	5	0.98	0.13	0.80	1.10
	Week 32	13	1.02	0.11	0.90	1.20
Basophils (%)	Baseline	11	0.70	0.67	0.00	2.50
	Week 16	4	0.63	0.39	0.20	1.00
	Week 20	19	0.62	0.28	0.00	1.00
	Week 24	6	0.38	0.19	0.10	0.60
	Week 28	1	0.90	.	0.90	0.90

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=IMIPRAMINE

N = 40

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Basophils (%)	Week 32	13	0.50	0.26	0.10	1.00
Eosinophils (%)	Baseline	11	4.63	3.40	0.00	8.90
	Week 16	4	3.18	1.99	0.30	4.90
	Week 20	19	3.46	4.36	0.00	15.90
	Week 24	6	3.57	3.78	0.20	9.80
	Week 28	1	2.00	.	2.00	2.00
	Week 32	13	2.72	1.48	0.70	6.40

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=IMIPRAMINE

N = 40

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Hematocrit (vol%)	Baseline	11	41.10	1.60	38.60	43.50
	Week 16	4	40.90	1.33	39.70	42.80
	Week 20	19	40.64	3.02	35.70	45.80
	Week 24	6	45.18	4.43	39.30	51.50
	Week 28	1	45.10	.	45.10	45.10
	Week 32	13	40.79	4.07	30.50	45.30
Hemoglobin (g%)	Baseline	11	14.09	0.60	13.40	15.20
	Week 16	4	13.98	0.74	13.30	15.00
	Week 20	19	13.93	1.11	12.00	15.80
	Week 24	6	15.45	1.44	13.30	17.40
	Week 28	1	15.70	.	15.70	15.70
	Week 32	13	13.97	1.41	10.50	15.70
Lymphocytes (%)	Baseline	11	36.85	7.17	23.00	49.00
	Week 16	4	35.13	7.83	28.00	44.20
	Week 20	19	35.96	12.01	18.20	72.00
	Week 24	6	31.42	6.80	23.20	42.50
	Week 28	1	25.90	.	25.90	25.90
	Week 32	13	30.89	7.75	10.80	42.90
Monocytes (%)	Baseline	11	7.32	2.03	3.00	10.00
	Week 16	4	6.83	1.54	4.60	7.90
	Week 20	19	6.78	1.80	3.00	12.00
	Week 24	6	9.43	0.89	8.00	10.60
	Week 28	1	10.40	.	10.40	10.40
	Week 32	13	6.98	2.88	3.20	12.10
Neutrophil Bands (%)	Baseline	1	0.00	.	0.00	0.00
Segmented Neutrophils (%)	Baseline	11	50.51	5.91	40.60	60.40
	Week 16	4	54.28	7.08	48.30	62.20
	Week 20	19	53.03	12.51	21.00	73.40
	Week 24	6	55.20	7.61	46.10	66.20
	Week 28	1	60.90	.	60.90	60.90
	Week 32	13	58.92	8.14	50.30	82.20
Platelets (k/mm**3)	Baseline	11	238455	50422.9	163000	306000
	Week 16	4	289500	80806.4	206000	375000
	Week 20	19	230000	54582.3	163000	334000
	Week 24	6	207333	96614.0	28000.0	292000

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=IMIPRAMINE

N = 40

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Platelets (k/mm**3)	Week 28	1	226000	.	226000	226000
	Week 32	13	242385	83383.2	162000	476000
White Blood Cell Count (k/mm**3)	Baseline	11	6.06	1.85	3.10	9.10
	Week 16	4	6.45	2.51	4.90	10.20
	Week 20	19	5.55	1.45	2.80	8.60
	Week 24	6	6.28	1.22	4.90	8.10
	Week 28	1	6.00	.	6.00	6.00
	Week 32	13	6.78	2.76	4.80	15.10

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PLACEBO

N = 33

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Alanine Aminotransferase (U/L)	Baseline	9	10.56	3.43	7.00	17.00
	Week 12	3	9.00	4.00	5.00	13.00
	Week 16	1	14.00	.	14.00	14.00
	Week 20	11	13.45	7.97	5.00	35.00
	Week 24	6	10.83	4.45	7.00	19.00
	Week 32	13	19.62	26.68	6.00	101.00
Alkaline Phosphatase (U/L)	Baseline	9	240.56	306.06	72.00	1028.00
	Week 12	3	80.67	13.05	66.00	91.00
	Week 16	1	89.00	.	89.00	89.00
	Week 20	11	134.45	83.96	53.00	359.00
	Week 24	6	107.33	73.35	36.00	220.00
	Week 32	13	114.69	70.47	41.00	316.00
Aspartate Aminotransferase (U/L)	Baseline	9	15.78	4.49	10.00	23.00
	Week 12	3	12.00	2.65	10.00	15.00
	Week 16	1	15.00	.	15.00	15.00
	Week 20	11	18.36	8.31	12.00	41.00
	Week 24	6	14.00	4.86	8.00	21.00
	Week 32	13	17.77	12.48	10.00	58.00
Total Bilirubin (mg/dL)	Baseline	9	0.74	0.19	0.50	1.10
	Week 12	3	0.77	0.06	0.70	0.80
	Week 16	1	0.70	.	0.70	0.70
	Week 20	11	0.71	0.14	0.60	1.00
	Week 24	6	0.75	0.30	0.50	1.30
	Week 32	13	0.73	0.23	0.20	1.20
Blood Urea Nitrogen (mg/dL)	Baseline	9	13.22	3.80	9.00	20.00
	Week 12	3	9.33	4.04	5.00	13.00
	Week 16	1	13.00	.	13.00	13.00
	Week 20	11	11.18	2.71	8.00	15.00
	Week 24	6	11.67	2.73	8.00	15.00
	Week 32	13	12.00	2.92	7.00	17.00
Creatinine (mg/dL)	Baseline	9	0.97	0.17	0.70	1.30
	Week 12	3	0.90	0.00	0.90	0.90
	Week 16	1	1.30	.	1.30	1.30
	Week 20	11	1.00	0.17	0.70	1.20
	Week 24	6	0.93	0.14	0.80	1.10
	Week 32	13	0.97	0.12	0.80	1.10

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PLACEBO

N = 33

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Basophils (%)	Baseline	8	0.34	0.23	0.00	0.60
	Week 12	3	0.47	0.47	0.10	1.00
	Week 16	1	0.00	.	0.00	0.00
	Week 20	11	0.59	0.24	0.00	0.80
	Week 24	6	0.60	0.59	0.00	1.50
	Week 32	12	0.48	0.28	0.00	1.00
Eosinophils (%)	Baseline	8	3.05	2.57	1.50	9.30
	Week 12	3	5.20	5.09	1.50	11.00
	Week 16	1	4.00	.	4.00	4.00
	Week 20	11	3.36	2.13	1.10	7.70
	Week 24	6	5.42	4.82	1.40	12.00
	Week 32	12	3.33	1.82	1.90	7.80

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PLACEBO

N = 33

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Hematocrit (vol%)	Baseline	8	41.78	2.30	39.80	46.60
	Week 12	3	40.33	2.34	38.60	43.00
	Week 16	1	46.00	.	46.00	46.00
	Week 20	11	41.98	3.15	37.50	48.20
	Week 24	6	37.97	2.10	35.40	41.30
	Week 32	12	40.43	2.76	36.70	46.50
Hemoglobin (g%)	Baseline	8	14.05	0.96	13.00	16.10
	Week 12	3	13.83	0.85	13.20	14.80
	Week 16	1	15.70	.	15.70	15.70
	Week 20	11	14.27	1.03	12.70	16.30
	Week 24	6	13.07	0.82	12.20	14.40
	Week 32	12	13.76	0.87	12.70	15.70
Lymphocytes (%)	Baseline	8	30.66	9.43	18.70	44.40
	Week 12	3	33.07	15.26	15.50	43.00
	Week 16	1	35.00	.	35.00	35.00
	Week 20	11	32.20	8.28	18.70	45.10
	Week 24	6	26.28	10.68	15.00	43.90
	Week 32	12	32.36	6.63	17.80	43.80
Monocytes (%)	Baseline	8	6.35	1.60	4.00	8.60
	Week 12	3	6.17	1.39	5.00	7.70
	Week 16	1	1.00	.	1.00	1.00
	Week 20	11	6.01	2.07	2.40	9.60
	Week 24	6	6.17	2.67	2.50	10.00
	Week 32	12	6.00	1.89	3.20	10.70
Neutrophil Bands (%)	Week 24	1	0.00	.	0.00	0.00
Segmented Neutrophils (%)	Baseline	8	59.56	12.22	41.10	75.70
	Week 12	3	55.13	17.05	40.00	73.60
	Week 16	1	60.00	.	60.00	60.00
	Week 20	11	57.86	10.41	42.20	75.00
	Week 24	6	61.53	10.14	43.50	74.90
	Week 32	12	55.71	9.78	39.00	75.70
Platelets (k/mm**3)	Baseline	8	252750	54818.5	193000	318000
	Week 12	3	256333	95928.8	188000	366000
	Week 16	1	225000	.	225000	225000
	Week 20	11	185455	58846.2	24000.0	241000

Table 16.13

Summary of Mean Laboratory Values at Each Visit by Treatment Group
Continuation Phase
Intent-to-Treat Population

Treatment Group=PLACEBO

N = 33

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Platelets (k/mm**3)	Week 24	6	297000	74339.8	183000	414000
	Week 32	12	227500	52201.5	188000	362000
White Blood Cell Count (k/mm**3)	Baseline	8	6.36	1.25	5.00	9.00
	Week 12	3	5.53	0.38	5.10	5.80
	Week 16	1	7.80	.	7.80	7.80
	Week 20	11	6.57	2.17	3.60	10.90
	Week 24	6	7.00	2.07	4.80	10.30
	Week 32	12	6.50	1.26	4.30	8.80

PAROXETINE - PROTOCOL 329

Table 16.14

Summary of Clinically Significant Abnormal Laboratory Values
Continuation Phase
Intent-to-Treat Population

Parameter		PAROXETINE N = 52 n	%	IMIPRAMINE N = 40 n	%	PLACEBO N = 33 n	%
Alanine Aminotransferase	H	0	0.0	0	0.0	0	0.0
Alkaline Phosphatase	H	0	0.0	0	0.0	0	0.0
Aspartate Aminotransferase	H	0	0.0	0	0.0	0	0.0
Total Bilirubin	H	0	0.0	0	0.0	0	0.0
Blood Urea Nitrogen	H	0	0.0	0	0.0	0	0.0
Creatinine	H	0	0.0	0	0.0	0	0.0
Basophils	H	0	0.0	0	0.0	0	0.0
Eosinophils	H	1	1.9	2	5.0	3	9.1
Hematocrit	L	0	0.0	2	5.0	0	0.0
Hemoglobin	L	0	0.0	0	0.0	0	0.0
Lymphocytes	H	0	0.0	0	0.0	0	0.0
Monocytes	H	0	0.0	0	0.0	0	0.0
Neutrophil Bands	H	0	0.0	0	0.0	0	0.0
Segmented Neutrophils	L	0	0.0	0	0.0	0	0.0
Platelets	H	0	0.0	0	0.0	0	0.0
	L	2	3.8	2	5.0	1	3.0
White Blood Cell Count	H	1	1.9	0	0.0	0	0.0
	L	0	0.0	0	0.0	0	0.0
Urine Glucose - Dipstick	H	0	0.0	0	0.0	0	0.0

Lab Abnormality Criteria: Blood Chemistry: AlkPhos: H = >=390; BUN: H = >=30.0; Creatinine: H = >=2.0; AST/SGOT: H = >=150;
ALT/SGPT: H = >=165; T.Bilirubin: H = >=2.0;
Hematology: HGB: (M) L = <=11.5 (F) L = <=9.5; HCT: (M) L = <=37.0 (F) L = <=32.0; WBC: L = <=2.8 H = >=16.0; Neut(Segs): L= <=15;
Neut(Bands): H = >10; Lymph: H = >=75; Monos: H = >=15; Eosins: H = >=10; Basos: H = >=10; Platelets: L = <=75000 H = >=700000.
Urinalysis: Protein: H = 4+; Glucose: H = 4+; RBC: (M) H = >8 (F) H = >10; WBC: H = >10.

Table 16.14

Summary of Clinically Significant Abnormal Laboratory Values
Continuation Phase
Intent-to-Treat Population

Parameter		PAROXETINE N = 52 n	%	IMIPRAMINE N = 40 n	%	PLACEBO N = 33 n	%
Urine Protein - Dipstick	H	0	0.0	0	0.0	0	0.0
Urine Red Blood Cells/HPF	H	5	9.6	1	2.5	1	3.0
Urine White Blood Cells/HPF	H	0	0.0	1	2.5	0	0.0

Lab Abnormality Criteria: Blood Chemistry: AlkPhos: H = >=390; BUN: H = >=30.0; Creatinine: H = >=2.0; AST/SGOT: H = >=150;
ALT/SGPT: H = >=165; T.Bilirubin: H = >=2.0;
Hematology: HGB: (M) L = <=11.5 (F) L = <=9.5; HCT: (M) L = <=37.0 (F) L = <=32.0; WBC: L = <=2.8 H = >=16.0; Neut(Segs): L= <=15;
Neut(Bands): H = >10; Lymph: H = >=75; Monos: H = >=15; Eosins: H = >=10; Basos: H = >=10; Platelets: L = <=75000 H = >=700000.
Urinalysis: Protein: H = 4+; Glucose: H = 4+; RBC: (M) H = >8 (F) H = >10; WBC: H = >10.

Table 16.14.1 Narratives for Patients with Laboratory Values of Potential Clinical Concern

PID 329.003.00289

Laboratory Parameter of Concern: Low hematocrit

Associated Adverse Event: Anemia

Demography: Age: 16 yrs Date of Birth: 16-May-79 Sex: Female
Height: 63 in Weight: 118.5 lbs Race: Hispanic

Country: United States

Medical History: Prior: Asthma
Current: Allergies to pollen, trees, and dust; dysmenorrhea; headaches

Study Diagnosis: Unipolar Major Depression

Study Medication: Imipramine

Start Acute Phase: 28-Feb-96 **End:** 23-Apr-96
Start Continuation Phase: 24-Apr-96 **End:** 10-Oct-96

Laboratory Remarks:
The patient entered the study on 28-Feb-96 and was randomized to double-blind imipramine. Baseline hematocrit was 35.3%, which was within the reference range of 35%-46%, and baseline hemoglobin was 12.3 g/dL, which was within the reference range of 12-15.6 g/dL. At week 8, the hematocrit had decreased to 30.4%, which was considered to be of potential clinical concern (≤32.0 female), and hemoglobin had decreased to 10.3 g/dL (below reference range). At week 20, both parameters were within reference range (36% and 12 g/dL, respectively). The patient completed the study as planned. At week 32, the hematocrit had decreased to 30.5%, which was again considered to be of potential clinical concern, and hemoglobin had decreased to 10.5 g/dL (below reference range). . The investigator reported an adverse event of mild anemia at that visit, considered not related to study medication.

PID 329.003.00289 (continued)

Other out-of-range laboratory values were lymphocytes (low at baseline), segmented neutrophils (high at baseline), eosinophils (high at baseline and week 8), RBC (low at weeks 8, 20, and 32), and uric acid (low at weeks 8 and 32). None of these values were considered to be of potential clinical concern and no associated adverse events were reported. In addition, systolic blood pressure was low at week 24 and weight was low at weeks 20 through 32. No adverse events were reported in association with these vital signs of potential clinical concern.

Laboratory Parameter	Week	Value	Units	Reference Range
Hematocrit	Baseline	35.3	%	35-46
	Week 8	30.4	%	35-46
	Week 20	36	%	35-46
	Week 32	30.5	%	35-46

Adverse Experiences:	Onset (Days into Study)	Duration (Days)
Headache	1	85
Dry mouth	13	31
Insomnia	15	129
Dysmenorrhea	57	Unknown

Concomitant Medications:	Start	End
Pamprin	Unknown	Ongoing
Tylenol	Unknown	Ongoing

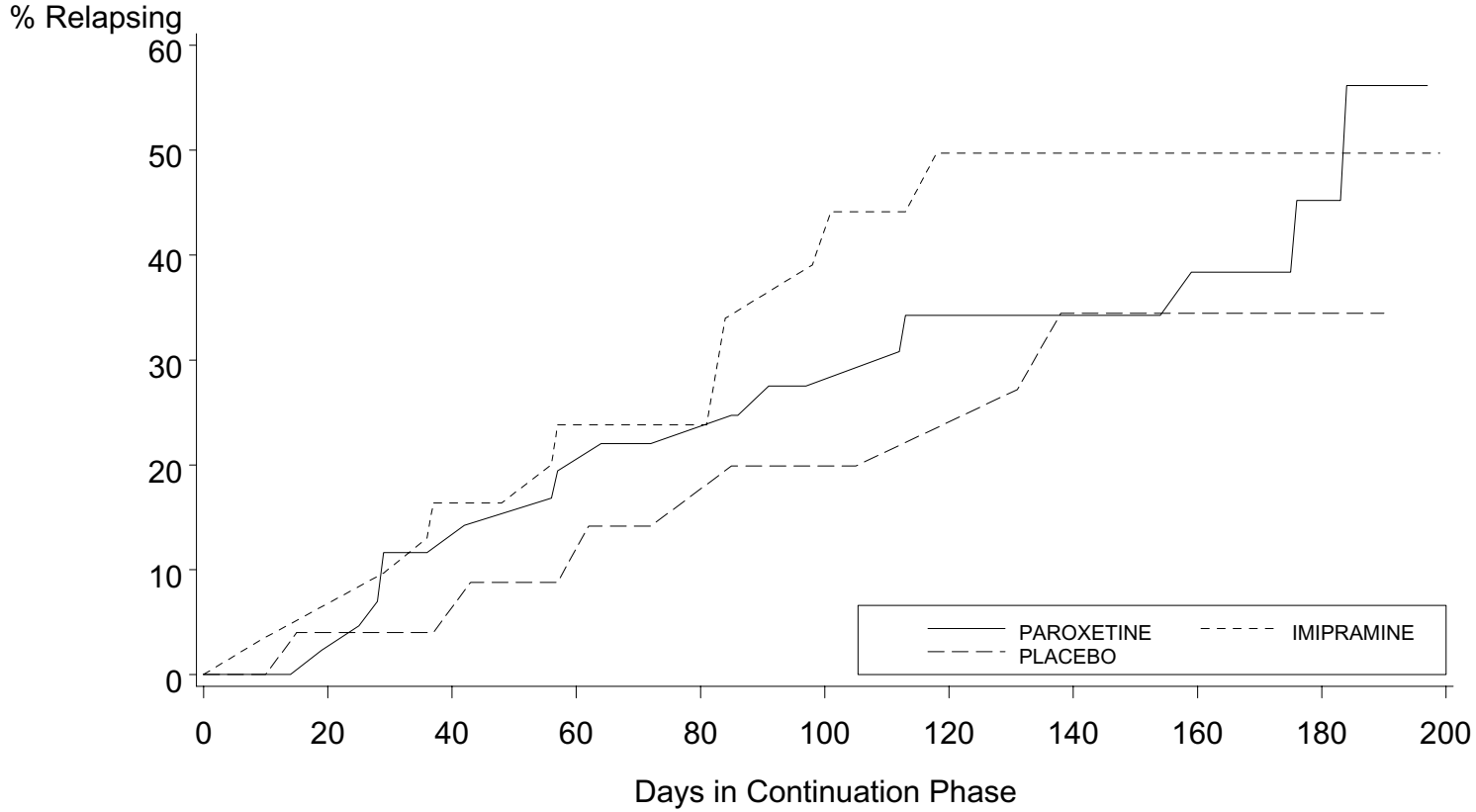
12 Data Source Figures

Figure 2

Kaplan Meier Survival Curves for Relapse during Continuation Phase

Paroxetine - Protocol 329

Intent to Treat Population



Relapse = HAMD Total Score greater than 8 OR decrease from baseline is less than 50%