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SmithKline Beecham

Paroxetine

29060

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

29060/329

Final Clinical Report

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Name(s) of Report Author(s):

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

Position: Vice President, CNS/GI

Date: 25-14 Nov'98.

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List of Abbreviations and Definitions

ADECS	Adverse Drug Experience Coding System (based on COSTART system)
AE	Adverse experience
AFC	Autonomous Functioning Checklist
ANOVA	Analysis of variance
BID	Twice a day (bis in die)
BP	Blood pressure
CATMOD	Categorical Modeling
C-GAS	Child Global Assessment Scale
CGI	Clinical Global Impression
CRF	Case Record Form
CNS	Central nervous system
DMI	Desipramine
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (1987)
EKG	Electrocardiogram
FH-RDC	Family History - Research Diagnostic Criteria
GLM	General Linear Model
HAM-D	Hamilton Depression Scale
hpf	High power field
HPLC	High-pressure liquid chromatography
IMI	Imipramine
IPL	Placebo match to imipramine

IRB	Institutional Review Board
ITT	Intent to treat
K-SADS-L	Schedule for Affective Disorders and Schizophrenia for School-age Children -- Lifetime Version
K-SADS-P	Schedule for Affective Disorders and Schizophrenia for School-Age Children -- Present Episode Version
LSMEANS	Least square means
LOCF	Last observation carried forward
PPL	Placebo matched to paroxetine
SADS-L	Schedule for Affective Disorders and Schizophrenia – Lifetime
SAS	Statistical Analysis System
SB	SmithKline Beecham
SD	Standard deviation
SE	Standard error of the mean
SGOT (AST)	Serum glutamic oxaloacetate transferase (aspartate transaminase)
SGPT (ALT)	Serum glutamic pyruvic transferase (alanine transaminase)
SIP	Sickness Impact Profile
SPP	Self Perception Profile
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TSH	Thyroid-stimulating hormone
WBC	White blood cell
WHO ATC	World Health Organization Anatomical Therapeutic Chemical

Report Synopsis

Title

A Multi-center, Double-blind, Placebo Controlled Study of Paroxetine and Imipramine in Adolescents with Unipolar Major Depression - Acute Phase (29060/329)

Investigators and Centers

Investigators from 10 centers in the United States and 2 in Canada participated in the study. All were affiliated with either a university or a hospital psychiatry department and had extensive experience in treating adolescent patients.

Publications

Keller MB, Ryan ND, Birmaher B, Klein RG, Strober M, Wagner KD, Weller EB, Paroxetine and Imipramine in the Treatment of Adolescent Depression. Abstract NR206, Annual Meeting of the American Psychiatric Association (APA), Toronto Ontario, Canada, 2 June 1998.

Wagner KD, Birmaher B, Carlson G, Clarke G, Emslie G, Geller B, Keller M, Klein R, Kutcher, S, Papatheodorou G, Ryan N, Strober M, Weller E, Safety of Paroxetine and Imipramine in the Treatment of Adolescent Depression. Abstract 69, Annual Meeting of New Clinical Drug Evaluation Program (NCDEU), Boca Raton, Florida, USA, 11 June, 1998,

Study Dates

The first patient received study medication on 20 April 94, the final patient was enrolled on 15 March 1997. The final study visit for the acute phase occurred on 07 May 1997, the final study visit for the continuation phase occurred on 15 February 1998.

Objectives

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

The secondary objectives were as follows: to identify predictors of treatment outcomes across clinical subtypes of major depressive disorder; to provide information on the safety profile of paroxetine and imipramine when these agents were given for an extended period of time; to estimate the rate of relapse among imipramine, paroxetine and placebo responders who were maintained on treatment.

This report presents the results from the 8 week acute phase. Findings from the continuation phase, which include long term safety and the analysis of relapse, will be reported separately.

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 plan 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 6 months. Eligible patients were randomized to treatment with paroxetine, imipramine or placebo for 8 weeks; clinic visits for efficacy and safety assessments were made weekly. 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 6 month continuation treatment phase; clinical visits were made monthly.

Study Population

Eligible patients were adolescents (12 years 0 months through 18 years 11 months inclusive), were currently in an episode of major depression (DSM-III-R criteria) for at least 8 weeks, and had a total score ≥ 12 on the 17-item Hamilton Depression Scale (HAM-D).

Treatment and Administration

Test product: Paroxetine was supplied as film coated, capsule shaped tablets, yellow containing 10 mg (batch no U95085) and pink containing 20 mg (batch no. U95086).

Reference therapies: Imipramine (50 mg) was bought commercially and supplied as green film coated round tablets (batch nos. U95121, U-93135, and U-93139). "Paroxetine placebos" (batch no. U95084) matched the paroxetine 20 mg tablets, and "imipramine placebos" (batch no. U95087) matched the imipramine tablets.

All tablets were over-encapsulated in bluish-green capsules to preserve blinding. Patients took their study medication twice daily, once in the morning and once at night. Total daily doses of imipramine were 50, 100, 150, 200, 250, and 300 mg for dosing levels 1 to 6, respectively. Daily doses of paroxetine were 20 mg for levels 1 to 4, 30 mg for level 5, and 40 mg for level 6. At the beginning of the study, all patients were started at level 1 and titrated up to level 4 at weekly intervals, regardless of response. Non-responders could be titrated up to level 5 or 6 during the next 4 weeks.

Evaluation Criteria

Efficacy Parameters: The efficacy assessments in the trial included the Hamilton Rating Scale for Depression (HAM-D), 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).

The protocol defined the primary efficacy parameters as the change from baseline in the HAM-D total score, and the proportion of responders defined as patients with a 50% reduction in the total HAM-D or a score of 8 or less. Secondary parameters included the change in baseline in the K-SADS-L depression subscale, the mean CGI score, and the functional/quality of life instruments. An analytical plan developed prior to opening of the blind also described additional outcome measures including patients in "remission" (a score of 8 or less on the HAM-D total), and the mean change in the depressed mood items from the HAM-D and the K-SADS-L instruments.

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

Other Parameters: Plasma paroxetine and serum IMI and DMI concentrations were determined at the completion of 4 and 8 weeks of treatment.

Statistical Methods

All patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment were included in the ITT efficacy population. Statistical conclusions concerning the efficacy of paroxetine and imipramine were made using data obtained from the last observation carried forward (LOCF) and observed cases (OC) datasets. The last observation carried forward consisted of each patient's last on-therapy assessment during the acute phase. All hypotheses were two sided. The comparisons of interest were paroxetine vs. placebo and imipramine vs. placebo at week 8 LOCF. Hypotheses concerning these comparisons were tested at the alpha level of 0.05. No comparisons were made between paroxetine and imipramine. Interactions were considered significant at the 10% level of significance. Continuous efficacy variables were analyzed by analysis of variance using the general linear model (GLM) procedure of SAS with effects for treatment and investigator. Categorical data were analyzed by logistic analysis using the categorical modeling procedures (CATMOD) of SAS with effects for treatment and investigator. Covariate analyses were also carried out using the general linear model procedures. For the covariate analyses, each analysis used a model including effects for treatment, covariate, and treatment by covariate interaction.

Patient Disposition and Key Demographic Data

Two hundred and seventy five patients were enrolled in the acute phase and randomized to the three treatment regimens: 93 paroxetine, 95 imipramine, 87 placebo. The baseline demographic features and the clinical features of depression of the three treatment groups were comparable at entry. Over 70% of the paroxetine and the placebo patients completed the 8-week acute phase. In contrast, 60% of imipramine patients completed the acute phase. The most common reason for early withdrawal for the imipramine group was adverse events.

Demographic and Clinical Characteristics at Entry			
	Paroxetine N = 93	**Imipramine N = 95**	**Placebo N = 87**
Age (yrs.) mean (S.D.)	14.8 (1.6)	14.9 (1.7)	15.1 (1.6)
Weight (lbs) mean (S.D.)	146.3 (38.9)	139.4 (36.7)	145.3 (40.8)
Race			
Caucasian	83%	87%	81%
Black	5%	3%	7%
Other	12%	9%	13%
Female	62%	59%	66%
Duration of current depressive episode (mos.) mean (S.D.)	14.4 (17.5)	14.2 (17.9)	12.5 (16.6)
Age at first episode (yrs.) mean (S.D.)	13.2 (2.8)	13.2 (2.7)	13.5 (2.3)
% patients with > 1 prior episode	18%	19%	22%
Baseline Mean HAM-D at entry (S.D.)	19.0 (4.1)	18.3 (4.3)	19.2 (4.3)

Patient Disposition			
	Paroxetine	**Imipramine**	**Placebo**
Entered	93	95	87
Completed 8 weeks	72%	60%	76%
Reason for Withdrawal			
Adverse Event	10%	32%	7%
Lack of efficacy	4%	1%	7%
Other reason+	14%	7%	10%
Mean dose (mg) (S.D.)	28.0 (8.5)	206 (64.0)	0

+ Other includes patients withdrawn for protocol violations and lost to follow-up

Efficacy Results

The protocol described two primary efficacy endpoints: the change in the total HAM-D score, and the percentage of responders, defined as patients with at least 50% reduction in the baseline HAM-D score or a score of 8 or less. There were six secondary measures. These included the change from baseline in the 9-item K-SADS-L depression subscore, the change in the depression item scores of both the HAM-D and the K-SADS-L, the mean global improvement scores, percent of patients rated "very much" or "much improved," and the percent of patients in remission defined as patients with a final HAM-D score of 8 or less.

The analyses of these measures support that paroxetine is beneficial in treating adolescents with major depression, but the support is derived mainly from the secondary measures. In the protocol defined primary endpoints, the placebo response was large and the magnitude of the benefit of paroxetine response over

placebo was modest and did not achieve statistical significance. For the LOCF dataset, the mean change in the HAM-D scores for the paroxetine group was approximately 2 points greater than placebo (-10.7 units vs -8.9; p=0.113). In the responder analyses, 67% of paroxetine patients and 55% of placebo patients were classified as responders (p=0.112).

In the secondary measures, however, paroxetine treatment was numerically superior to placebo in all six endpoints and achieved statistical significance in four: the depression item of the HAM-D (p=0.003), the depression item from the K-SADS-L (p=0.049), the percent of patients rated "very much" or "much improved" (p=0.020), and the percent of patients in remission (p=0.019).

There was little evidence to support the benefit of imipramine at the doses tested in treating adolescents with depression.

Mean Change from Baseline in HAM-D Total Score, Depression Item, K-SADS-L Depression Subgroup, K-SADS-L Depression Item, Mean CGI Score, and Percent of Patients Meeting Definition of Responder or Remission

	Week 8 ITT Population				
	Paroxetine	**Imipramine**	**Placebo**	**Paroxetine vs Placebo**	**Imipramine vs Placebo**
***Mean Change in HAM-D Total (SEM)**					
Wk 8 OC	-12.2 ± 0.88	-10.6 ± 0.97	-10.5 ± 0.88	p = 0.153	p = 0.945
Wk 8 LOCF	-10.7 ± 0.81	-8.9 ± 0.81	-9.1 ± 0.83	p = 0.133	p = 0.873
Mean Change HAM-D Depressed Mood (SEM)					
Wk 8 OC	-2.21 ± 0.17	-1.76 ± 0.18	-1.56 ± 0.17	p = 0.003	p = 0.358
Wk 8 LOCF	-2.0 ± 0.14	-1.62 ± 0.14	-1.33 ± 0.14	p = 0.001	p= 0.135
Mean Change in K-SADS-L 9-Item Depression Subscore (SEM)					
Wk 8 OC	-12.0 ± 0.93	-10.7 ± 1.02	-10.8 ± 0.93	p = 0.348	p = 0.883
Wk 8 LOCF	-11.7 ± 0.84	-9.6 ± 0.83	-9.6 ± 0.83	p = 0.065	p = 0.984
Mean Change in K-SADS-L Depression Item (SEM)					
Wk 8 OC	-2.35 ± 0.20	-2.05 ± 0.22	-1.93 ± 0.20	P = 0.113	P = 0.661
Wk 8 LOCF	-2.20 ± 0.18	-1.77 ± 0.18	-1.73 ± 0.19	P = 0.049	P = 0.868
Mean Clinical Global Improvement Score (SEM)					
Wk 8 OC	1.9 ± 0.15	2.2 ± 0.17	2.4 ± 0.16	p = 0.030	p = 0.371
Wk 8 LOCF	2.4 ± 0.16	2.7 ± 0.15	2.7 ± 0.16	p = 0.094	p = 0.896
***% Responders (50% ↓ HAM-D Total or a Score ≤ 8)**					
Wk 8 OC	81% (54/67)	73% (41/56)	65% (43/66)	p = 0.051	p = 0.363
Wk 8 LOCF	67% (60/90)	59% (55/94)	55% (48/87)	p = 0.112	p = 0.612
% Responders (CGI Rating of "Very Much Improved" or "Much Improved")					
Wk 8 OC	79% (53/67)	68% (38/56)	61% (40/66)	p = 0.020	p = 0.506
Wk 8 LOCF	66% (59/90)	52% (49/94)	48% (42/87)	p = 0.020	p = 0.642
% Remission (HAM-D Score ≤ 8)					
Wk 8 OC	76% (51/67)	64% (36/56)	58% (38/66)	p = 0.019	p = 0.440
Wk 8 LOCF	63% (57/90)	50% (47/94)	46% (40/87)	p = 0.019	p = 0.574

* Protocol defined primary measures of efficacy.

Safety Results

Adverse Experiences:

The nature and incidence of adverse events reported for the paroxetine group were similar to that reported for adult depressed patients receiving paroxetine in controlled trials of comparable duration[1] and as described in the Paxil U.S. prescribing information. Two exceptions to the profile seen in adults include tooth disorder and hostility. The latter term includes aggressiveness and conduct disorders. These exceptions may be related to the age of the study population. As in the adult, adverse events were more likely to occur during the initial weeks of treatment. Analysis by age suggests that events associated with the nervous

system (dizziness, sleep problems, and conduct disorders) were more likely to occur in the younger subset (<15 yrs.).

There were no deaths during the trial. Serious adverse events occurred in 18 patients, 11 in the paroxetine group, 5 in the imipramine group, and 2 in the placebo group. One of the paroxetine patients experienced migraine headache during down titration after completing 8 weeks of treatment. For the remaining patients the events were psychiatric in nature and included worsening depression, suicidal ideation/gestures, and conduct disturbances (hostility). In the imipramine group, one patient developed a maculopapular rash, one had dyspnea associated with chest pain, one reported auditory hallucinations, and two were reported to have serious conduct disturbances (hostility). In the placebo group, the two serious events were worsening depression.

Adverse Events Occurring in ≥ 5% of Any Group and at Least 2X Placebo			
	Paroxetine N = 93	**Imipramine N = 95**	**Placebo N = 87**
Cardiovascular			
Tachycardia	2 (2%)	18 (19%)	1 (1%)
Postural Hypotension	1 (1%)	13 (14%)	1 (1%)
Vasodilatation	0 (0)	6 (6%)	2 (2%)
Chest Pain	2 (2%)	5 (5%)	2 (2%)
Gastrointestinal			
Dry Mouth	19 (20%)	43 (45%)	12 (14%)
Dyspepsia	6 (7%)	9 (9%)	4 (5%)
Constipation	5 (5%)	9 (10%)	4 (5%)
Tooth Disorder	5 (5%)	2 (2%)	2 (2%)
Central Nervous System			
Somnolence	16 (17%)	13 (14%)	3 (3%)
Insomnia	14 (15%)	13 (14%)	4 (5%)
Hostility	7 (8%)	3 (3%)	0 (0)
Emotional Lability	6 (7%)	3 (3%)	1 (1%)
Dizziness	22 (24%)	45 (47%)	16 (18%)
Tremor	10 (11%)	14 (15%)	2 (2%)
Other			
Abnormal Vision	1 (1%)	7 (7%)	2 (2%)
Sweating	1 (1%)	6 (6%)	1 (1%)

Vital Signs:

Changes in vital signs (blood pressure and pulse rate) as well as body weights were small in the paroxetine and placebo treatment groups. In the imipramine treatment group, however, marked increases were seen in the mean pulse rate.

Laboratory Tests:

The number of patients identified with laboratory values of clinical concern was low in all treatment groups. None were considered to be of clinical significance.

Conclusions

This study supports that paroxetine is beneficial in treating adolescents with major depression although the support is derived mainly from secondary measures. The superiority of the paroxetine response over placebo appears less than seen in adults; this may be a result of the weekly supportive psychotherapy sessions allowed by the protocol producing a large "placebo" response. The safety profile of paroxetine in the adolescent appears similar to that reported in adults. The study provided little support for the benefit of imipramine in treating adolescent depression.

1 Introduction

Similarities between adolescent and adult depression in symptomatology, family history, and prospective course provide compelling rationale for investigating the efficacy of antidepressant drug therapy in young patients with depression. But unlike adults, the evidence from trials in adolescents has not supported drug efficacy, although the existing studies reported at the start of this trial had collectively evaluated fewer than 200 patients, a number hardly adequate for reliable clinical or statistical inferences. [2] A placebo controlled trial reported during the conduct of the present study, however, supports the benefit of fluoxetine in children and adolescents with major depression [3], but remission of symptoms was rare.

This apparent difference in response between adults and younger patients has been the subject of much debate. Recent reviews have focused on three major areas of concern.[2][4][5] These include: deficiencies in study design, methodology and conduct; the adequacy of diagnostic criteria and various nosological problems and developmental issues, in that children and adolescents who suffer from adult-like depression may respond in a pharmacologically different manner due to quantitative and/or qualitative developmental differences in neurotransmitter/receptor systems.

The study that is summarized in this report was performed to examine the efficacy and safety of two active antidepressant therapies in adolescents with unipolar major depression. The study plan included several features designed to avoid the perceived flaws of previous studies. The study design was placebo-controlled and double-blind. The study was conducted at multiple sites to achieve a target enrollment that would provide sufficient statistical power to detect clinical differences among treatment groups, should those differences exist. The inclusion and exclusion criteria for patient participation were rigorous, so that the study population was more homogenous than reported from previous trials. Diagnostic interviews were reviewed among the various sites to confirm the criteria for symptoms of depression and to promote uniformity in diagnosis.

One of the treatment arms was paroxetine (Paxil), an orally administered antidepressant with a chemical structure unrelated to other members of its class, the selective serotonin reuptake inhibitors (SSRI). Paroxetine had not been systematically studied in adolescent depression. The other active treatment arm was imipramine, a tricylic antidepressant (TCA) that had been previously studied in two small open-labeled clinical trials in adolescents, one of which

demonstrated a modest therapeutic response in patients with nondelusional depression.[6]

Patients eligible for inclusion in the study were adolescents who were currently in an episode of major depression, according to the Diagnostic and Statistical Manual of Mental Disorders III-R, [7] with a minimum duration of 8 weeks. Each patient had a 17-item Hamilton Depression Scale total [8] score of 12 or greater upon entry.

During the treatment period, interpersonal, cognitive or behavioral psychotherapy focusing on psychological themes was not permitted. Investigators and their staff were instructed to provide psychosocial interaction between the investigator and the patient that would maximize the chance of observing a pharmacotherapeutic effect and assure careful and safe monitoring of patients. To this end, the Clinical Management for Adolescent Depression Manual was used to define the boundaries of the supportive therapy and to assure consistency of approach among the investigators.

Non-responders at the end of the 8-week period were withdrawn from study medication and additional treatment was at the discretion of the investigator. The blind was not to be broken.

Patients who responded to treatment were eligible to continue on the same blinded medication at the same dosage level for an additional 6 months in a continuation phase of the study. It should be noted that the continuation phase of this trial was not designed to determine whether paroxetine or imipramine are superior to placebo in preventing relapse. The prevention of relapse is more adequately addressed using designs in which responders are re-randomized to remain on therapy or to receive placebo. Rather, the purpose of the continuation phase was to provide an estimate of the long-term safety profile of paroxetine and imipramine and to provide information on the relapse rates of responders over an extended period. The results of the continuation phase are reported as an addendum to this report.

2 Objectives

2.1 Primary

- To compare the efficacy and safety of imipramine and paroxetine to placebo in the treatment of adolescents with major depression.

2.2 Secondary

- To identify predictors of treatment outcomes across clinical subtypes (e.g. endogenous subtype, age at onset, number of prior episodes, duration and severity of current episode, comorbidity with separation anxiety disorder, attention deficit disorder, and conduct disorder).

- To estimate the rate of relapse among imipramine, paroxetine and placebo responders who were maintained on treatment. Analysis of relapse will be reported separately.

- To provide information on the safety profile of paroxetine and imipramine when these agents are given for an extended period of time. Results of this evaluation will be reported separately as an addendum to this report.

3 Methodology

3.1 Study Design[1]

This was a multi-center, double-blind, placebo-controlled, parallel group trial. Patients were eligible for inclusion if they were adolescents from ages 12 years 0 months through 18 years 11 months inclusive. The patients were diagnosed as being currently in an episode of major depression according to DSM-IIIR criteria [7] with a minimum duration of 8 weeks, using the Schedule for Affective Disorders and Schizophrenia for Adolescents - Lifetime Version (K-SADS-L). They were required to have a Hamilton Depression Scale (HAM-D) [8] total score of 12 or greater.

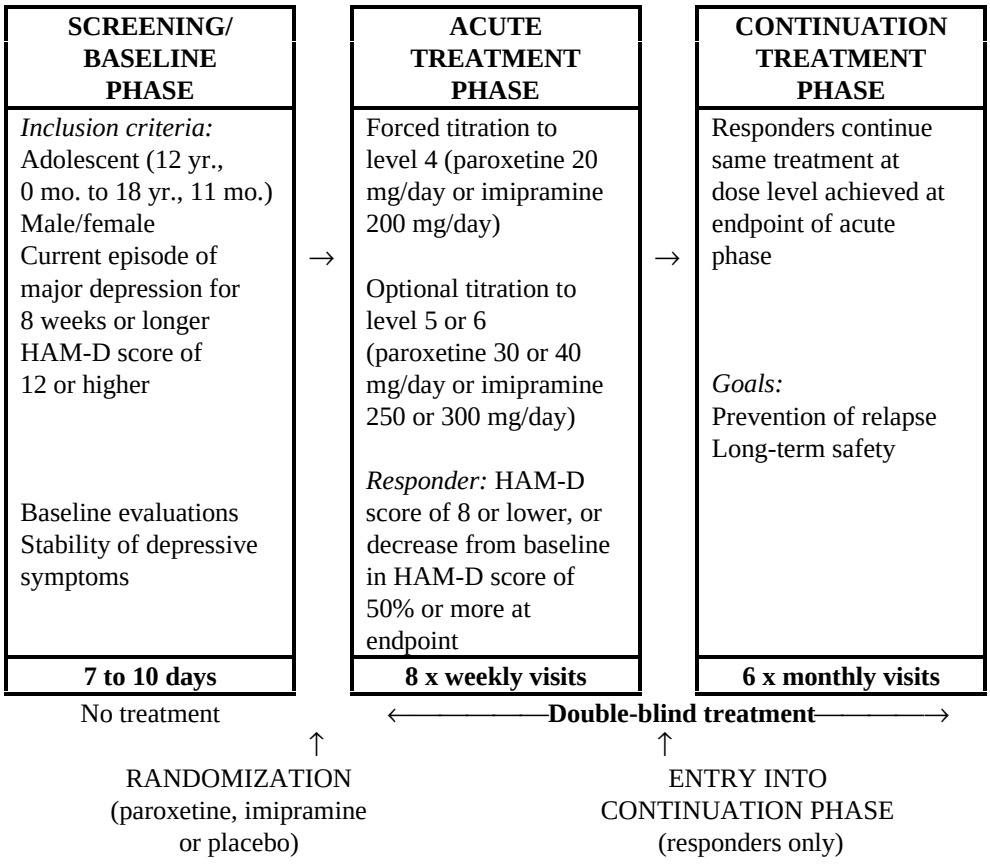
Eligible patients were randomized to treatment with paroxetine, imipramine or placebo for 8 weeks. During this time, the patients made weekly visits to the clinic. The effects of treatment on depression were evaluated using standardized instruments and global assessments. Safety assessments were also performed at each visit.

At the completion of the 8 week acute study, patients who met specific criteria for a clinical response could be continued on the same medication in a double blind manner for a 6 month continuation treatment phase. Patients who were non-responders at the end of the 8-week treatment period were withdrawn from the study and were to be treated as clinically indicated. The blind was not to be broken.

The study design is illustrated on the next page.

[1] Appendix A contains the protocol and sample case report forms.

Figure 1 Study Design



3.1.1 Protocol Amendments[2]

Amendment 1 (approved 17 April, 1994)

This amendment was instituted prior to enrollment of the first patient.

The diagnosis of major depression was made using the Schedule for Affective Disorders and Schizophrenia for Adolescents - Lifetime Version (K-SADS-L) in place of an earlier version, the K-SADS-P. The K-SADS-L includes the elements of the K-SADS-P but also assesses additional disorders (e.g., attention deficit/hyperactivity disorder, antisocial personality disorder, social phobia) omitted from the K-SADS-P, and it provides for lifetime inquiry in addition to the current disorder.

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[2] Appendix A contains the protocol amendments.

If the diagnosis of major depressive disorder was uncertain, the investigator was to contact one of the senior investigators at a separate site to discuss the case. The external reviewer was to review the audiotape of the screening interview, if available, and to return a decision within 2 days. The external reviewer's opinion was to take precedence in the event that the external reviewer and the investigator disagreed on the patient's eligibility for the study.

The amendment also included additional safety measures. In addition to the 12-lead EKGs performed at weeks 4 and 8, rhythm strip EKGs were to be obtained during the other weekly visits.

Sampling for plasma concentrations of imipramine and desipramine and for plasma concentrations of paroxetine was to be performed at the week 4 and 8 visits. The plasma 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 mcg/L (500 ng/mL), the investigator was to be notified by telephone to withdraw the patient from the trial.

The criterion for heart rate elevation requiring a dose adjustment was changed to agree with FDA guidelines for studies in adolescents. Patients whose heart rate exceeded 110 bpm on two consecutive visits or 130 bpm at any time had their dosage decreased by one level if they were at dose level 5 or 6 or were removed from the study if they were at dose level 4 or below. These dose adjustments were to be made without breaking the blind.

Amendment 2 (approved 28 October 1996)

Clinical supplies for the trial were prepared in two batches, the first in 1991 and the second in 1993. Due to a slower-than-expected rate of enrollment, part of the initial batch of study medication expired before use. The remaining supplies were insufficient to provide for both acute and continuation phase treatment of 300 patients.

Without opening the blind, the variability in HAM-D scores was assessed using the initial 189 patients who completed the acute phase. Based on this assessment, the target for total enrollment into the acute phase was reduced from 300 to approximately 275 patients (see Section 3.13.1). It was anticipated that this reduction in sample size would have no adverse effects on the estimated 80%

power of this study to detect a four point difference between placebo and active groups.

The number of individual study medication packets for the continuation study presented additional problems. This is because the number of patients entering the continuation phase from each treatment regimen could not be estimated exactly. With the reduced study supplies, it was anticipated that there may not be study supplies for a small number of patients who qualified for the continuation phase. Accordingly, the following two options were provided for patients who qualified for continuation treatment but for whom blinded medication may not be available. With both options, the patient was withdrawn from the trial, and his medication assignment was not revealed to any personnel (investigator, investigator staff or sponsor personnel) associated with the trial. The first option was that treatment could be continued by a third party not associated with the trial, who was provided with the identity of the study medication by the SB safety group. The second option was that the patient be treated with open-label paroxetine for up to 6 months following down titration over a 1-week washout period. In this case, the patient could elect to remain under the care of the present study physician.

3.2 Investigators[3]

The study was performed at ten centers in the United States and two in Canada, as shown in Table 1. The investigators were chosen for their interest in the study and their ability to enter eligible patients.

The initial study plan called for six investigative sites to enroll a minimum of one patient per center per month beginning in April 1994. Using this rate it was anticipated that approximately four years would be needed to randomize the 300 patients required by the protocol. However, after completion of the first year of enrollment, both the sponsor and the investigators concluded that the projected initial enrollment rate could not be met with only six sites. Accordingly, six additional sites were recruited for participation in the trial. The study enrollment was completed in March 1997.

To ensure that study procedures were standardized across all investigator sites, representatives of SmithKline Beecham reviewed the protocol, CRF and safety reporting procedures with each investigator and his/her personnel responsible for the conduct of the study. Two investigator meetings were held in Philadelphia.

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[3] Appendix A contains the curriculum vitae of each principal investigator.

The first of these meetings occurred in September 1993 before initiation of the study. The second meeting was held in June 1995, and included the original investigators (sites 1-6) as well as the six additional investigators (sites 7-12). In addition, scheduled teleconferences between representatives of SB and the investigators were held twice monthly to resolve any issues that had arisen at any of the study centers, and resolutions to major issues were documented in the form of written monitoring guidelines.[4] Adherence to the protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each investigator site.

Table 1 Principal Investigators, the SB Assigned Center Number and Affiliations

Center	Investigator	Affiliated Institution	City/State/Provence
001	xxxxxxx xxxxx, MD	xxxxxxxxxx xxxxxxxxxx xxxxxxx xx xxxxxxx	xx.xxxxxx, xx
002	xxxxx x.xxxxx, MD	xxxxxx xxxxxxxxxx xx xxxxxxxx	xxxxxxxxx, xx
003, Site 1	xxxxxx xxxxx, PhD xxxxx xxxxxxxxx, MD	xxx xxxx xxx xxxxxxxxxxx xxxxxxxxx	xxx xxxx, xx
003, Site 2	xxxxx xxxxxx MD	xxxx xxxx xxxxx xxxxx xxxxx	xx xxx xxxx xx
004	xxxx xxxxx, MD* x. xxxxxxxxxxx, MD	xxxxxxxxxxxxxxxxxxxxx xxxxx	xxxxxx, xxxxxx, xxxxx
005	xxxx xxxx, MD xxxx xxxxxxx, MD	xxxxxxxx xxxxxxxxxx xxxxxx xx xxxxxxx	xxxxxxxx, xx
006	xxxxxx xxxxxx, PhD xxxx xxxxxx, MD	xxxxxxxxxx xxxxxxxxxx xxx xxxxxx xxxxxxx xxxxx	xxx xxxxxxx xx
007	xxxxx xxxxx, MD, PhD	xxxxxxxxx xxxxxx xxxxx xxxxx	xxxxxxxx, xx
008	xxxx xxxx, PhD xxxxxx xxx, MD	xxxxx xxxxx xxxxxx xxxxxxxxx	xxxxxx, xx
009	xxxxx xxxxxx, MD	xxxxxxxx xx xxxxx xxxxxxxx xxxxxxx	xxxxx, xx
010	xxxxxxx xxxxxx, MD	xxxx xxxx xxxxxxxxx xxxxxxx xxxxxx	xxxxxxxx, xx
011	xxxxxx xxxxx, MD	xxxxx xxxxxxxxxx xx xxxx xx xxxx xxxxx	xxxxx xxxxx, xx
012	xxxx xxxxxx, MD xxxx xxxxxx, MD*	xxxxx xxxxx xxxxx xxxxxx'x xxxxxxx	xxxxx, xxxx xxxx, xxxx

Source: Appendix A contains the curriculum vitae (or biographical sketch) of each principal investigator

* Dr. xxxxxxx participated at site 004 from March 1994 through April 1995, and at site 012 from May 1995 through study completion.

[4] Appendix A contains the monitoring guidelines for the study.

3.3 Ethics

The study was conducted in accordance with good Clinical Practices and the Declaration of Helsinki as amended in Hong Kong (1989). The protocol and statement of informed consent[5] were approved by an Institutional Review Board (IRB) prior to each center's initiation, in compliance with 21 United States Code of Federal Regulations (CFR) Part 56. Written informed consent was obtained from each patient prior to entry into the study, in compliance with 21 CFR Part 50. Case report forms were provided for each patient's data to be recorded.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

Before entry into the study, each patient was to satisfy all of the following criteria:

- Adolescent between the ages of 12 years 0 month and 18 years 11 months inclusive.
- Currently in an episode of major depression for at least 8 weeks. A diagnosis of major depression was to be made on summary data aggregating parent and child reports using the K-SADS-L as a diagnostic tool. In addition, both adolescent and parent(s) were to agree that the adolescent had a disorder meriting treatment.
- A severity score less than 60 on the Child Global Assessment Scale (C-GAS).
- A score of 12 or greater on the 17-item Hamilton Depression Scale (HAM-D).
- Medically healthy as determined by physical examination, medical history and laboratory screening.
- IQ ≥ 80 by Peabody Picture Vocabulary Test.

3.4.2 Exclusion Criteria

A patient was to be excluded from the study if any of the following criteria applied to that patient:

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[5] Appendix A contains the protocol. The sample informed consent is an appendix to the protocol.

- Current or lifetime DSM-III-R diagnosis of bipolar disorder, schizo-affective disorder, anorexia nervosa, bulimia, alcohol or drug abuse/dependence, obsessive/compulsive disorder, autism/pervasive mental disorder, or organic psychiatric disorder.

- Current diagnosis (within 12 months) of post traumatic stress disorder per DSM-III-R criteria.

- Adequate trial of antidepressants within 6 months prior to beginning this study. An adequate trial was defined as a treatment of at least 4 weeks or more with imipramine, desipramine, or amitriptyline at a dosage of 150 mg per day or greater, with nortriptyline at a dosage of 50 mg per day or greater, or with fluoxetine at a dosage of 20 mg per day or greater.

- Presence of suicidal ideation with a definite plan or of a suicide attempt within the current episode, or any past history of attempting suicide by medication overdose.

- Medical illness contraindicating the use of heterocyclic antidepressants (e.g. cardiovascular disease).

- Use of :

    - any psychotropic medication including anticonvulsants, anxiolytics, neuroleptics or lithium carbonate

    - any illicit drug, as documented by a drug screen within two weeks of starting the study.

- Presence of organic brain disease, epilepsy, or mental retardation.

- Pregnancy or lactation.

- If female, sexual activity without using a reliable methods of contraception (oral contraception, surgical sterilization, IUD, or diaphragm in conjunction with spermicidal foam and condom on partners).

- Use of an investigational drug within 30 days of entry into the study or within five half lives of the investigational drug (the longer period was to apply).

3.5 Treatments and Administration

3.5.1 Study Medication

Table 2 shows the presentation, formulation and clinical trial supply numbers of the study medications, which were provided as over-encapsulated tablets to preserve the blind. Paroxetine was formulated as 10 mg and 20 mg bisected tablets. Imipramine (50 mg tablets; debossed with B1 on one side and 21 on the other side) was obtained commercially. "Paroxetine placebos" matched to 20-mg paroxetine tablets and "imipramine placebos" matched to imipramine tablets were prepared at SB.

Table 2 Appearance, Formulation, Dosage Strengths, and Batch Numbers of Study Medication

Study drug	Appearance	Formulation	Dosage strength	Batch numbers
Paroxetine	Yellow, film coated, capsule-shaped tablet	Over encapsulated tablet	10 mg	U95085 U93127
Paroxetine	Pink, film coated, capsule-shaped tablet	Over encapsulated tablet	20 mg	U95086 U93128
Placebo matched to paroxetine	Pink, film coated, capsule-shaped tablet	Over encapsulated tablet	-	U95084 U93126
Imipramine*	Green, film-coated, round tablet	Over encapsulated tablet	50 mg	U95121 U93135 U93139
Placebo matched to imipramine	Green, film-coated, round tablet	Over encapsulated tablet	-	U95087 U93178

Data source: Appendix A contains the batch numbers for SB manufactured products, lot numbers for purchased comparators, and Certificates of Analysis for SB batches of formulated products.

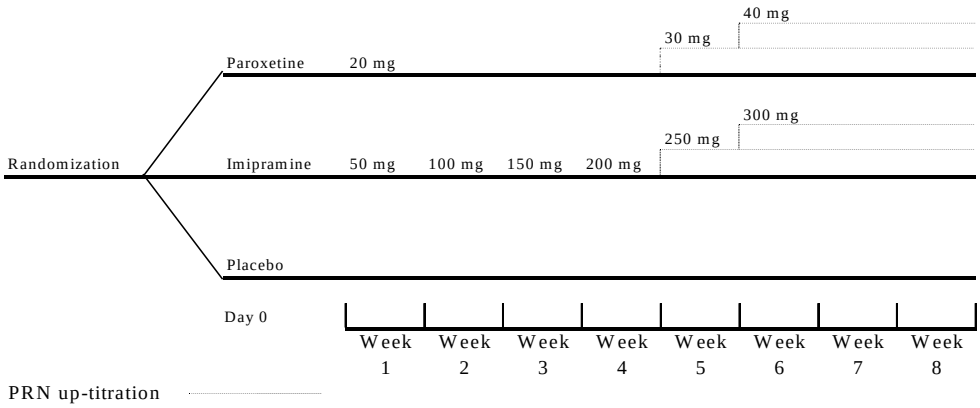
* Imipramine tablets (lot numbers 18857, 20154, and 27763) were purchased from Biocraft Laboratories, Fairlawn, NJ USA.

Study medication was issued to the patients as foil-backed blister cards containing sufficient supplies for a 1-week treatment period (10 days). The tear-off portion of the double-blind label was affixed to the CRF at the time that study medication was dispensed to the patient. Study medication was kept in a locked area at each study site.

3.5.2 Dosage and Administration

The patients were instructed to take study medication twice daily, one dose in the morning and one at night. There were 6 dosing levels. During the first 4 weeks, all patients were titrated to level 4 (corresponding to paroxetine 20 mg or imipramine 200 mg bid) regardless of response. Non-responders could be titrated up to level 5 or 6 during the next 4 weeks. The number of capsules per dose depended on the dosing level, so that the number of capsules to be taken daily ranged from two to six. The titration design is shown in Figure 2 and the dosing schedule for each treatment group and dose level is shown in Table 3.

Figure 2 Titration Design



Source: Appendix A contains the study protocol

Table 3 Dosing Schedule

Dose level	Paroxetine			Imipramine			Placebo	
	Daily dose	a.m.	p.m.	Daily dose	a.m.	p.m.	a.m.	p.m.
1 (Days 1-7)	20 mg	1 x P20	1 x PPL	50 mg	1 x I50	1 x IPL	1 x PPL	1 x PPL
2 (Days 8-14)	20 mg	1 x P20	1 x PPL	100 mg	1 x I50	1 x I50	1 x PPL	1 x PPL
3 (Days 15-21)	20 mg	1 x P20	1 x PPL 1 x PPL	150 mg	1 x I50	2 x I50	1 x PPL	2 x PPL
4 (Days 22-28)	20 mg	1 x P20 1 x PPL	2 x PPL	200 mg	2 x I50	2 x I50	2 x PPL	2 x PPL
5*	30 mg	1 x P20 1 x PPL	1 x P10 2 x PPL	250 mg	2 x I50	3 x I50	2 x PPL	3 x PPL
6*	40 mg	1 x P20 2 x PPL	1 x P20 2 x PPL	300 mg	3 x I50	3 x I50	3 x PPL	3 x PPL

Source: Appendix A contains the study protocol
*Optional
Key: P20, paroxetine 20 mg; P10, paroxetine 10 mg; PPL, placebo matched to paroxetine 20mg; I50, imipramine 50 mg; IPL, placebo matched to imipramine 50 mg

Dosage Adjustment Based on Cardiovascular Parameters

The following cardiovascular criteria were established as limits which warrant reduction in dosage:

- Sitting heart rate ≥ 130 bpm
- Sitting systolic BP ≥ 140 mmHg with sitting diastolic BP < 85 mmHg
- PR interval ≥ 0.21 sec
- QRS interval ≥ 0.12 sec and ≥ 150% of baseline value
- QTC interval ≥ 0.48 sec

Cardiovascular parameters outside these limits resulted in reduction of dose level by one step for patients who were at a dose level of 5 or 6 and withdrawal from the study for patients who were at a dose level of 4 or lower.

In addition, patients who had a sitting heart rate exceeding 110 bpm on two successive visits were to have their dosage reduced or to be withdrawn from the study.

At weeks 4 and 8, blood samples were obtained to assess serum levels of study medication. If the combined serum concentration of imipramine and desipramine exceeded 500 mcg/L (500 ng/mL) the patient was to be withdrawn from study medication, using down-titration if necessary.

3.5.3 Methods of Blinding

“Paroxetine placebo” tablets were identical in size, color and shape to the paroxetine 20 mg tablets. “Imipramine placebo" tablets were identical in appearance to the imipramine tablets. All tablets were placed inside identically appearing bluish-green Supro B locking capsules to preserve the blinded nature of the study.

Copies of the randomization codes were stored at SB's Clinical Safety Department. The blind was to be broken only in the event of a serious adverse experience that the investigator felt could not be adequately treated without knowing the identity of the study medication. Amendment #2 to the protocol, which addressed the expiration of the study supplies, allowed the identity of the study medication to be provided to a third party. The condition for such unblinding was that a patient had completed 8 weeks of the acute phase, qualified as a "responder" but no continuation study medication was available. Under this circumstance, the blind was provided by a member of the SB Worldwide Safety staff to the third party. Neither the investigator nor SB personnel associated with the trial were told the identity of the study medication.

3.5.4 Other Protocol-specified Therapy

Supportive psychotherapy for the depressive episode was provided in a manner similar to that described by Fawcett and coworkers in the Adolescent Depression Collaborative Research Group.[10] Psychotherapy was intended to provide the psychosocial interaction between the patient and the therapist that would permit observation of any pharmacotherapeutic effect of the study medication. Therefore, the sessions were to focus on providing supportive therapy rather than implementing interpersonal or cognitive/behavioral strategies. At each weekly visit, the patient had a 45-minute visit with the therapist. However, emergency contact of greater duration was permitted under unusual circumstances.

3.6 Compliance with Study Medication

Compliance with taking study medication was assessed by recording the amount of drug dispensed, taken, and returned in the CRF for each patient. The patient was instructed to return the previous interval's drug container, including any unused medication, at each visit. Non-compliance with study medication was defined as a return capsule count of less than 80% or more than 120% of the predicted capsule return count at two consecutive visits, and resulted in withdrawal of the patient from the study. Any patient who missed two consecutive visits was also to be withdrawn.

3.7 Prior and Concomitant Medication

3.7.1 Prior Medication

Antidepressants in adequate dosage (see Section 3.4.2) had to be discontinued for a minimum of 6 months, and all other psychotropic drugs had to be stopped at least 2 weeks before entry into the study. Investigational drugs were to be discontinued at least 30 days or 5 half-lives. Use of illicit drugs was forbidden and was screened out using the results from a urine sample obtained within 2 weeks before the start of the study.

3.7.2 Concomitant Medication

The patients were not allowed to take any concomitant psychotropic medications during the study. Medications that are not psychotropic, but may have CNS side effects (e.g. prednisone or antihistamines) were to be avoided or to be used for the minimum length of time consistent with good medical care.

The use of medications without any CNS effects was permitted as necessary for the treatment of medical illnesses or conditions.

All concomitant medication taken during the study was recorded in the case report form with indication, daily dose, and dates of administration.

3.8 Study Procedures

3.8.1 Schedule of Assessments

The study consisted of the following: 1) a screening period of 7-10 days to assess the suitability of a patient for inclusion into the trial; 2) a treatment period of 8

weeks in which patients were randomly assigned to receive either imipramine, paroxetine, or placebo; and 3) a continuation phase of 6 months' duration during which clinical responders were blindly continued on their randomization medication. Non responders at the end of the 8-week study were withdrawn from the study and treated in an open-label manner.

The timing of study visits and the procedures to be carried out at each visit are shown in Table 4.

Table 4 Schedule of Assessments

Assessments	**Baseline**		**Acute Phase**								**Continuation Phase**					
Time (Weeks)	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**20**	**24**	**28**	**32**
Informed Consent	X															
Medical History, Physical Exam	X															
Clinical Laboratory Studies	X									X			X			X
Serum Pregnancy Test	X						X*							X*		
EKG-12 Lead	X					X				X			X			X
EKG Rhythm Strip			X	X	X		X	X	X		X	X		X	X	
Hamilton Depression Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full K-SADS-L	X															X
Affect Section of K-SADS-L		X		X		X		X		X	X	X	X	X	X	X
C-GAS		X														
CGI-I			X	X	X	X	X	X	X	X	X	X	X	X	X	X
SADS-L		X														
FH-RDC		X														
Autonomous Functioning Checklist	X									X						
Self Perception Profile	X									X						
Sickness Impact Scale	X									X						
Randomization		X														
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Supportive Psychotherapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum/Plasma Samples for Drug Analyses		X				X				X			X			X
Study Medication Record			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Record	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* On suspicion of pregnancy

Data source: Appendix A, Protocol and Sample CRF

3.8.2 Prestudy Screening and Enrollment

Prospective patients were initially screened by telephone, and those who appeared likely to meet the study criteria were evaluated promptly thereafter at the study

site. Diagnostic assessment was done using the K-SADS-L with both the adolescent and parent(s). The K-SADS-L was developed using the adult Schedule for Affective Disorders and Schizophrenia (SADS) [11] as a point of departure and is in the form of a semi-structured clinical interview.[12] The Lifetime version includes both present and past psychiatric disorders. The parent(s) and the adolescent were interviewed separately. The clinician formed a summary rating based on the best overall information combining all sources. For those symptoms where there was significant discrepancy between information provided by the adolescent and information provided by the parent(s), the clinician, adolescent and parent(s) were to sit together, discuss the information provided by each source and reach a best conclusion. The diagnostic interviews were audiotaped at most of the study sites. However, refusal of a prospective subject to be audiotaped was not a reason to deny entry.

The K-SADS-L interview data were to be reviewed at the study site by a senior clinician (psychiatrist or psychologist), who interviewed both the adolescent and parent(s) at the first medication visit (before dispensing medication cards) and confirmed each of the positive criteria for depression. The senior clinician also reviewed each of the items for the Hamilton Depression Rating Scale.

If the diagnosis of major depressive disorder was uncertain, the investigator was to contact one of the senior investigators at a separate site to discuss the case. The external reviewer was to review the audiotape and return a decision within 2 days. The external reviewer’s opinion was to take precedence in the event that the external reviewer and the investigator disagreed on the patient’s eligibility for the study.

Following the initial assessment of the patient's eligibility and signing of the informed consent form by both the patient and parent, the 7 to 10 day screening period was used to obtain medical or psychiatric records of prior treatment and to document that the depressive symptomatology was stable. Safety evaluations, including a physical examination, clinical laboratory studies, and a cardiovascular evaluation (12-lead EKG and heart rate and blood pressure measurements) were performed during this time.

Also during the screening period, the adolescent's overall global functioning was assessed using the Child Global Assessment Scale (C-GAS). A family history was obtained on all first degree family members using the Family History-Research Diagnostic Criteria (FH-RDC). The mother was the preferred informant but the other parent or a parent surrogate could be used, if necessary.

At the end of the screening period, the patient returned to the clinic for re-evaluation. Only patients continuing to meet the inclusion criteria (DSM-III-R major depression and the Hamilton Rating Scale total score of 12 or greater) were randomized to study medication.

The Autonomous Functioning Checklist [13], Harter's Self Perception Profile for Adolescents [14], and the Sickness Impact Scale [15] modified for an adolescent, medically healthy population were administered at the end of the screening period.

3.8.3 Treatment Period

During the 8-week treatment period of the study, each patient made weekly visits to the clinic. The following assessments were performed:

- HAM-D (every visit)
- Depression section from the K-SADS-L (every other visit)
- Clinical Global Impressions (CGI) Improvement Item (every visit after baseline)
- Adverse events (every visit)
- Cardiovascular functioning
    - Electrocardiogram (12-lead EKG at Weeks 4 and 8 and rhythm strip EKG at all other visits)
    - Sitting and standing blood pressure and heart rate (every visit)
- Clinical laboratory studies (Week 8)
- Serum/plasma drug concentration (Weeks 4 and 8)
- Self Perception Profile, Autonomous Functioning Checklist and Sickness Impact Profile (Week 8)

At the end of treatment, each patient was classified as a "responder" or a "non-responder." A "responder" was defined as a patient who had either a HAM-D score ≤8 or a decrease from baseline in HAM-D total score ≥50% at this time. In addition, a patient whose HAM-D score was ≤8 at the end of the acute phase was defined as being "in remission."

Evaluation for responders who entered into the continuation phase are discussed in an addendum to this report.

3.8.4 Post-treatment Period

The following evaluations were carried out at the patient's final visit:

- HAM-D
- Full K-SADS-L
- CGI Improvement Scale
- Adverse events
- Cardiovascular functioning (12-lead EKG; sitting and standing blood pressure and heart rate)
- Clinical laboratory studies
- Serum/plasma drug concentration

If a patient was withdrawn before the end of the study, the safety evaluations (adverse events, cardiovascular functioning, and clinical laboratory studies) specified for the final visit were obtained, if possible. For early terminations a discontinuation taper over a 7-17 day period was recommended in a blinded manner. Study medication was unblinded for safety reasons only.

3.8.5 Reasons for Concluding Study

A patient could withdraw or be withdrawn from the study prior to completion for one of the following six reasons:

- Adverse experiences, including intercurrent illness
- Lack of efficacy
- Protocol deviation, including non-compliance
- Loss to follow-up
- Termination of the study by SB
- Other (reason was to be specified).

The investigator determined the primary reason for withdrawal and recorded it in the CRF. A patient who withdrew for a drug-related adverse experience was followed up for a minimum of 30 days.

3.9 Efficacy Assessments

Efficacy in the treatment of depressive symptomatology was assessed by the investigator using the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions (CGI) Improvement Scale, and the 9-item depression subscale of the K-SADS-L scale.

Effects on psychological functioning were assessed using the Self Perception Profile (SPP), the Autonomous Functioning Checklist (AFC), and the Sickness Impact Profile (SIP).

Hamilton Rating Scale for Depression (HAM-D) [8]

The HAM-D assessed the following 17 items: depressed mood; feelings of guilt; suicide; early insomnia; middle insomnia; late insomnia; work and activities; retardation; agitation; psychic anxiety; somatic anxiety; gastrointestinal somatic symptoms; general somatic symptoms; genital symptoms; hypochondriasis; loss of weight; and insight. Eight items (three insomnia items, two somatic symptom items, genital symptoms, loss of weight, and insight were graded on an ordinal scale of 0 to 2. The remaining items were graded on an ordinal scale of 0 to 4. A higher number indicates a greater severity of illness for each item.

Clinical Global Impressions (CGI) Improvement Scale [16]

The change in the severity of depression relative to baseline was rated using the CGI Improvement Scale, an ordinal scale that ranges from 1 (very much improved) to 7 (very much worse).

K-SADS-L Depression Subscale

The K-SADS is a validated schedule in assessing depression in children and adolescents. It is essentially a modification of the Schedule for Affective

Disorders and Schizophrenia (SADS, Spitzer, 1978). The version employed in this trial was an additional modification by one of the investigators, Dr. x. x. xxxxx, Ph.D., to provide for lifetime inquiry (thus the "K-SADS-L" designation). It also provided for the diagnosis of ADHD, oppositional disorder, antisocial personality disorder, social phobia, PTSD, tic schedules, and to expand the anxiety complexes.

The depression subscale of the K-SADS-L consisted of the following nine items of the full K-SADS-L affect schedule: depressed mood; excessive or inappropriate guilt; anhedonia, lack of interest, apathy, low motivation, or boredom; difficulty concentrating, inattention, or slowed thinking; psychomotor agitation; psychomotor retardation; hypersomnia; insomnia; and suicidal ideation. Depressed mood and suicidal ideation were rated on an ordinal scale from 1 to 7, and the remaining items were rated on an ordinal scale from 1 to 6. A higher number indicates a greater severity of illness for each item. The total score for the 9-item depression subscale of the K-SADS-L is 56. A comparison with the 17 item HAM-D, which has a total score of 55, is presented below in Table 5:

Table 5 Comparison of HAM-D 17-Item Scale and K-SADS-L 9-Item Depression Subscale

Symptom	HAM-D 17-Item Scale		K-SADS-L 9-Item Depression Subscale	
	# Items	Total Score	# Items	Total Score
Depressed Mood	1	4	1	7
Guilt	1	4	1	6
Suicidality	1	4	1	7
Sleep Disturbances	3	6	2	12
Work/Activity	1	5	1	6
Psychomotor Retardation	1	4	2	12
Agitation	1	4	1	6
Anxiety	2	8		
Somatic Symptoms	3	8		
Hypochondriasis	1	4		
Weight Loss	1	2		
Insight	1	4		
Total	17	55	9	56

Self Perception Profile (SPP) [14]

The Self Perception Profile for adolescents consisted of 45 pairs of “opposite” statements pertaining to issues of self-esteem. For each pair of statements, the patient was to choose the statement that reflected his/her self-perception and rate

it as being either “really true for me” or “sort of true for me”. The results of each pair of statements were coded on an ordinal scale ranging from 0 (response of “really true for me” for the statement that indicated negative self-esteem) to 3 (response of “really true for me” for the statement that indicated positive self-esteem). A total score was calculated, with a high score indicating a more positive overall perception of self-esteem.

Autonomous Functioning Checklist (AFC) [13]

The Autonomous Functioning Checklist was completed by the patient’s parent. It consisted of 78 questions grouped into 4 categories to assess the patient’s level of autonomy in performing daily activities. Twenty-two questions on self and family care, 20 questions on management, and 16 questions on recreational activities were rated on an ordinal scale ranging from 0 (“does not do”) to 4 (“does every time there is an opportunity”). Twenty questions on social and vocational activities were answered as “yes” (coded 1) or “no” (coded 0). A total score and a subscore for each of the 4 categories were calculated, with higher values indicating a greater degree of autonomy.

Sickness Impact Profile (SIP) [15]

The Sickness Impact Profile was used in a modified version appropriate for adolescent patients in good medical health. The patients rated their present health and their present quality of life on an ordinal scale ranging from 1 (very good) to 5 (very poor). Then they answered 53 questions pertaining to negative effects of illness on 6 aspects of daily living as “yes” (coded as 1) or “no” (coded as 0). The 6 aspects were sleep/rest, home management, social interaction, alertness behavior, communication, and recreation/pastimes. A total score and a subscore for each of the 6 categories were calculated, with higher values indicating a greater impact of illness on the patient’s life.

3.9.1 Primary Efficacy Parameters

The primary efficacy parameters as defined by protocol were as follows:

- The change from baseline in the total score on the HAM-D from beginning of treatment to end of the 8 week acute phase

- The percentage of responders (≥50% reduction in HAM-D and/or a HAM-D score ≤8) at the end of the acute phase

3.9.2 Secondary Efficacy Parameters

The secondary efficacy parameters for the acute phase defined by protocol were change from baseline in the following parameters:

- Depression subscale of K-SADS-L
- The CGI Improvement score
- Autonomic Function Checklist
- Self Perception Profile
- Sickness Impact Scale

Prior to opening the blind, the sponsor and investigators developed a plan to analyze the efficacy data. The plan described a definition of responders and called for additional measures of effectiveness. These included the depression items from the HAM-D and K-SADS-L instruments, and the plan provided for a status of remission. Further description of the analysis plan is provided in Section 3.13.4 and in the statistical report in Appendix A.

3.10 Safety Assessments

3.10.1 Adverse Experiences

Adverse experiences (AEs) were elicited by the investigator asking the patient a non-leading question such as ***"Do you feel differently in any way since starting the new treatment?"*** If the patient responded ***"Yes"***, details of the treatment emergent AE and its severity including any change in study drug administration, investigator attribution to study drug, any corrective therapy given, and outcome status were documented on the case report form. Attribution or relationship to study drug was judged by the investigator to be unrelated, probably unrelated, possibly related, probably related, or related. All adverse experiences were coded from the verbatim term by body system and preferred term according to the Adverse Drug Experience Coding System (ADECS), which is based on the COSTART system.

Serious Adverse Experiences

Serious adverse experiences were defined as those that were 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.

All serious adverse experiences that occurred during the study or within 30 days of receiving the last dose of study medication were reported by the investigator to the study monitor within 24 hours.

3.10.2 Laboratory Monitoring

Clinical laboratory tests were performed at the screening visit and at the end of the study week 8. These tests included hematology, clinical chemistry, and urinalysis. All laboratory tests were performed at the Clinical Trials Center of SmithKline Beecham Clinical Laboratories (SBCL) in Van Nuys, California.

The following hematology variables were measured in blood: hemoglobin; hematocrit; red blood cell (RBC) count; mean corpuscle hemoglobin; mean corpuscle volume; white blood cell (WBC) count, including total and differential; and platelet count.

The following clinical chemistry variables were measured in serum: liver function tests (consisting of total bilirubin, alkaline phosphatase, SGOT, and SGPT); renal function tests (consisting of blood urea nitrogen and creatinine), at screening only; human chorionic gonadotrophin (HCG), only in females of child-bearing potential; and other tests (consisting of albumin, globulin, total protein, uric acid, and random glucose).

Urine specimens were tested using dipstick for the presence of protein and glucose. If protein was noted, microscopy was performed. In addition, a urine test for drugs of abuse was performed at the screening visit.

Any laboratory abnormalities considered clinically significant were to be recorded in the adverse experience pages of the CRF. In addition, laboratory values of clinical concern were defined by the sponsor and tabulated.

3.10.3 Vital Signs and Body Weight

Sitting and standing blood pressures and heart rates were measured at every clinic visit, as was body weight. Values of clinical concern were defined by the sponsor and tabulated.

3.10.4 Electrocardiogram

Twelve-lead EKGs were obtained at the screening evaluation and after 4 and 8 weeks of treatment. Rhythm strip EKGs were obtained at all other clinic visits. All clinically significant abnormalities were to be recorded in the adverse experience pages of the CRF.

3.10.5 Pregnancy Tests

Serum for assay of human chorionogonadotrophin (HCG) was obtained from all female patients of childbearing potential at the screening visit. Serum was also to be obtained at the week 5 and 24 visits or at any other time during the study if pregnancy was suspected. The samples were assayed for serum HCG at SBCL, and the results were reported promptly to the investigator.

Any patient who became pregnant during the study was withdrawn from the study immediately. In addition, any patient who discovered that she had become pregnant during the study or within 30 days (or 5 half-lives, whichever was longer) after the treatment period was to notify the investigator of this fact. Whenever possible, the pregnancy was to be followed to term, any premature termination reported, and the status of mother and child after delivery reported to SB.

3.11 Plasma/Serum Concentrations

Serum samples to be assayed for imipramine and desipramine concentrations and plasma samples to be assayed for paroxetine concentrations were obtained at baseline and after 4 and 8 weeks of treatment. Patients scheduled for a morning clinic visit were to delay taking their morning dose of study drug until after completion of the blood draws, while patients scheduled for a visit later in the day were to take their morning dose as usual.

Blood (10 mL) for imipramine/desipramine assay was drawn into red-topped tubes and allowed to clot. Following centrifugation, the serum sample (≥3 mL) was transferred to a plastic screw-cap vial and shipped to the Clinical Trials

Center at SBCL. The serum samples were assayed immediately using a standard high-pressure liquid chromatography (HPLC) method for detection of tricyclic antidepressants. Following addition of protriptyline as an internal standard, each sample was extracted with hexane and isoamyl alcohol at basic pH. The organic layer was separated, evaporated to dryness, and reconstituted with mobile phase before injection onto the HPLC. Imipramine and desipramine were chromatographed using a cyano column (Supelco) and detected using ultraviolet absorbance at 215 nm. For both analytes, the standard curve was linear from 25 to 750 ng/mL (mcg/L), the coefficient of variation for replicate low and high control samples was ≤10%, and the detection limit was determined to be 25 ng/mL (mcg/L).

The imipramine and desipramine results were blinded on the lab report sent to the investigator. However, if the sum of the imipramine and desipramine concentrations exceeded 500 mcg/L (500 ng/mL), the investigator was notified by telephone, and the patient was withdrawn from imipramine treatment (see Section 3.5.2).

Blood (5 mL) for paroxetine assay was drawn into lavender-topped tubes, mixed, and centrifuged. The plasma sample (≥ 2 mL) was transferred to the inner vial of a “vial within a vial” and frozen. The frozen samples were shipped to SBCL and stored there in a frozen state until assayed in batch mode using a previously validated HPLC method. Following addition of protriptyline as an internal standard, interfering substances were removed from the samples by applying them to C-2 solid-phase columns. Paroxetine was eluted with 0.3 N HCl in methanol. The eluates were dried and reconstituted in mobile phase prior to injection onto the HPLC. Paroxetine was chromatographed using a cyano-propyl column (Supelco) and detected using ultraviolet absorbance at 215 nm. Any sample with a paroxetine concentration above 200 ng/mL was re-assayed following dilution with water. The standard curve was linear from 20 to 200 ng/mL. Coefficients of variation for replicates were 13.2% for low controls (25 ng/mL) and 9.7% for high controls (125 ng/mL). The detection limit was determined to be 10 ng/mL.

Blood levels for paroxetine, imipramine, and desimipramine will be reported separately with the continuation phase data as an addendem to this report.

3.12 Data Quality Assurance

To the best of our knowledge, this study was conducted according to Good Clinical Practices. Pharmaco LSR, Inc. (Austin, TX), a Contract Research

Organization (CRO), was employed to perform data management according to an agreed contract. The responsibilities of Pharmaco were conducted according to its standard operating procedures (SOPs), consistent with guidelines provided by SB.

Upon receipt at SB, the case report forms (CRFs) were photocopied and forwarded to Pharmaco, where they were manually reviewed for completeness and accuracy according to pre-determined monitoring guidelines. Any issues or inconsistencies arising from this review were resolved according to SB standard data management practices, in conjunction with the SB medical monitor, clinical investigation staff, and the external investigators. The data were then entered by Pharmaco and transferred and loaded onto the SB database.

Subsequent data handling and reporting processes were subject to in-process Quality Control at SB. Programmed computer validations were run against the database to test the reasonableness of the data. A final audit of the frozen database against the CRF was performed, in which approximately five percent of the patient population was randomly selected. This audit showed an error rate less than 0.5 percent for the database as a whole.

Except for the data entry and management functions performed by Pharmaco, all of the above procedures were performed according to methodologies detailed in SmithKline Beecham's SOPs.

This study was subject to audit by SmithKline Beecham's department of Worldwide Regulatory - GCP (WRC-GCP). A list of audited sites can be found in Appendix A.

3.13 Statistical Evaluation

A description of the statistical analyses can be found in the Statistical Appendix. The data are presented in the form of data listings and tables of counts, means and standard deviations/standard error. These listings and tables were obtained using the Statistical Analysis System (SAS) statistical package, Version 6.08.

Summary tables of demographic and baseline characteristics, safety variables, and secondary efficacy variables are presented for the intent-to-treat population only. Summary tables of the primary efficacy variables are presented for both the intent-to-treat and the per-protocol efficacy populations.

Data listings are presented for all patients and support the summary tables. Although the tables for this report describe data from the acute phase, the listings,

which present individual patient information, provide the data from both the acute and continuation phase. This allows a reviewer to follow an individual patient's participation through the entire study.

3.13.1 Comparison of Interest

The comparisons of interest were paroxetine vs. placebo and imipramine vs. placebo. Hypotheses concerning these comparisons were tested at the alpha level of 0.05 using the acute phase (8 week) data of the study. No comparisons were made between paroxetine and imipramine.

3.13.2 Target Sample Size

The sample size of the study was chosen to ensure adequate power for detection of a difference between both of the active treatments and placebo with a two tailed alpha level of 0.05 and a power of 0.80. A difference was defined as a between-treatment difference in the change from baseline of total HAM-D score that was 4.0 at the endpoint of the acute phase. A standard deviation of 10 was initially chosen to reflect the greater variability in response expected in an adolescent population. Subsequently, the standard deviation of the HAM-D scores was found to be 8 in a blinded evaluation of approximately 100 patients. Therefore, a total population of 275 patients was expected to provide adequate power to detect a difference according to the criteria outlined above.

3.13.3 Method of Randomization

A computer-generated randomization list of 360 numbers for the acute phase was generated in which the treatments were balanced in blocks of 6 consecutive patients. Each investigator was allocated a block of consecutively numbered treatment packs, and patients were assigned treatment numbers in strict sequential order. Patients were randomized in a 1:1:1 ratio to treatment with paroxetine, imipramine, or placebo.

3.13.4 Planned Efficacy Evaluations

No interim analyses were planned for the study.

Primary Efficacy Variables

The protocol defined the primary efficacy parameters for comparing the efficacy of each active treatment with that of placebo to be:

- The change from baseline in total HAM-D score at endpoint of the acute phase.

- The percentage of responders at the endpoint of the acute phase.

Initially the protocol defined a "responder" as a patient whose HAM-D at endpoint was at least 50% lower than the baseline score. This definition was to be used as "operational" criteria for entry into the continuation phase.

Prior to opening the blind, the sponsor and the investigators developed an analytical plan. Among other issues, this agreed plan included a definition of a "responder" and a "remission" status. The intent was to provide a robust definition of "response" and to describe a status of "remission" in order to provide a rigorous anchor point in analyzing relapses in the continuation phase.

The agreed analytical plan described a "responder" as a patient whose HAM-D score was 8 or less or was reduced from baseline by at least 50%. The remission status was defined as a HAM-D score of 8 or less.

The agreed analytical plan also called for the following measure of effectiveness to be included in the analysis: the 9-item depression subscale of the K-SADS-L, the depression item from both the HAM-D and the K-SADS-L, and two methodologies for analyzing the clinical global improvement score: 1) the mean scores and 2) the proportion of patients with rating of "1" or "2" ("very much" or "much improved" respectively). The initial protocol described the K-SADS-L and CGI instruments as secondary measures.

The protocol defined as secondary measures the behavior and functional instruments. These included the Autonomic Function Checklist (AFC), the Self-Perception Profile (SPP), and the Sickness Impact Scale (SIP). The agreed analytical plan included a time to sustained response and various subsidiary covariate analysis of response as secondary analyses.

3.13.5 Methods of Analysis

The demographic characteristics, description of the baseline depressive episode, additional psychiatric diagnoses, and personal history variables of the patients were summarized descriptively by treatment group.

Tests of hypotheses regarding model assumptions, such as the significance of treatment-by-investigator interactions, were made at the 10% level. All other statistical tests were two-tailed and performed at the 5% significance level.

Endpoint was defined as the patient's last observed assessment (i.e., last observation carried forward [LOCF] dataset) during the acute phase of the study.

Changes from baseline to endpoint in the total HAM-D score were analyzed by using an analysis of variance (ANOVA) via the General Linear Models (GLM) procedure of SAS. The model included terms for treatment group (paroxetine, imipramine, and placebo) and investigator. Since interaction was not significant ($p>0.10$), it was dropped from the model. Pair-wise comparisons between paroxetine and placebo and between imipramine and placebo were made at the 0.05 level of significance using the CONTRAST statement.

In addition to the endpoint analyses, analyses of the efficacy variables were done at each weekly visit using the model determined from the endpoint analyses.

Analysis of covariance was used to evaluate the effect of possibly important prognostic variables using the endpoint of responders (defined by 50% reduction or score of 8 or less in the total HAM-D). These included endogenous subtype, age at onset, number of prior episodes, comorbidity with separate anxiety disorder.

CGI Improvement Scale scores and changes from baseline in the 9-item depression subscale of the K-SADS-L were analyzed using analysis of variance as described above for the change from baseline in HAM-D scores.

Categorical variables (e.g., the percent of patients who responded to treatment) were analyzed using logistic analysis via the Categorical Modeling (CATMOD) procedure of SAS. The model included terms for treatment group and investigator. The nonsignificant ($p>0.10$) interaction effect was removed from the model. Pair-wise comparisons between treatments were made at the 0.05 level of significance using the CONTRAST statement.

3.13.6 Populations/Data Sets to be Evaluated

Intent-to-Treat Efficacy Population

The intent-to-treat efficacy population consisted of all patients who were randomized to study medication and had at least one post-treatment efficacy evaluation. The intent-to-treat population was the primary population in the efficacy analyses.

Per-Protocol Efficacy Population

A per-protocol patient population was identified from the intent-to-treat population and excluded those patients for whom any of the following applied:

1 Compliance < 80% or >120% on two consecutive visits

2 C-GAS score ≥ 60 at screening

3 Younger than 12 years or older than 18 years

4 Not in an episode of major depression for at least 8 weeks

5 HAM-D score < 12 on the first 17 items at screen or baseline visit

6 An adequate trial of antidepressants within 6 months prior to beginning the study. An adequate trial was defined as treatment for 4 or more weeks with imipramine, desipramine, or amitriptyline at a dosage of 150 mg/day or higher, with nortriptyline at a dosage of 50 mg/day or higher, or with fluoxetine at a dosage of 20 mg/day or higher.

7 Use of an investigational drug within 30 days of entry into the study or within five half lives of the investigational drug (the longer period applied)

8 Current use of (1) psychotropic medication including anticonvulsants, anxiolytics, neuroleptics, lithium carbonate, (2) any illicit drug, as documented by a drug screen within 2 weeks of starting the study

9 Suicidal ideation with a definite plan, or made a suicide attempt within the current episode, or made a suicide attempt by medication overdose

10 Did not give written informed consent

11 Evidence of organic brain disease, epilepsy, or mental retardation

12 A medical illness which contraindicated the use of heterocyclic antidepressants (e.g., cardiovascular disease)

13 Did not have an IQ ≥ 80

14 Not medically healthy at screening

15 A current diagnosis (within 12 months) or post-traumatic stress disorder

16 Have or had a diagnosis of bipolar disorder, schizo-affective disorder, anorexia, bulimia, alcohol or drug abuse/dependence, obsessive/compulsive disorder, autism/pervasive mental disorder, or organic psychiatric disorder

Only the primary efficacy variables were analyzed for the per protocol population.

Defined Datasets

Two datasets were considered in the analysis of the efficacy data:

1 Last Observation Carried Forward (LOCF) Dataset

This dataset consists of each patient's last on-therapy assessment of the acute phase. If the first visit on the active treatment was missing, the baseline visit was not used to extend forward.

2 Observed Cases (OC) Datasets

The observed cases dataset consists of each patient's observation at each visit. Missing data are not estimated.

Defined Timepoints

Day 1 was defined as the day on which the randomized, double-blind study medication was started. Assessments were included in the analyses at a particular timepoint (study week) if they occurred within the following day windows relative to Day 1:

Timepoint		Day Window
Week 1	=	Days 1 to 11
Week 2	=	Days 12 to 18
Week 3	=	Days 19 to 25
Week 4	=	Days 26 to 32
Week 5	=	Days 33 to 39
Week 6	=	Days 40 to 46
Week 7	=	Days 47 to 53
Week 8	=	Days 53 to 70

If multiple observations for a patient fell into a visit window, then the last (furthest from the start of the study) observation was used to represent that patient's result for that time period in the tabulations and analyses. However, all values within a visit window were presented in the data listings.

3.13.7 Safety Evaluations

These analyses were performed only on the intent-to-treat population, which consisted of all patients who received double-blind medication.

Adverse Experiences

Adverse experiences were coded for each subject with reference to body system and preferred terms using the ADECS coding dictionary. The incidence of adverse experiences was tabulated by treatment group with reference to both preferred term and body system and summarized using descriptive statistics.

Summary narratives were written for patients with adverse experiences that were serious (Data Source Tables 14.8 and 14.8.a in Section 12) or led to withdrawal from the study (Data Source Tables 14.9.1 and 14.9.1.a in Section 12).

Vital Signs and Body Weight

Based on clinical criteria, a normal range and a change from baseline were identified for blood pressure, heart rate, and body weight. These are shown in Table 6.

Table 6 Criteria for Assessment of Vital Signs

		Predetermined Change	
Variable	**Normal Range**	**Decrease**	**Increase**
Systolic BP (mmHg)	90-180	-30	+40
Diastolic BP (mmHg)	50-105	-20	+30
Pulse rate (bpm)	50-120	-30	+30
Body weight (lb)	-	-7%	+7%

Source: Appendix A

A low value was considered to be of clinical concern and was flagged as "L" if it represented a decrease from baseline greater than the pre-determined value in Table 6 and was below the normal range, if applicable. Similarly, a high value of clinical concern was flagged as "H" if it represented an increase from the baseline value larger than the pre-determined value and was above the normal range, if applicable. Summary narratives were written for patients with vital sign or body weight values that were of potential clinical concern (Data Source Table 14.12.a in Section 12).

Summary statistics for vital sign variables are presented by study week and at endpoint.

Laboratory Data

Laboratory values were compared with the appropriate normal ranges and also with extended ranges. A Table of the extended ranges can be found in Section 6.10. Values above or below these extended ranges were considered to be of potential clinical concern. Summary narratives were written for patients with laboratory values of potential clinical concern (Data Source Table 14.14.a in Section 12).

Summary statistics for clinical laboratory variables are presented by study week and at endpoint.

Electrocardiograms (EKGs)

Findings in the screening or baseline EKGs that the investigator judged to be clinically important and findings in post-treatment EKGs that indicated a clinically important change from baseline were to be recorded on the Adverse Event page of the CRF.

Serum Concentrations of Imipramine and Desipramine

These data were presented as listing and tabulated using summary statistics. Patients who had a total serum concentrations of imipramine and desipramine that exceeded 500 mcg/L (500 ng/mL) were to be withdrawn from the study. Serum drug levels will be reported separately.

Serum Pregnancy Tests

Serum pregnancy test results are reported in the listing of laboratory results by treatment group and patient (Appendix F.1). Any positive result was to be reported to the investigator by the laboratory immediately, so that the patient could be withdrawn from the study.

4 Study Populations

4.1 Study Dates

The first patient received study medication on 20 April 94, the final patient was enrolled on 15 March 1997. The final study visit for the acute phase occurred on 07 May 1997, the final study visit for the continuation phase occurred on 15 February 1998.

4.2 Patient Disposition

4.2.1 Number and Distribution of Patients

A total of 275 patients was entered into the study at 12 centers, ten of the centers were in the United States and two centers were in Canada. Of the 275 patients randomized, a total of 190 completed the 8 week acute phase treatment period; 67 (72.0%) in the paroxetine group, 57 (60.0%) in the imipramine group, and 66 (75.9%) in the placebo group. The number of patients randomized at each study center and the number who completed treatment is shown by treatment group in Table 7.

Table 7 Number of Patients Who Were Randomized (R) to Each Treatment Group and Who Completed* (C) Acute Phase of Treatment at Each Center

			Treatment Group					
Center	**Investigator**		**Paroxetine**		**Imipramine**		**Placebo**	
No.	**Last Name**	**Site**	**R**	**C**	**R**	**C**	**R**	**C**
001		St. Louis, MO	7	3	5	1	6	4
002		Providence, RI	9	6	11	6	10	10
003		New York, NY	10	8	14	9	11	10
004		Toronto	5	3	4	1	4	2
005		Pittsburgh, PA	16	14	15	10	14	13
006		Los Angeles,	4	3	2	1	3	2
007		Galveston, TX	9	5	7	1	5	4
008		Portland, OR	5	5	6	5	3	3
009		Dallas, TX	17	13	18	13	18	9
010		Columbus, OH	3	2	2	2	4	3
011		Stony Brook, NY	2	1	5	4	4	3
012		Halifax, Nova Scotia	6	4	6	4	5	3
		Total	**93**	**67**	**95**	**57**	**87**	**66**

Source: Data Source Table 12.1and 12.2 in Section 10; Patient Data Listing in Appendix B.1; Investigator CV in Appendix A

*Completed treatment is defined as receiving 8 weeks of study medication.

4.2.2 Number of Patients Present at Each Visit

The number of randomized patients who remained at each study visit is presented by treatment group in Table 8. The weeks identified in table 8 are the visit windows as defined in the analytical plan (Section 3.13.3).

Table 8 Number of Patients Remaining in the Study by Visit and Treatment Group

		Treatment Group			
		Paroxetine	Imipramine	Placebo	Total
Phase	**Visit**				
Randomization	**Baseline**	**93**	**95**	**87**	**275**
Acute phase	Week 1	86	91	85	262
	Week 2	80	83	80	243
	Week 3	78	79	76	233
	Week 4	76	75	75	226
	Week 5	75	68	70	213
	Week 6	72	61	70	203
	Week 7	68	57	67	192
	Week 8	67	57	66	190

Source: Data Source Table 12.2 in Section 10; Patient Data Listing in Appendix B.1
N.B. Visits defined by analytical plan (see Section 3.13.3)

4.2.3 Withdrawal Reasons

There were 85 (31%) patients who failed to complete the 8 weeks of the acute phase. The number of patients who withdrew and the reasons for withdrawal are shown in Table 9. The imipramine group had a higher percentage of patients stopping treatment than either the paroxetine or the placebo group. The predominant reasons for stopping imipramine therapy were adverse events, and the predominant events were cardiovascular in nature (13 patients). A description of all the adverse events leading to withdrawal is presented in section 6.7. There were no significant differences among the treatment regimens for withdrawals for lack of efficacy, protocol violations, or other non-treatment related reasons.

Table 9 Number (%) of Randomized Patients Who Completed or Were Withdrawn from the Study, by Reason for Withdrawal

STUDY CONCLUSION STATUS	Treatment Group			
	Paroxetine	**Imipramine**	**Placebo**	**Total**
	(N=93)	**(N=95)**	**(N=87)**	**(N=275)**
COMPLETED	67 (72.0%)	57 (60.0%)	66 (75.9%)	190 (69.1%)
Withdrawal Reason				
Adverse Experiences	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*	5 (5.4%)	1 (1.1%)	1 (1.1%)	7 (2.5%)
WITHDRAWN	26 (28.0%)	38 (40.0%)	21 (24.1%)	85 (30.9%)

Source: Data Source Table 12.3 in Section 10; Patient Data Listing in Appendix B.1
* Other includes patients who withdrew consent

Table 10 shows the numbers of patients who withdrew at each weekly interval. For the paroxetine and the placebo groups, the withdrawals for adverse events occurred more often early in treatment. In contrast, withdrawals for adverse events in the imipramine group occurred throughout the 8 week period. Withdrawals for lack of effect occurred during the latter weeks of the study in all groups. Only one imipramine patient stopped drug because of the lack of therapeutic benefit. A review of the reasons for stopping therapy other than for an adverse event or for lack of efficacy reveals no apparent association with time of treatment.

Table 10 Number and Cumulative Percentage of Patients Withdrawn from the Study by Reason and by Week

Study	Paroxetine (N=93)				Imipramine (N=95)				Placebo (N=87)			
Week	AE	LOE	Other	Total	AE	LOE	Other	Total	AE	LOE	Other	Total
	n	n	n	n (%)	n	n	n	n (%)	n	n	n	n (%)
Week 1	2	0	5	7 (26.9%)	2	0	2	4 (10.5%)	1	0	1	2 (9.5%)
Week 2	4	0	2	13 (50.0%)	7	0	1	12 (31.6%)	2	0	3	7 (33.3%)
Week 3	0	0	2	15 (57.7%)	4	0	0	16 (42.1%)	3	0	1	11 (52.4%)
Week 4	0	0	2	17 (65.4%)	3	0	1	20 (32.6%)	0	0	1	12 (57.1%)
Week 5	0	1	0	18 (69.2%)	5	0	2	27 (71.1%)	0	2	3	17 (81.0%)
Week 6	0	2	1	21 (80.8%)	6	1	0	34 (89.5%)	0	0	0	17 (81.0%)
Week 7	2	1	1	25 (96.2%)	3	0	1	38 (100.0%)	0	3	0	20 (95.2%)
Week 8	1	0	0	26 (100.0%)	0	0	0	38 (100.0%)	0	1	0	21 (100.0%)
Total	9	4	13	26	30	1	7	38	6	6	9	21

Source: Data Source Table 12.4 in Section 10; Patient Data Listing in Appendix B.1
Key: AE, adverse experiences; LOE, lack of efficacy; Other, includes protocol violations, lost to follow-up, etc.

4.3 Protocol Violations

4.3.1 Protocol Violations Excluded from the Per-Protocol Population

Prior to opening the study blind the sponsor reviewed all cases for protocol violations relative to the study entry criteria and violations relative to compliance to the study medication. This analysis identified thirty (30) patients, 13 (14.0%) in the paroxetine group, 10 (10.3%) in the imipramine group, and 7 (8.9%) in the placebo group who violated the protocol sufficiently to be excluded from the per-protocol population.

The number of patients in each treatment group and the reasons for exclusion are summarized in Table 11. The most common reason for exclusion was a functional score of greater than 60 on the C-GAS. This instrument is scored 0 to 100 based on psychiatric symptoms and the impact these symptoms have on functioning at home, at school, and with peers and family. Scores above 60 signify milder functional impairment. However, the violation here may be minor. This is because the case record form only provided for discrete units of 10. All of the 16 patients with C-GAS scores of >60 were identified as having a score between 61 and 70. However, as a conservative approach, these patients were excluded from the per-protocol analysis. Other entry criteria violations were infrequent.

Nine patients were judged to be non-compliant with study medication, i.e. they took <80% on two consecutive visit. None were in the placebo group.

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Table 11 Numbers of Patients With Protocol Violations Leading to Exclusion From the Per-Protocol Analysis

	Treatment Group			
Protocol Violations	**Paroxetine**	**Imipramine**	**Placebo**	**Total**
	N = 93	**N = 95**	**N = 87**	**N = 275**
	n	**n**	**n**	**n = 30 (10.9%)**
C-Gas Score ≥ 60 at screening	6	5	5	16 (5.8%)
Medical/surgical history and physical examination findings	1	1	0	2 (0.7%)
Disallowed medications taken within 6 months prior to screening	0	0	1	1 (0.4%)
Younger than 12 years	1	0	0	1 (0.4%)
Not in an episode of major depression for at least 8 weeks	0	0	1	1 (0.4%)
Non Compliance	5	4	0	9 (3.3%)

Data Source: Table 1 Statistical Report in Appendix A

4.3.2 Protocol Deviations Included in the Per-Protocol Population

There were 28 (10.2%) patients with other protocol exceptions which were not considered serious enough to exclude them from the per-protocol analyses. These exceptions have been termed "protocol deviations" and are presented in Table 12.

Twelve patients (patients 329.003.00080, 329.003.00081, 329.003.00094, 329.003.00247, 329.003.00250, 329.003.00251, 329.003.00290, 329.003.00291, 329.003.00292, 329.003.00315, 329.003.00316, and 329.003.00317) listed as having HAM-D scores < 12 on the first 17 items at screen were actually patients who were missing screening HAM-D scores due to a procedural error at one center. These 12 patients all had baseline scores ≥12. All HAM-D scores are listed in Appendix C.2.

Ten patients had currently used psychotropic medications. In the paroxetine group, Patient 329.002.00245 had taken sertraline for 14 days and stopped 14 days prior to screening, Patient 329.009.00204 had taken methylphenidate for 14 days and stopped 12 days prior to screening, Patient 329.009.00303 had taken fluoxetine for 7 days and stopped 8 days prior to screening, and Patient 329.012.00220 had taken methylphenidate SR for almost 4 months and stopped 19 days prior to screening. In the imipramine group, Patient 329.008.00192 had taken methylphenidate for 18 months and stopped 13 days prior to screening. In the placebo group, Patient 329.009.00135 had taken amitriptyline for 2 days and

stopped 1 day prior to screening, Patient 329.009.00330 had taken pemoline for 1 day and stopped 7 days prior to screening, and Patient 329.012.00218 had taken clonazepam for 3 days and stopped 18 days prior to screening. Patient 329.004.00018 received diazepam for one day and patient 329.012.00027 received lorazepam for six days during the study. In the imipramine group, Patient 329.002.00057 tested positive for cannabis on a drug screen; however, the patient was authorized by the sponsor to continue in the study. Patient 329.012.00227 also tested positive for cannabis during the study. The number of patients in each treatment group with protocol deviations is summarized in Table 12.

Table 12 Numbers of Patients With Protocol Deviations Included in the Per-Protocol Analysis

	Treatment Group			
Protocol Deviations	**Paroxetine**	**Imipramine**	**Placebo**	**Total**
	N = 93	**N = 95**	**N = 87**	**N = 275**
Total number of patients with protocol deviations	**n = 8**	**n = 8**	**n = 12**	**n = 28 (10.2%)**
HAM-D score < 12 on first 17 items of screen	4	3	5	12 (4.4%)
Current use of				
(1) psychotropic medication:	4	1	5	10 (3.6%)
(2) illicit drugs	0	2	0	2 (0.7%)
Females of child-bearing potential not practicing protocol-approved birth control	0	2	1	3 (1.1%)
Did not undergo down-titration at end of study	0	0	1	1 (0.4%)

Data Source: Appendix B.13 and B.14, C.1 and C.2

The investigators at all 12 centers enrolled patients with symptoms compatible with the criteria for a major depressive episode. The sponsor reviewed the K-SADS-L symptoms at baseline and compared them to the diagnostic symptom criteria for a major depressive episode specified in the DSM-IIIR. This review verified that out of a randomized population of 275 patients, 269 patients (98%) met the minimum number of symptoms (five) required for the diagnosis and that the severity of these index symptoms was at least moderate (score of 4 or more) in severity. The remaining six patients all had the required severity score of 4 or greater for depressed mood or irritability and anger, but had less than sufficient severity on one of the four other symptoms. These six patients were not considered as exceptions to the protocol and were included in the per protocol analysis.

4.4 Demographic and Baseline Characteristics

4.4.1 Demographic Characteristics

Table 13 summarizes the demographic characteristics of all patients who entered the study. There were more female than male patients and more than 80% of the patients were Caucasian in all three treatment groups. In the paroxetine and imipramine treatment groups, more patients fell between the ages of 14 - 15 years than in the placebo group where there were more patients between 16-17 years of age. There were few patients 18 years of age in all treatment groups. One patient (329.007.00140) in the paroxetine group entered the study at age 11 years 10 months, which was under the required age of 12 years. Demographic characteristics were generally balanced among the three treatment groups.

Table 13 Demographic Characteristics of Randomized Patients

		Treatment Group		
Demographic Characteristic		**Paroxetine (N=93)**	**Imipramine (N=95)**	**Placebo (N=87)**
Sex				
	Male	35 (37.6%)	39 (41.1%)	30 (34.5%)
	Female	58 (62.4%)	56 (58.9%)	57 (65.5%)
Age (years)				
	<12	1 (1.1%)	0 (0.0%)	0 (0.0%)
	≥12 but <14	19 (20.4%)	24 (25.3%)	18 (20.8%)
	≥14 but <16	38 (40.9%)	35 (36.8%)	27 (31.0%)
	≥16 but <18	32 (34.4%)	31 (32.6%)	39 (44.8%)
	≥18 but <19	3 (3.2%)	5 (5.3%)	3 (3.4%)
	Mean ± SD	14.8 ± 1.6	14.9 ± 1.6	15.1 ± 1.6
Race				
	Caucasian	77 (82.8%)	83 (87.4%)	70 (80.5%)
	Black	5 (5.4%)	3 (3.2%)	6 (6.9%)
	Oriental	1 (1.1%)	2 (2.1%)	2 (2.3%)
	Other	10 (10.8%)	7 (7.4%)	9 (10.3%)
Weight (lb)		(n=88)	(n=91)	(n=84)
	Mean ± SD	146.3 ± 38.9	139.4 ± 36.7	145.3 ± 40.8
	Range	74.0 - 308.3	76.0 - 261	80.9 - 287.6
Height (in)		(n=88)	(n=91)	(n=84)
	Mean ± SD	65.4 ± 3.51	64.6 ± 4.81	65.1 ± 4.11
	Range	54.0 - 76.0	52.0 - 80.0	56.0 - 75.0

Source: Data Source Tables 12.5.1 & 12.5.2 in Section 10; Patient Data Listings in Appendix B.2 & E.1

4.4.2 Baseline Characteristics

Table 14 summarizes baseline characteristics regarding the psychiatric profile for all patients in the intent-to-treat population. The three groups were balanced in terms of baseline characteristics. Most of the patients were in their initial depressive episode and almost all had a first degree relative with a diagnosis of major depression. About a third had features of melancholy. Approximately half the patients in each treatment arm were reported to have symptoms of one or more concomitant psychiatric disorder. The predominant cormorbid symptoms were anxiety related such as separation anxiety and social phobia. Also common were features of externalizing disorders to include attention deficit problems, and conduct and various behavioral problems.

A summary of patients personal history including parent education level and occupation is presented by group in Table 12.8 in Section 10 and Appendix B.5.

Table 14 Baseline Characteristics Regarding Major Depressive Disorder of All Randomized Patients

Baseline Characteristic	Treatment Group		
	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Screening C-GAS score			
Mean (SD)	42.7 ± 7.5	42.5 ± 7.4	42.8 ± 8.2
Duration of current episode (mo)			
Mean (SD)	14 ± 18	14 ± 18	13 ± 17
Number of depressive episodes			
1	81%	79%	77%
2	12%	14%	14%
≥ 3	7%	6%	8%
Family history of major depression			
	86%	90%	95%
Age at onset of first episode (yr)			
Mean (SD)	13.1 ± 2.8	13.2 ± 2.7	13.5 ± 2.3
Features of Melancholic/endogenous depression[1]			
	37%	35%	40%
Features of Atypical depression[1]			
	25%	16%	9%
Concomitant diagnosis			
Any concomitant diagnosis[1]	41%	50%	45%
Anxiety disorder [1,2]	19%	26%	28%
Externalizing disorder [1,3]	25%	26%	20%

Source: Data Source Tables 12.6, 12.20, 12.21, 12.22, 12.23, 12.24, 12.25, 12.26, 12.27, 12.28 in Section 10; Patient Data Listings in Appendix B.3, B.4, B.6, C.1 & C.2

[1] Items from the K-SADS-L

[2] Includes separation anxiety, panic with or without agoraphobia, agoraphobia, social phobia, and generalized anxiety.

[3] Includes conduct disorder, oppositional defiant disorder, and attention deficit/hyperactivity.

4.5 Presenting Conditions and Medical History

Table 15 shows medical or surgical conditions occurring at baseline in 3 or more patients in any treatment group for the intent-to-treat population. Various operations were the most commonly occurring conditions across all three treatment groups. These included ear and hernia repair, and nose and mouth procedures. A history of various respiratory system illnesses occurred in approximately 10% of the study population somewhat more frequently in the imipramine and placebo treatment groups than in the paroxetine group, and in all groups consisted mostly of asthma. Acute nasopharyngitis occurred slightly more

frequently in the placebo group. Across all groups, there were no unexpected trends in medical or surgical history findings.

Table 15 Medical or Surgical Conditions Occurring in 3 or More of Patients in Any Treatment Group at Baseline (number (%) of patients)

Medical/Surgical Condition	Treatment Group			Total
	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)	(N=275)
Any medical/surgical condition	33 (35.5%)	42 (44.2%)	38 (43.7%)	113 (41.1%)
Operations (all)	11 (11.8%)	11 (11.6%)	13 (14.9%)	35 (12.7%)
Asthma	3 (3.2%)	5 (5.3%)	4 (4.6%)	12 (4.4%)
Upper limb fracture	2 (2.2%)	2 (2.1%)	4 (4.6%)	8 (2.9%)
Sprains/strains	0 (0.0%)	3 (3.2%)	4 (4.6%)	7 (2.5%)
Chlamydia	1 (1.1%)	2 (2.1%)	3 (3.4%)	6 (2.2%)
Otitis media	0 (0.0%)	4 (4.2%)	1 (1.1%)	5 (1.8%)
Pregnancy, complications*	0 (0.0%)	3 (5.4%)	1 (1.8%)	4 (2.3%)
Nasopharyngitis, acute	0 (0.0%)	1 (1.1%)	3 (3.4%)	4 (1.5%)

Source: Data Source Table 12.9 in Section 10; Patient Data Listings in Appendix B.7 and B.8.
Note: Condition was indicated as being "previous" in the medical/surgical history or presenting condition pages of the CRF.
* Adjusted for gender

Table 16 shows the medical conditions occurring in 3 or more of patients in any treatment group at baseline. The most common presenting condition across all three treatment groups was headache which was reported to occur in more than 30% of patients in all treatment groups. Other common presenting conditions were allergic rhinitis and genital female disorders.

Table 16 Presenting Conditions Occurring in 3 or More of Patients in Any Treatment Group at Baseline (number (%) of patients)

Presenting Condition	Treatment Group			Total
	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)	(N=275)
Headache	41 (44.1%)	34 (35.8%)	28 (32.2%)	103 (37.5%)
Genital female disorder*	4 (6.9%)	12 (21.4%)	7 (12.3%)	23 (13.5%)
Rhinitis, allergic	6 (6.5%)	8 (8.4%)	9 (10.3%)	23 (8.4%)
Skin/subcutaneous disorder, other	7 (7.5%)	6 (6.3%)	6 (6.9%)	19 (6.9%)
Asthma	6 (6.5%)	9 (9.5%)	3 (3.4%)	18 (6.5%)
Abdomino-plevic pain	6 (6.5%)	5 (5.3%)	5 (5.7%)	16 (5.8%)
Allergy, nec	5 (5.4%)	5 (5.3%)	0 (0.0%)	10 (3.6%)
Obesity	3 (3.2%)	1 (1.1%)	5 (5.7%)	9 (3.3%)
Sinusitis, nos	2 (2.2%)	1 (1.1%)	3 (3.4%)	6 (2.2%)
Back pain	2 (2.2%)	0 (0.0%)	3 (3.4%)	5 (1.8%)
Nasopharyngitis, acute	1 (1.1%)	4 (4.2%)	0 (0.0%)	5 (1.8%)
Insomnia	1 (1.1%)	3 (3.2%)	1 (1.1%)	5 (1.8%)
Otitis media	0 (0.0%)	1 (1.1%)	4 (4.6%)	5 (1.8%)
Upper respiratory disorder, other	2 (2.2%)	0 (0.0%)	3 (3.4%)	5 (1.8%)
Nausea	3 (3.2%)	1 (1.1%)	0 (0.0%)	4 (1.5%)
Allergic reaction, food	0 (0.0%)	3 (3.2%)	0 (0.0%)	3 (1.1%)

Source: Data Source Table 12.10 in Section 10; Patient Data Listings in Appendix B.7 & B.8
N.B.: Condition was indicated as being “current” in the medical/surgical history or presenting condition pages of the CRF.
* Adjusted for gender
nec=not elsewhere classified

4.6 Prior and Concomitant Medications

A summary of medications used prior to entry into the study is presented in Tables 12.11 and 12.12 in Section 10. The most common medication used by patients prior to entry was paracetamol.

Table 17 presents concomitant medications received by 5% or more of patients in any treatment group during the trial. Across all three treatment groups, paracetamol (30.9%), ibuprofen (12.0%), and acetylsalicylic acid (7.6%), were the most commonly taken medications. Antibiotics (amoxicillin) and cough/cold remedies, (diphenhydramine and phenylephrine) were commonly used. There were no notable differences among treatment groups as to concomitant medication use except for diphenhydramine hydrochloride, which was not used by any patients in the placebo group.

Table 17 Concomitant Medications Received by 5% or More of Patients in Any Treatment Group (number (%) of patients)

Concomitant Medication	Treatment Group			Total
	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)	(N=275)
Any concomitant medication	53 (57.0%)	53 (55.8%)	51 (58.6%)	157 (57.1%)
Amoxicillin trihydrate	5 (5.4%)	1 (1.1%)	1 (1.1%)	7 (2.5%)
Acetylsalicylic acid	8 (8.6%)	5 (5.3%)	8 (9.2%)	21 (7.6%)
Caffeine	6 (6.5%)	3 (3.2%)	2 (2.3%)	11 (4.0%)
Paracetamol	30 (32.3%)	27 (28.4%)	28 (32.2%)	85 (30.9%)
Diphenhydramine hydrochloride	6 (6.5%)	8 (8.4%)	0 (0.0%)	14 (5.1%)
Ibuprofen	12 (12.9%)	9 (9.5%)	12 (13.8%)	33 (12.0%)
Phenylephrine hydrochloride	5 (5.4%)	1 (1.1%)	2 (2.3%)	8 (2.9%)
Guaifenesin	4 (4.3%)	3 (3.2%)	7 (8.0%)	14 (5.1%)
Pseudoephedrine hydrochloride	3 (3.2%)	7 (7.4%)	4 (4.6%)	14 (5.1%)

Source: Data Source Table 12.14 in Section 10; Patient Data Listings in Appendix B.9, B.10, B.13 & B.14

Note: Either the medication was started during the study, or was started prior to randomization and was continued during the study.

4.7 Treatment Compliance and Titration

4.7.1 Treatment Compliance

Overall compliance for the acute phase was calculated as the number of capsules consumed divided by the number prescribed. The number of capsules consumed was calculated by subtracting the total number dispensed and the total number returned. It was assumed that all capsules not returned were taken by the patient. If the return number was not known, then the capsule count was not included in the calculations.

*[number consumed/number prescribed]*100%.*

Compliance with study medication is presented by treatment group in Table 18. Overall compliance was good with 16 patients identified as taking less than 80% of the prescribed study medication, half of these were in the imipramine group. There were no patients with compliance reported at greater than 120%. Note: Compliance to calculate protocol violations used the formula described above, but the calculations were done for each visit. A protocol violation was defined as two consecutive visits of non-compliance.

Table 18 Summary of Patient Compliance with Study Medication over the 8 Week Treatment Period (number (%) of patients)

Percentage Compliance with Taking Study Medication	Treatment Group		
	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Less than 80%	3 (3.2%)	8 (8.4%)	5 (5.7%)
≥80% and ≤120%	85 (91.4%)	85 (89.5%)	81 (93.1%)
Unknown	5 (5.4%)	2 (2.1%)	1 (1.1%)

Source: Data Source Table 12.16 in Section 10; Patient Data Listing in Appendix B.15

4.7.2 Titration of Dose

The number of patients titrated up to each of the six dose levels is shown by treatment group in Table 19. The number of patients currently enrolled at each visit are presented by dose level. Also presented are the numbers of patients at each dose level at endpoint and the maximum dose achieved at anytime during the study. Protocol required all patients to be titrated to level 4 by the fourth week of treatment. The percentage of patients who were titrated beyond this level was 55% (51/93) in the paroxetine group, 40% (38/95) in the imipramine group, and 59% (51/87) in the placebo regimen. A higher number of placebo patients (n=36) than paroxetine patients (n=28) were treated with level 6 study medication. The mean (SD) dose at endpoint for the paroxetine and imipramine groups were 28.0 ± 8.54 mg and 205.8 ± 63.94 mg respectively.

Table 19 Number of Patients at Dose Level by Treatment Group and Study Week

Titration Dose (Dose Level)	Week 1	2	3	4	5	6	7	8	End-point	Maxi-mum
Paroxetine (n=93)										
20 mg/day (level 1)	9	1	0	0	0	0	0	0	8	8
20 mg/day (level 2)	82	5	0	0	0	0	0	0	3	3
20 mg/day (level 3)	2	78	5	0	0	1	0	0	3	3
20 mg/day (level 4)	0	2	75	43	33	25	24	23	31	28
30 mg/day (level 5)	0	0	0	34	26	23	20	20	22	23
40 mg/day (level 6)	0	0	0	0	17	25	27	22	26	28
Mean ± SD dose at endpoint									**28.0 ± 8.54 mg**	
Imipramine (n=95)										
50 mg/day (level 1)	6	1	0	0	0	0	0	0	3	3
100 mg/day (level 2)	88	13	0	0	0	0	0	0	11	11
150 mg/day (level 3)	1	76	10	0	0	0	0	0	5	5
200 mg/day (level 4)	0	1	70	56	40	33	29	26	45	38
250 mg/day (level 5)	0	0	0	19	18	14	14	12	15	18
300 mg/day (level 6)	0	0	0	0	11	16	15	15	16	20
Mean ± SD dose at endpoint									**205.8 ± 63.94 mg**	
Placebo (n=87)										
0 mg/day (level 1)	5	0	0	0	0	0	0	0	2	2
0 mg/day (level 2)	81	7	0	0	0	0	0	0	3	3
0 mg/day (level 3)	1	78	8	0	0	0	0	0	5	5
0 mg/day (level 4)	0	0	71	43	30	25	23	20	27	26
0 mg/day (level 5)	0	0	0	33	23	16	9	11	14	15
0 mg/day (level 6)	0	0	0	0	21	27	35	35	36	36

Source: Data Source Table 12.18 in Section 10; Patient Data Listing in Appendix B.16

5 Efficacy Results

5.1 Efficacy Evaluation

5.1.1 Data Sets Analyzed

Unless otherwise stated, all tables show the efficacy results obtained from the intent-to-treat (ITT) population, using observed cases (OC) dataset and the last observation carried forward (LOCF). The analytical plan provided for an additional analysis to be repeated at the last timepoint for which there were at least 70% of the patients remaining in the study. For this study 70% of patients remained at week 8, therefore, a separate analysis is not provided.

Hypothesis testing using the per protocol population was limited to the HAM-D, the K-SADS, and responder analyses. The results of these analyses (shown in Section 11, Tables 13.1.1, 13.2.1, and 13.3.1) parallel the findings from the ITT population.

5.2 Efficacy Results

The primary efficacy measures defined by the protocol include the HAM-D change from baseline and percent responders. Other measures used to assess benefit included the CGI and the K-SADS-L.

5.2.1 Change from Baseline in Total HAM-D Score

The mean baseline HAM-D scores ranged between 18-19 and were comparable across the paroxetine, imipramine and placebo groups. With treatment, there was improvement over time on all three regimens as evidenced by a progressive decrease in the HAM-D scores (Table 20). For the imipramine group the magnitude of the decreases were comparable to that seen in the placebo group, while in the paroxetine group the decreases exceeded the placebo response by up to 2 points (week 3 OC). At the protocol defined endpoint (week 8), there was a 1.7 point greater decrease in the HAM-D in the paroxetine group compared to placebo in both the OC and LOCF datasets. This difference did not achieve statistical significance (OC p=0.153, LOCF p=0.133; Table 21, Figure 3). For the imipramine group at endpoint, the decreases in HAM-D were the same as placebo in the OC datasets and less than placebo in the LOCF datasets.

Table 20 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total HAM-D Score for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8

	Treatment Group					
Visit	**Paroxetine**	**n**	**Imipramine**	**n**	**Placebo**	**n**
Baseline	18.98 ± 0.43	90	18.11 ± 0.43	94	18.97 ± 0.44	87
Week 1	-3.75 ± 0.47	88	-3.35 ± 0.47	91	-3.23 ± 0.48	84
Week 2	-6.08 ± 0.62	81	-5.49 ± 0.60	88	-5.34 ± 0.62	80
Week 3	-8.74 ± 0.75	76	-6.98 ± 0.76	77	-6.77 ± 0.75	75
Week 4	-9.20 ± 0.71	76	-8.09 ± 0.77	69	-7.84 ± 0.72	73
Week 5	-9.52 ± 0.81	72	-9.23 ± 0.85	67	-9.43 ± 0.85	70
Week 6	-10.68 ± 0.81	72	-9.18 ± 0.87	62	-10.17 ± 0.84	66
Week 7	-11.98 ± 0.84	67	-9.83 ± 0.95	54	-10.49 ± 0.86	63
Week 8	-12.18 ± 0.88	67	-10.59 ± 0.97	56	-10.51 ± 0.88	66
Week 8 LOCF	-10.74 ± 0.81	90	-8.91 ± 0.81	94	-9.09 ± 0.83	87

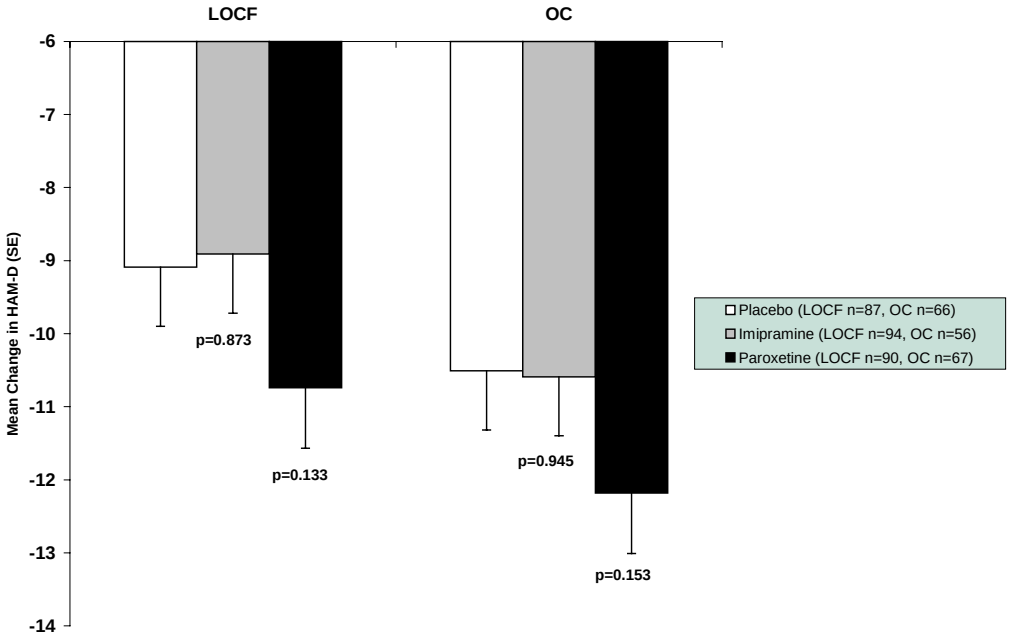
Source: Data Source Table 13.1 in Section 11; Patient Data Listing in Appendix C.1
Note: A minus sign represents an improvement (decrease in score).

Table 21 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) in Total HAM-D Score

	Paroxetine vs. Placebo			Imipramine vs. Placebo		
	Treatment Difference	**(95% C.I.)**	**p**	**Treatment Difference**	**(95% C.I.)**	**p**
Week 8 OC	-1.7	(-4.11, 0.77)	0.153	0.1	(-2.65, 2.49)	0.945
Week 8 LOCF	-1.7	(-3.92, 0.62)	0.133	0.18	(-2.09, 2.45)	0.873

Data Source: Item G of the Statistical Appendix in Appendix A

Figure 3 Mean Change from Baseline (SE) in Total HAM-D Score for the Week 8 LOCF and Week 8 OC Datasets



Source: Data Source Table 13.1 in Section 11
N.B.: Treatment p-value from ANOVA with factors of treatment and investigator in the model.

5.2.2 Change from Baseline in HAM-D Subscales

Five items and factors of the HAM-D were analyzed. These included the Depressed Mood item (Item 1), the Anxiety/Somatization factor (Items 10, 11, 12, 13, 15 and 17), the Psychomotor Retardation factor (Items 7, 8, and 14), Sleep Disturbances factor (Items 4, 5, and 6) and Cognitive Disturbances factor (Item 2, 3, and 9). The results of these analyses are presented in Table 22.

The baseline scores for the mood item and factors were comparable across the three treatment regimens. At week eight, the scores in each item and factor were reduced for all three treatment regimens for both the OC and LOCF datasets.

The decreases in the imipramine group were comparable to that seen in the placebo regimen for all of the subscale groupings examined. In the paroxetine group, however, the decreases in symptoms were larger than placebo in the Depressed Mood item , the Anxiety/Somatization factors, as well as the Psychomotor Retardation factor and the Sleep Disturbance factor. The largest

difference was seen in the Depressed Mood item (week 8 LOCF difference, 95% C.I.: -0.67 (-1.06, -0.28)) and this achieved statistical significance (p=0.001). Statistical significance was also achieved in the OC dataset (p=0.003).

Table 22 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Mood Item and Factors* of the HAMD for the Week 8 LOCF and OC Week 8 Datasets

Item/Factor	Treatment Group						Paroxetine vs Placebo**	Imipramine vs Placebo**
Visit	**Paroxetine**	**n**	**Imipramine**	**n**	**Placebo**	**n**		
Depressed Mood								
Baseline	2.99 ± 0.08	90	2.79 ± 0.08	94	2.86 ± 0.08	87	0.227	0.514
Week 8 OC	-2.21 ± 0.17	67	-1.76 ± 0.18	56	-1.54 ± 0.17	66	0.003	0.358
Week 8 LOCF	-2.00 ± 0.14	90	-1.62 ± 0.14	94	-1.33 ± 0.14	87	0.001	0.135
Anxiety/ Somatization								
Baseline	5.82 ± 0.23	90	5.29 ± 0.23	94	5.60 ± 2.30	87	0.477	0.312
Week 8 OC	-3.79 ± 0.35	67	-2.54 ± 0.39	56	-2.88 ± 0.35	66	0.051	0.491
Week 8 LOCF	-3.18 ± 0.33	90	-2.07 ± 0.33	94	-2.59 ± 0.33	87	0.184	0.231
Psychomotor Retardation***								
Baseline	7.32 ± 0.21	90	6.84 ± 0.21	94	7.12 ± 0.21	87	0.479	0.367
Week 8 OC	-4.82 ± 0.43	67	-4.25 ± 0.54	56	-4.09 ± 0.41	66	0.221	0.821
Week 8 LOCF	-4.36 ± 0.34	90	-3.76 ± 0.35	94	-3.59 ± 0.34	87	0.104	0.722
Sleep								
Baseline	2.41 ± 0.19	90	2.49 ± 0.19	94	2.50 ± 0.20	87	0.735	0.969
Week 8 OC	-1.41 ± 0.25	67	-1.46 ± 0.27	56	-1.35 ± 0.25	66	0.852	0.767
Week 8 LOCF	-1.26 ± 0.21	90	-1.20 ± 0.21	94	-1.10 ± 0.22	87	0.605	0.746
Cognitive Disturbances								
Baseline	3.25 ± 0.20	90	3.09 ± 0.20	94	3.44 ± 0.20	87	0.458	0.182
Week 8 OC	-1.74 ± 0.26	67	-2.28 ± 0.29	56	-2.10 ± 0.26	66	0.296	0.609
Week 8 LOCF	-1.71 ± 0.25	90	-1.63 ± 0.25	94	-1.71 ± 0.25	87	0.989	0.827

Source: Data Source Tables 13.7, 13.8, 13.9, 13.10 & 13.35 in Section 11; Patient Data Listing in Appendix C.2

*Mood item and factors on HAM-D scale are anxiety/somatization (summed items 10, 11, 12, 13, 15 and 17), sleep (summed items 4, 5 and 6), cognitive disturbance (summed items 2, 3 and 9), and psychomotor slowing (summed items 1, 7, 8 and 14).

**Treatment p-value from ANOVA with treatment and investigator in the model.

*** Treatment-by-investigator interaction was significant (p=0.042, Statistical Report in Appendix A). Hypotheses testing for the subgroup included the interaction factor in the model.

Note: A minus sign represents an improvement (decrease in score).

5.2.3 Responders and Remission Analysis

Using predefined reductions in the total HAM-D score, we examined the number of patients who responded to treatment as well as the number of patients

considered to have achieved remission. A patient was considered to be a responder if the baseline HAM-D score was reduced on treatment by at least 50%, or the total score was 8 or less. A patient was considered to be in remission if the HAM-D score was 8 or less. To compare rates between regimens, logistic analysis, which included treatment effects and center, was used. Tables 23 and 25 present the analysis of the responders and remission data respectively.

Through the initial four weeks of treatment, the percentage of responders progressively increased at a comparable rate in all three-treatment regimens. At week 4, about half the patients in each group achieved responder status. During weeks 4 through 8, the number of responders in the paroxetine group continued to increase such that at week eight, over 80% of the patients met criteria for a responder. In the placebo group, however, the increase in the percentage of responders was less and achieved a maximal level of 67% during weeks six through eight. For the OC dataset this difference between paroxetine and placebo at Week 8 was over 15% (80.6% vs 65.2%; p=0.051; Table 24, Figure 4). For the LOCF dataset, the percentage of responders for the paroxetine and placebo groups were 67% and 55% respectively (p=0.112; Table 24, Figure 4). The responder rate at endpoint for the imipramine group was 73% and 59% for the OC and LOCF datasets respectively. Neither was statistically significant from placebo (p=0.363, p=0.612; Table 24, Figure 5).

Using remission as a measure of efficacy, the pattern was similar to the analysis described for responders. However, given the higher hurdle, fewer patients overall met the criterion, but the differential in rates between paroxetine and placebo at week 8 was greater and achieved statistical significance for both the OC (76% vs 58%; p=0.019; Table 26, Figure 4) and LOCF dataset (63% vs 46%, p=0.019; Table 26, Figure 4). Remission rates for the imipramine group at week 8 were higher than the placebo rate, but did not achieve statistical significance for either the OC (64% vs 58%) or LOCF (50% vs 46%) datasets.

Table 23 Number (%) of Patients Who Responded* to Treatment for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8

	Treatment Group		
Visit	**Paroxetine**	**Imipramine**	**Placebo**
Week 1	13/88 (14.8%)	10/91 (11.0%)	6/84 (7.1%)
Week 2	29/81 (35.8%)	24/88 (27.3%)	19/80 (23.8%)
Week 3	40/76 (52.6%)	33/77 (42.9%)	26/75 (34.7%)
Week 4	43/76 (56.6%)	35/69 (50.7%)	39/73 (53.4%)
Week 5	47/72 (65.3%)	37/67 (55.2%)	38/70 (54.3%)
Week 6	48/72 (66.7%)	37/62 (59.7%)	44/66 (66.7%)
Week 7	48/67 (71.6%)	39/54 (72.2%)	39/63 (61.9%)
Week 8	54/67 (80.6%)	41/56 (73.2%)	43/66 (65.2%)
Wk 8 LOCF	60/90 (66.7%)	55/94 (58.5%)	48/87 (55.2%)

Source: Data Source Table 13.3 in Section 11; Patient Data Listing in Appendix C.1
*Response is defined as a HAM-D score ≤ 8 and/or a decrease from baseline in HAM-D ≥ 50%

Table 24 Week 8 (OC and LOCF) Mean Treatment Difference (95% C.I.) of Patients who Responded*

	Paroxetine vs. Placebo			Imipramine vs. Placebo		
	Treatment Difference	**(95% C.I.)**	**p**	**Treatment Difference**	**(95% C.I.)**	**p**
Week 8 OC	15%	(0.5, 30.3)	0.051	8%	(-8.3, 24.3)	0.363
Week 8 LOCF	12%	(-2.8, 25.7)	0.112	3%	(-11.1, 17.7)	0.612

Data Source: Item G of the Statistical Appendix in Appendix A
*Response is defined as a HAM-D score ≤ 8 and/or a decrease from baseline in HAM-D ≥ 50%

Table 25 Number (%) of Patients in Remission* for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8

	Treatment Group		
Visit	**Paroxetine**	**Imipramine**	**Placebo**
Week 1	12/88 (13.6%)	8/91 (8.8%)	5/84 (6.0%)
Week 2	24/81 (29.6%)	18/88 (20.5%)	15/80 (18.8%)
Week 3	33/76 (43.4%)	28/77 (36.4%)	23/75 (30.7%)
Week 4	36/76 (47.4%)	31/69 (44.9%)	33/73 (45.2%)
Week 5	40/72 (55.6%)	32/67 (47.8%)	31/70 (44.3%)
Week 6	40/72 (55.6%)	33/62 (53.2%)	39/66 (59.1%)
Week 7	45/67 (67.2%)	35/54 (64.8%)	38/63 (60.3%)
Week 8	51/67 (76.1%)	36/56 (64.3%)	38/66 (57.6%)
Wk 8 LOCF	57/90 (63.3%)	47/94 (50.0%)	40/87 (46.0%)

Source: Data Source Table 13.11 in Section 11; Patient Data Listing in Appendix C.1
* Remission is defined as a HAM-D Score ≤ 8

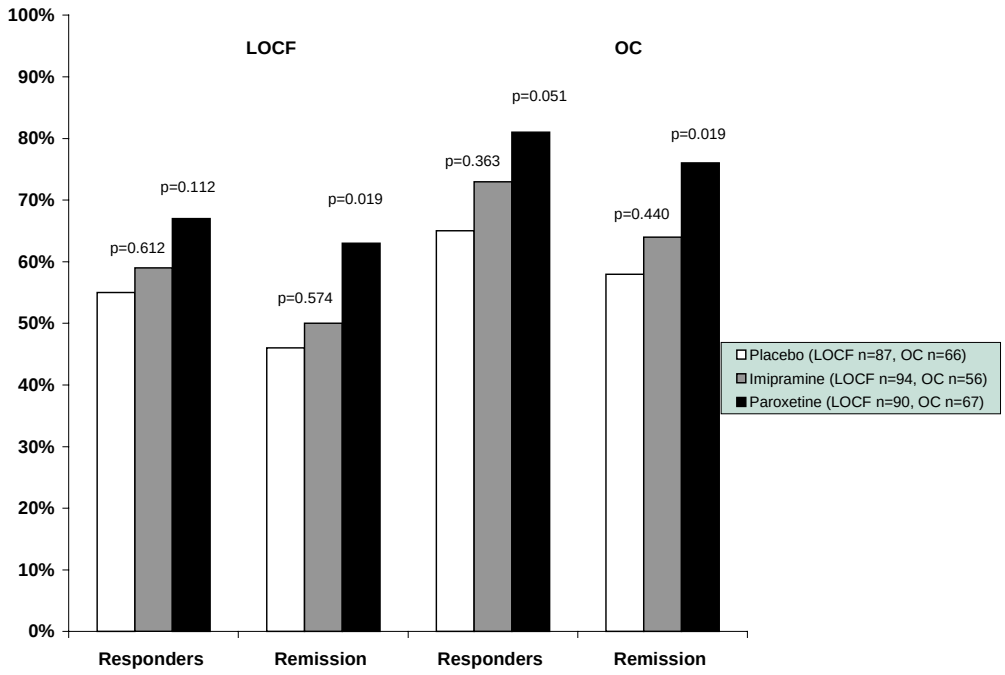
Table 26 Week 8 (OC and LOCF) Mean Treatment Difference (95% C.I.) of Patients in Remission*

	Paroxetine vs. Placebo			Imipramine vs. Placebo		
	Treatment Difference	**(95% C.I.)**	**p**	**Treatment Difference**	**(95% C.I.)**	**p**
Week 8 OC	19%	(2.8, 34.2)	0.019	7%	(-10.06, 24.0)	0.440
Week 8 LOCF	17%	(2.8, 31.8)	0.019	4%	(-10.6, 18.6)	0.574

Data Source: Item G of the Statistical Appendix in Appendix A

* Remission is defined as a HAM-D Score ≤ 8

Figure 4 Percent of Patients in LOCF and OC Datasets Achieving Responder and Remission Status*



Source: Data Source Tables 13.3 & 13.11 in Section 11; Patient Data Listing in Appendix C.1
N.B.:Treatment p-value from categorical analysis using a model with efects for treatment and investigator.
* Response = HAM-D ≤ 8 or decrease from baseline ≥ 50%; remission = HAM-D ≤ 8

5.2.4 Sustained Response

Survival analysis was performed for time until sustained response, defined as response lasting until endpoint of the acute phase. Response was defined as a HAM-D total score less than or equal to 8 or a decrease from baseline in HAM-D total score of 50% or greater. Patients were classified as being a responder or non-responder.

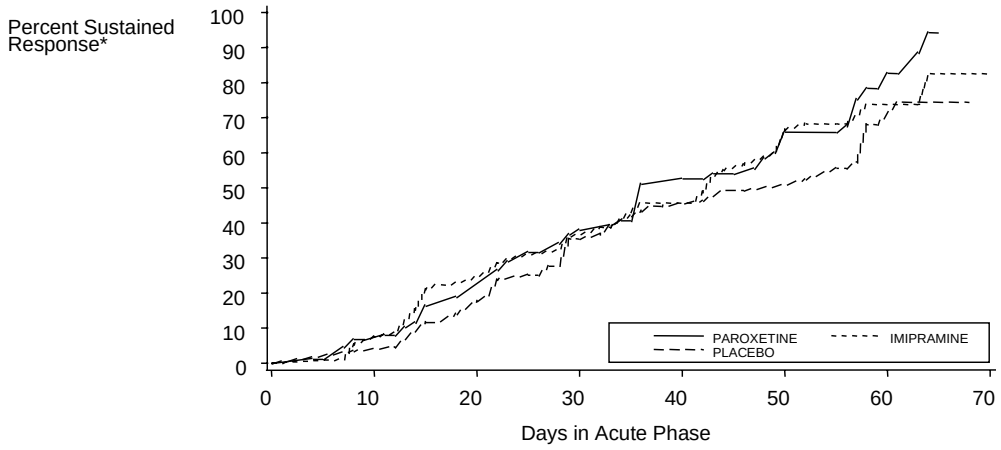
The results are presented in Table 27. When comparing each active drug to placebo, no significant treatment effect was observed (p=0.095). A plot of the Kaplan Meier curves is presented in Figure 5.

Table 27 Survival Analysis of Sustained Response During the Acute Phase

	Paroxetine vs Placebo	Imipramine vs Placebo
P-value	0.095	0.222
Risk Ratio	1.383	1.272
95% C.I.	(0.946, 2.022)	(0.864, 1.877)

Source: Section IIID of Statistical Appendix in Appendix A
N.B.: Treatment p-value from Cox proportional hazards with treatment in the model

Figure 5 Kaplan Meier Survival Curves for Time to Sustained Response During Acute Phase



*Sustained Response = HAMD Total Score less than or equal to 8 OR decrease from baseline of 50% or greater (lasting until endpoint).

Source: Figure 4, Section D of the Statistical Appendix in Appendix A

5.2.5 CGI Improvement Scale

The seven point Clinical Global Improvement score was analyzed two ways: 1) using the mean scores and 2) by tabulating the proportion of patients rated "1" or "2" ("very much improved" and "much improved" respectively) at endpoint. 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. The results of these two analyses are presented in Tables 28 and 30, and Figures 6 and 7.

As seen with the analysis of the HAM-D the mean CGI scores showed progressive improvement with continuing treatment in all treatment regimens. However, the improvement for the paroxetine group was greater than seen with imipramine or placebo. In the LOCF dataset at week 8, the mean improvement score was numerically superior in the paroxetine group when compared to placebo (2.37 vs 2.73; p=0.094; Table 29, Figure 6). For the OC dataset, the difference achieved significance (19.9 vs 2.73; p=0.030; Table 29, Figure 6). Mean CGI scores for the imipramine group approximated the placebo CGI assessments at most timepoints.

Table 28 Mean Improvement Score (+/- SE) on the CGI Scale for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8

	Treatment Group					
Visit	**Paroxetine**	**n**	**Imipramine**	**n**	**Placebo**	**n**
Week 1	3.52 ± 0.08	88	3.58 ± 0.08	90	3.52 ± 0.08	84
Week 2	3.04 ± 0.11	80	3.19 ± 0.10	89	3.15 ± 0.11	79
Week 3	2.68 ± 0.12	76	2.91 ± 0.12	78	2.90 ± 0.12	75
Week 4	2.49 ± 0.13	76	2.76 ± 0.14	69	2.79 ± 0.13	73
Week 5	2.55 ± 0.14	72	2.49 ± 0.15	67	2.73 ± 0.15	70
Week 6	2.44 ± 0.15	73	2.61 ± 0.17	61	2.58 ± 0.16	66
Week 7	2.20 ± 0.16	66	2.38 ± 0.18	53	2.41 ± 0.16	63
Week 8	1.91 ± 0.15	68	2.16 ± 0.17	56	2.36 ± 0.16	66
Wk 8 LOCF	2.37 ± 0.16	90	2.70 ± 0.15	94	2.73 ± 0.16	87

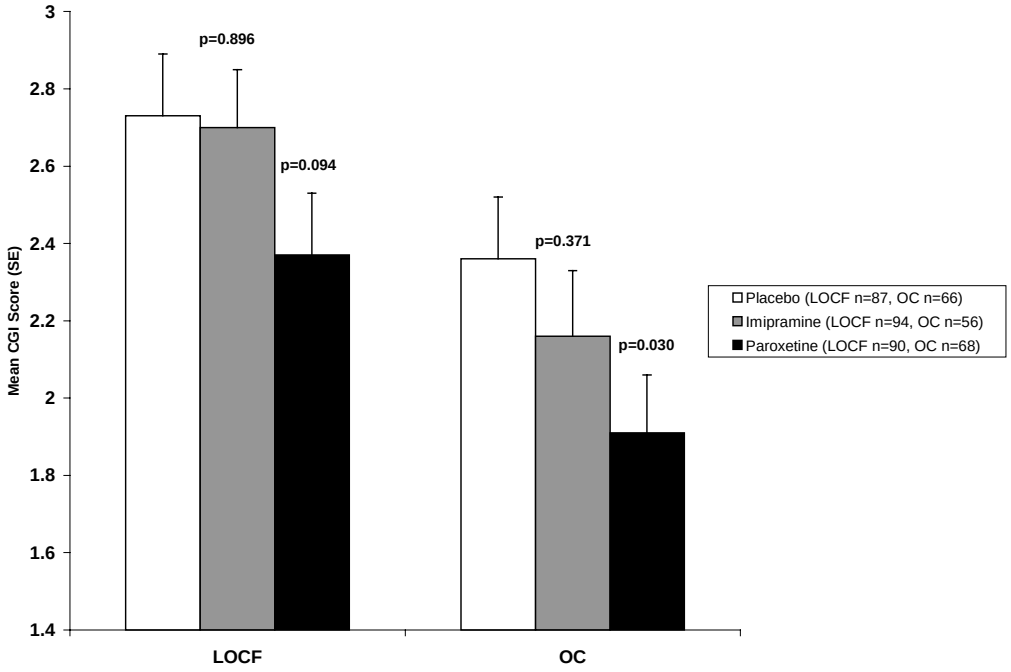
Source: Data Source Table 13.4 in Section 11; Patient Data Listing in Appendix C.4
N.B.: a lower score indicates a greater degree of improvement.

Table 29 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) on the CGI Scale

	Paroxetine vs. Placebo			Imipramine vs. Placebo		
	Treatment Difference	**(95% C.I.)**	**p**	**Treatment Difference**	**(95% C.I.)**	**p**
Week 8 OC	-0.45	(-0.88, -0.02)	0.030	-0.2	(-0.66, 0.26)	0.371
Week 8 LOCF	-0.36	(-0.80, 0.08)	0.094	-0.03	(-0.46, 0.40)	0.896

Data Source: Item G in the Statistical Appendix in Appendix A

Figure 6 Mean CGI Score (SE) for Week 8 LOCF and Week 8 OC Datasets



Source: Data Source Table 13.4 in Section 11; Patient Data Listing in Appendix C.4
N.B.: Treatment p-value from ANOVA with factors of treatment and investigator in the model.

Using the categories of "1" or "2" of the CGI, there were significantly more paroxetine patients (66%) than placebo patients (48%) rated "very much" or "much improved" for the Week 8 LOCF dataset (Table 30). Similar results were also seen in the OC dataset (paroxetine 79% vs placebo 61%). This difference is statistically significant for both populations (p=0.020, p=0.020; Table 31, Figure 7). The proportion of imipramine patients rated "1" or "2" was only slightly higher than placebo in the LOCF dataset (52% vs 48%) and the OC dataset (68% vs 61%). These differences were not statistically significant (p=0.642 LOCF, p=0.506 OC; Table 31).

Table 30 Number and Percent of Patients Having a CGI Score of "Very Much Improved" or "Much Improved" for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8

	Treatment Group					
	Paroxetine		Imipramine		Placebo	
Visit	n/N	%	n/N	%	n/N	%
Week 1	6/88	6.8%	3/90	3.3%	3/84	3.6%
Week 2	17/80	21.3%	16/89	18.0%	17/79	21.5%
Week 4	33/76	43.4%	22/78	28.2%	23/75	30.7%
Week 4	39/76	51.3%	25/69	36.2%	32/73	43.8%
Week 5	33/72	45.8%	35/68	51.5%	31/70	44.3%
Week 6	44/73	60.3%	37/61	60.7%	41/66	62.1%
Week 7	43/66	65.2%	34/53	64.2%	38/63	60.3%
Week 8	53/67	79.1%	38/56	67.9%	40/66	60.6%
Wk 8 LOCF	59/90	65.6%	49/94	52.1%	42/87	48.3%

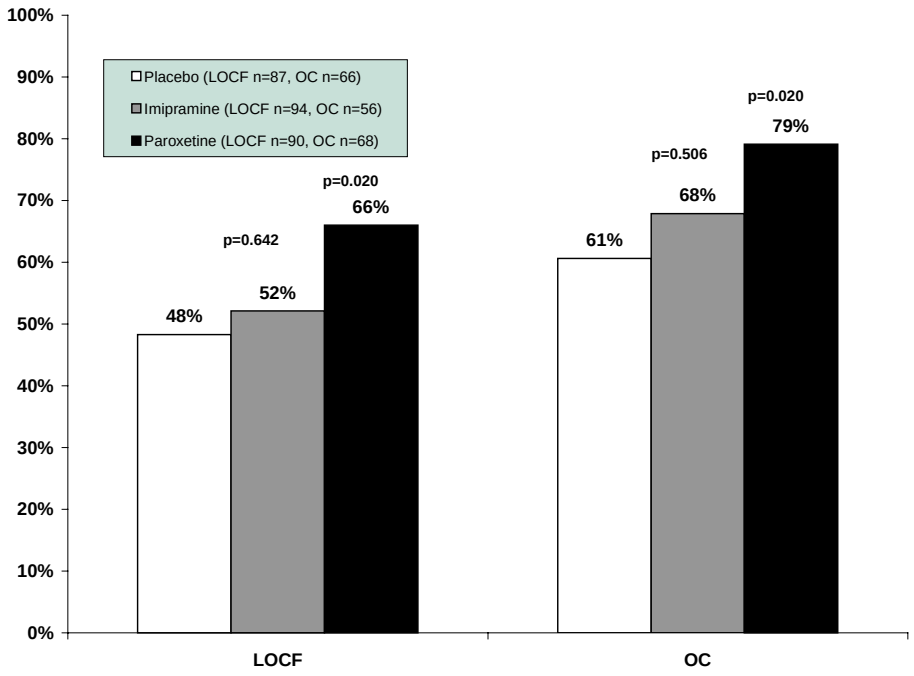
Source: Data Source Table 13.37 in Section 11; Patient Data Listings in Appendix C.4
N.B.: Only patients with one or more on-therapy evaluations are included.

Table 31 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) of Patients Having a CGI Score of "Very Much Improved" or "Much Improved"

	Paroxetine vs. Placebo			Imipramine vs. Placebo		
	Treatment Difference	(95% C.I.)	p	Treatment Difference	(95% C.I.)	p
Week 8 OC	18%	(3.2, 33.8)	0.02	7%	(-9.7, 24.3)	0.506
Week 8 LOCF	18%	(2.9, 31.7)	0.02	4%	(-10.6, 18.4)	0.642

Data Source: Item G of the Statistical Appendix in Appendix A

Figure 7 Percent of Patients Very Much Improved and Much Improved in CGI Global Improvement at Endpoint



Source: Data Source Table 13.37 in Section 11
N.B.: Treatment p-value from categorical analysis with treatment and investigator in the model.

5.2.6 K-SADS-L - Depression 9-Item Scale - Change from Baseline

The mean baseline scores for the 9-item depression subscale of the K-SADS-L were similar across the three treatment regimens ranging between 27 and 29 points (Table 32). During treatment, there was a progressive reduction in the mean scores seen in the three treatment regimens. Similar to that observed in the HAM-D analysis, the decrease from baseline at week 8 for the paroxetine group exceeded that of placebo and imipramine. For the LOCF dataset a difference of 2.1 points was observed relative to placebo (p=0.065; Table 33, Figure 8). In the OC dataset, the difference between placebo and paroxetine was 1.2 units. This failed to achieve statistical significance (p=0.384; Table 33, Figure 8). Mean changes in the imipramine group were comparable to placebo.

Table 32 Baseline Mean (+/- SE) and Change from Baseline (+/- SE) in K-SADS-L - Depression 9-Item Scale for OC Dataset at Each Treatment Week and the LOCF Dataset at Week 8

	Treatment Group					
Visit	**Paroxetine**	**n**	**Imipramine**	**n**	**Placebo**	**n**
Baseline	28.25 ± 0.52	83	27.54 ± 0.51	88	28.84 ± 0.52	85
Week 2	-5.51 ± 0.67	77	-5.53 ± 0.65	82	-6.26 ± 0.67	76
Week 4	-9.01 ± 0.83	70	-8.55 ± 0.91	60	-8.17 ± 0.85	66
Week 6	-11.00 ± 0.89	67	-11.02 ± 1.02	50	-11.22 ± 1.01	54
Week 8	-12.03 ± 0.93	67	-10.68 ± 1.02	56	-10.87 ± 0.93	65
Wk 8 LOCF	-11.66 ± 0.84	83	-9.55 ± 0.83	88	-9.57 ± 0.83	85

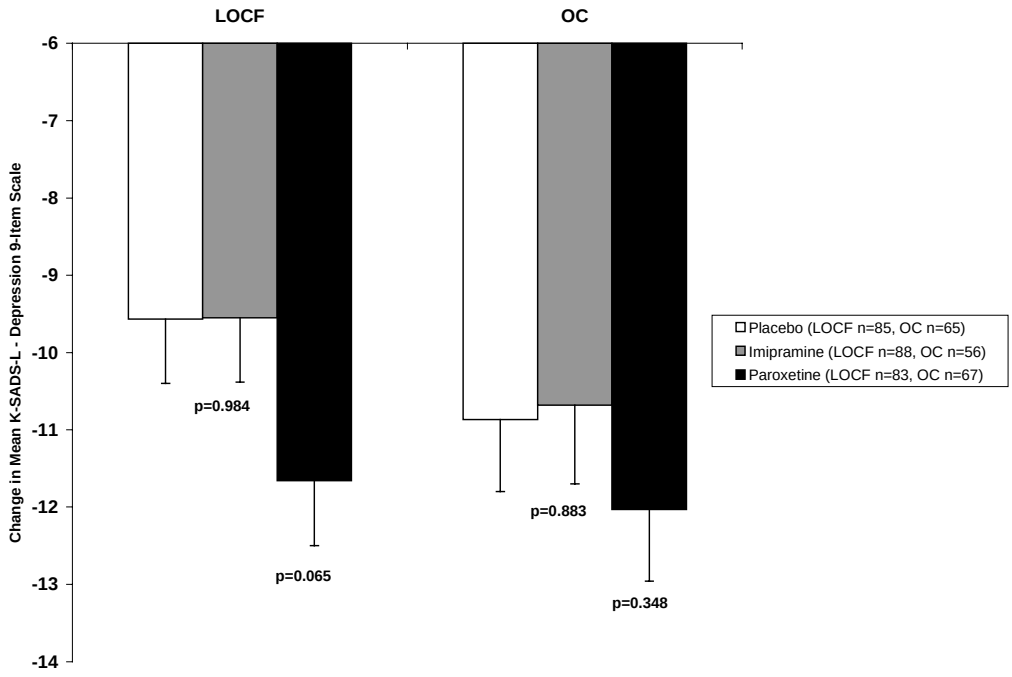
Source: Data Source Table 13.2 in Section 11; Patient Data Listing in Appendix C.3.
Note:A minus sign represents an improvement (decrease in score).

Table 33 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) in K-SADS-L Depression 9-Item Scale

	Paroxetine vs. Placebo			**Imipramine vs. Placebo**		
	Treatment Difference	**(95% C.I.)**	**p**	**Treatment Difference**	**(95% C.I.)**	**p**
Week 8 OC	-1.2	(-3.74, 1.42)	0.348	0.2	(-2.52, 2.90)	0.883
Week 8 LOCF	-2.1	(-4.40, 0.22)	0.065	0.0	(-2.28, 2.32)	0.984

Data Source: Item G of the Statistical Appendix in Appendix A

Figure 8 Mean Change From Baseline (SE) in K-SADS-L - Depression 9-Item Scale For Week 8 LOCF and Week 8 OC Datasets



Source: Data Source Table 13.2 in Section 11
N.B.: Treatment p-value from ANOVA with treatment and investigator in the model.

5.2.7 Change from Baseline in K-SADS-L Depressed Mood Item

Table 34 presents the analysis of the depressed mood item from the K-SADS-L instrument. A score of 1 on this item indicates no feeling of depressed mood, a score of 7 indicates extreme depressed mood with suicidal ideation. The average baseline score was above 4 (indicating definite dysphoric mood with functional impairment) for all three groups, but the mean score for the imipramine regimen was significantly lower than those patients randomized to placebo. The mean baseline scores in the paroxetine and placebo groups were comparable.

The mean scores at baseline on the K-SADS-L Depressed Mood Item were comparable for the paroxetine and placebo groups (4.57 ± 0.09 vs 4.63 ± 0.09). For the imipramine group the mean baseline score on the K-SADS-L Depressed Mood Item was lower at 4.29 ± 0.09 and statistically different than placebo ($p=0.006$). With treatment, improvement was seen in all three regimens with the largest difference observed in the paroxetine group. For the LOCF dataset, this

difference between paroxetine and placebo reached statistical significance (p=0.049; Table 35). The difference did not reach statistical significance for the OC dataset (p=0.133; Table 35). Changes in the depression mood item score for the imipramine regimen paralleled those seen with the placebo group. No significant differences were observed in either the LOCF or OC dataset.

Table 34 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Depressed Mood Item of the K-SADS-L Depression Scale for the Week 8 OC and Week 8 LOCF Datasets

Visit	Treatment Group						Paroxetine	Imipramine
	Paroxetine	n	Imipramine	n	Placebo	n	vs Placebo*	vs Placebo*
Baseline	4.57 ± 0.09	83	4.29 ± 0.09	87	4.63 ± 0.09	85	0.640	0.006
Week 8 OC	-2.35 ± 0.20	66	-2.05 ± 0.22	55	-1.93 ± 0.20	65	0.113	0.661
Week 8 LOCF	-2.20 ± 0.18	83	-1.77 ± 0.18	87	-1.73 ± 0.18	85	0.049	0.868

Source: Data Source Table 13.36 in Section 11; Patient Data Listing Appendix C3.
N.B.: Negative sign indicates improvement.
* Treatment p-value from ANOVA with treatment and investigator in the model.

Table 35 Week 8 (OC and LOCF) Mean Treatment Differences (95% C.I.) in Depressed Mood Item

	Paroxetine vs. Placebo			Imipramine vs. Placebo		
	Treatment Difference	(95% C.I.)	p	Treatment Difference	(95% C.I.)	p
Week 8 OC	-0.42	(-0.97, 0.13)	0.113	-0.12	(-0.70, 0.46)	0.661
Week 8 LOCF	-0.47	(-0.97, 0.03)	0.049	-0.04	(-0.54, 0.46)	0.868

Data Source: Item G in the Statistical Appendix in Appendix A

5.3 Functional, Self Perceptive and Behavioral Scales

5.3.1 Autonomous Functioning Checklist

The autonomous functioning checklist (AFC) is a parent-completed checklist designed to measure behavioral autonomous functioning in adolescents. It was administered at entry (baseline) and at Week 8. The AFC includes four components: 1) the self and family care subscale that addresses the extent to which daily maintenance activities are carried out; 2) a management subscale that measures the extent to which the adolescent independently handles his or her interactions with the environment; 3) a recreational subscale which measures use of free time; and 4) a social and vocational subscale that addresses social and

vocational direction. The four components and the total score were analyzed; the results of the analysis are presented in Table 36.

The mean baseline scores for each of the four components and the mean total score were comparable across the three treatment regimens. At week 8 (OC and LOCF) there was a larger improvement in each subscale and the total score for the paroxetine group compared to placebo. For the paroxetine group the mean change from baseline was approximately 15 points (s.e. ± 2.80; week 8 LOCF). This was larger than placebo (9.30 ± s.e. 2.75), however, not statistically significant (p=0.148).

Table 36 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total Score and Subscores on the Autonomous Functioning Checklist at Endpoint

Score / Visit	Treatment Group: Paroxetine	n	Imipramine	n	Placebo	n	Paroxetine vs Placebo*	Imipramine vs Placebo*
Total Score								
Baseline	91.41 ± 3.80	60	96.02 ± 3.97	57	94.18 ± 3.74	62	0.584	0.719
Week 8 OC	14.37 ± 2.83	58	13.37 ± 13.04	52	9.32 ± 2.80	60	0.184	0.297
Week 8 LOCF	14.70 ± 2.80	60	11.57 ± 2.92	57	9.30 ± 2.75	62	0.148	0.546
Self/Family Care								
Baseline	25.68 ± 1.37	60	27.70 ± 1.44	56	28.21 ± 1.35	62	0.167	0.784
Week 8 OC	3.78 ± 1.28	58	3.67 ± 1.38	51	1.10 ± 1.27	60	0.119	0.145
Week 8 LOCF	3.68 ± 1.24	60	3.31 ± 1.30	56	1.23 ± 1.22	62	0.138	0.213
Management								
Baseline	36.71 ± 1.71	60	38.31 ± 1.79	57	37.40 ± 1.69	62	0.762	0.691
Week 8 OC	5.64 ± 1.23	58	4.94 ± 1.32	52	4.04 ± 1.22	60	0.331	0.592
Week 8 LOCF	5.97 ± 1.22	60	4.03 ± 1.28	57	3.95 ± 1.20	62	0.217	0.965
Recreational								
Baseline	22.00 ± 1.16	60	23.51 ± 1.21	57	21.96 ± 1.14	62	0.979	0.320
Week 8 OC	3.51 ± 0.90	58	3.33 ± 0.97	52	3.22 ± 0.89	60	0.809	0.932
Week 8 LOCF	3.59 ± 0.89	60	2.93 ± 0.39	57	3.17 ± 0.88	62	0.726	0.841
Social/ Vocational								
Baseline	7.09 ± 0.46	60	6.69 ± 0.48	57	6.65 ± 0.45	62	0.465	0.944
Week 8 OC	1.46 ± 0.35	58	1.15 ± 0.37	52	1.04 ± 0.35	60	0.362	0.819
Week 8 LOCF	1.49 ± 0.34	60	1.04 ± 0.35	57	1.03 ± 0.33	62	0.980	0.980

Source: Data Source Table 13.14, 13.15, 13.16, 13.17, 13.18 in Section 11; Patient Data Listing in Appendix C5.
* Treatment p-value from ANOVA with treatment and investigator in the model.
N.B.: An increase in score represents an improvement in autonomous functioning.

5.3.2 Self Perception Profile

The analysis of the Self-Perception Profile (SPP) is presented in Table 37. This instrument assesses the following domains: scholastic competence, social acceptance, athletic competence, physical appearance, behavior, and global

selfworth. The mean baseline scores for the SPP were comparable across the three treatment regimens. At Week 8, there was an increase from the baseline score in the OC and LOCF datasets for all three regimens suggesting a more positive overall perception of self occurring over the treatment period. The mean increases in the paroxetine and placebo group were higher than placebo, but no statistical significance was achieved.

Table 37 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total Score on the Self Perception Profile for the Week 8 OC and Week 8 LOCF Datasets

Score	Treatment Group						Paroxetine	Imipramine
Visit	Paroxetine	n	Imipramine	n	Placebo	n	vs Placebo*	vs Placebo*
Baseline	63.48 ± 2.58	61	60.87 ± 2.67	60	60.69 ± 2.52	63	0.418	0.960
Week 8 OC	12.93 ± 2.31	60	13.25 ± 2.46	55	12.66 ± 2.30	60	0.930	0.853
Week 8 LOCF	13.25 ± 2.33	61	13.07 ± 2.41	60	11.36 ± 2.27	63	0.542	0.586

Source: Data Source Table 13.13 in Section 11; Patient Data Listing in Appendix C6.
* Treatment p-value from ANOVA with treatment and investigator in the model.
N.B.: An increase in score represents a more positive perception for self-esteem.

5.3.3 Sickness Impact Profile

The Sickness Impact Profile (SIP) was designed to measure the impact of illness on the performance of daily activities. The analysis of the Sickness Impact Profile (SIP) is presented in Table 38. The mean baseline scores for the SIP were comparable across the three treatment regimens with the exception of the present health subscore which was significantly lower for the paroxetine and imipramine groups compared to placebo (p=0.025, p=0.058). At week 8 in both the OC and the LOCF datasets there was a reduction from baseline in the overall scores and in the subscores, but the magnitude of these reductions were similar in the paroxetine and placebo group. In the imipramine group, there were trends toward improvement for the total score (p=0.143) and for the social interaction (p=0.084) and alertness behavior (p=0.057).

Table 38 Baseline Mean (+/- SE) and Mean Change from Baseline (+/- SE) in Total Score and Subscores on the Sickness Impact Profile for the Week 8 OC and Week 8 LOCF Datasets

Score	Treatment Group						Paroxetine	Imipramine
Visit	Paroxetine	n	Imipramine	n	Placebo	n	vs Placebo*	vs Placebo*
Total Score								
Baseline	30.90 ± 1.46	63	30.38 ± 1.52	60	32.17 ± 1.42	65	0.511	0.363
Week 8 OC	-11.19 ± 1.57	62	-13.45 ± 1.70	55	-10.61 ± 1.57	62	0.786	0.193
Week 8 LOCF	-11.36 ± 1.55	63	-12.92 ± 1.62	60	-9.85 ± 1.51	65	0.463	0.143
Present health								
Baseline	2.39 ± 0.12	61	2.44 ± 0.12	60	2.74 ± 0.11	63	0.025	0.058
Week 8 OC	-0.27 ± 0.12	60	-0.22 ± 0.13	55	-0.25 ± 0.12	60	0.888	0.845
Week 8 LOCF	-0.28 ± 0.12	61	-0.17 ± 0.12	60	-0.25 ± 0.12	63	0.812	0.622
Present quality of life								
Baseline	3.38 ± 0.11	61	3.40 ± 0.12	60	3.52 ± 0.11	63	0.343	0.414
Week 8 OC	-0.66 ± 0.15	60	-0.97 ± 0.16	55	-0.69 ± 0.15	60	0.913	0.165
Week 8 LOCF	-0.67 ± 0.15	61	-0.96 ± 0.15	60	-0.60 ± 0.14	63	0.737	0.072
Sleep/Rest								
Baseline	3.55 ± 0.26	63	3.18 ± 0.27	60	3.85 ± 0.26	65	0.398	0.064
Week 8 OC	-1.30 ± 0.29	62	-1.52 ± 0.31	55	-1.51 ± 0.29	62	0.587	0.975
Week 8 LOCF	-1.30 ± 0.29	63	-1.46 ± 0.30	60	-1.34 ± 0.28	65	0.921	0.746
Home maintenance								
Baseline	2.47 ± 0.23	63	2.07 ± 0.24	59	2.32 ± 0.22	65	0.613	0.416
Week 8 OC	-1.08 ± 0.24	62	-0.84 ± 0.26	54	-0.66 ± 0.24	62	0.191	0.577
Week 8 LOCF	-1.08 ± 0.24	63	-0.88 ± 0.25	59	-0.55 ± 0.23	65	0.098	0.310
Social Interaction								
Baseline	7.65 ± 0.52	63	7.69 ± 0.55	60	7.97 ± 0.51	65	0.640	0.689
Week 8 OC	-3.00 ± 0.59	62	-4.40 ± 0.63	55	-3.07 ± 0.58	62	0.930	0.104
Week 8 LOCF	-3.02 ± 0.58	63	-4.19 ± 0.60	60	-2.84 ± 0.56	65	0.815	0.084
Alertness Behavior								
Baseline	5.60 ± 0.39	62	5.73 ± 0.41	60	5.49 ± 0.38	65	0.835	0.654
Week 8 OC	-2.19 ± 0.40	61	-2.92 ± 0.43	55	-1.82 ± 0.40	62	0.487	0.047
Week 8 LOCF	-2.27 ± 0.39	62	-2.77 ± 0.41	60	-1.75 ± 0.38	65	0.321	0.057
Communication								
Baseline	1.96 ± 0.19	62	2.00 ± 0.20	58	2.05 ± 0.18	65	0.721	0.873
Week 8 OC	-0.94 ± 0.20	61	-0.53 ± 0.22	54	-0.57 ± 0.20	62	0.179	0.884
Week 8 LOCF	-0.94 ± 0.20	62	-0.58 ± 0.21	58	-0.50 ± 0.19	65	0.102	0.774
Recreational Pastimes								
Baseline	3.86 ± 0.29	62	3.70 ± 0.31	58	4.26 ± 0.28	65	0.303	0.157
Week 8 OC	-1.56 ± 0.36	61	-1.95 ± 0.38	54	-2.02 ± 0.35	62	0.339	0.900
Week 8 LOCF	-1.61 ± 0.35	62	-1.84 ± 0.37	58	-1.97 ± 0.34	65	0.443	0.783

Source: Data Source Table 13.19, Table 13.20, Table 13.21, Table 13.22, Table 13.23, Table 13.24, Table 13.25, Table 13.26, Table 13.27 in Section 11; Patient Data Listing in Appendix C.7
Note: a decrease in score represents an improvement (less impact of illness on the patient's life)
*Treatment p-value from ANOVA with treatment and investigator in the model

5.4 Efficacy Subgroup Analysis

A secondary objective of the protocol was to investigate predictors of response. This was an exploratory analysis with no hypotheses postulated, and was accomplished by using a covariate analysis model including effects for treatment,

covariate, and treatment-by covariate interaction. The covariates examined included clinical subtypes, age at onset of depression, comorbidity, family history, and number of previous episodes of major depression.

The effects of covariates were evaluated using the endpoint of responders (defined by 50% reduction or score of 8 or less in the total HAM-D). The results for selected covariates are presented in Tables 39 and 40. The full analysis is present in the statistical appendices.

Significant covariate effects were seen for patients with features of atypical depression (p=0.023), features of melancholia (p=0.025), and for patients who had a history of prior episodes of depression (p=0.311). There was no evidence that age at onset, coexistence of anxiety or the other comorbid disorders had an effect on response.

With no covariate in the model, there was a weak trend for a treatment effect (p=0.275). Only the adjustment for the coexistence of an anxiety disorder produces a stronger trend toward a treatment effect (p=0.116).

Table 39 Summary of Responders by Subgroup at Endpoint

Covariate		Paroxetine	Imipramine	Placebo
None		67% (60/90)	59% (55/94)	55% (48/87)
Features of Atypical Depression	Yes	86% (19/22)	67% (10/15)	75% (6/8)
	No	60% (40/67)	57% (44/77)	54% (42/78)
Melancholic Features	Yes	55% (18/33)	52% (17/33)	49% (17/35)
	No	73% (41/56)	62% (37/60)	61% (31/51)
Anxiety Disorder	Yes	75% (9/12)	33% (7/21)	48% (10/21)
	No	65% (50/77)	65% (47/72)	59% (38/65)
Any Comorbid Disorder	Yes	70% (21/30)	54% (20/37)	47% (16/34)
	No	64% (38/59)	61% (34/56)	62% (32/52)
Family Hx of Depression	Yes	66% (51/77)	61% (51/84)	53% (44/83)
	No	60% (3/5)	50% (2/4)	100% (3/3)
Age at Onset	< 12	50% (11/22)	63% (15/24)	58% (7/12)
	≥ 12	71% (47/66)	57% (39/69)	55% (41/74)
Number of Depressive Episodes	≤ 1	68% (50/73)	55% (41/74)	61% (41/67)
	> 1	56% (9/16)	68% (13/19)	37% (7/19)

Source: Table 13.28.2 Statistical Appendix in Appendix A

Table 40 Summary of Covariate Analysis for Responders at Endpoint

Covariate	Treatment p-Value	Covariate p-Value	Treatment-by covariate p-Value
None	0.275		
Features of Atypical Depression	0.356	0.023	0.503
Melancholic Features	0.413	0.025	0.797
Anxiety Disorder	0.116	0.208	0.114
Any Comorbid Disorder	0.227	0.440	0.436
Age at Onset	0.904	0.569	0.217
Number of Depressive Episodes	0.260	0.311	0.118

Source: Table 13.28.1 Statistical Appendix in Appendix A

6 Safety Results

6.1 Extent of Exposure

The exposure of the patients to each dose level of the study drugs and the duration of that exposure during the acute phase is summarized in Table 41.

The mean duration of patient exposure to study drug was comparable between the paroxetine and imipramine groups. Patients in the placebo group were exposed to study drug an average of approximately one week longer than patients in either the paroxetine or imipramine groups.

More patients in the paroxetine group were maintained over the course of the study at the lowest dose (20 mg) of study drug compared to patients in the imipramine group who were titrated up to higher levels. However, those patients in the imipramine group who were exposed to higher levels of study drug were maintained at those levels for shorter periods of time. Patients in the paroxetine group had longer exposure to the two highest dose levels (levels 5 and 6) compared to patients in the imipramine group.

Table 41 Exposure of Patients to Each Daily Dose of Study Drug (in mg) and Duration of Exposure, by Treatment Group (number (%) of patients)

Study Drug Exposure	Paroxetine (N=93)			Imipramine (N=95)						Placebo (N=87)
	Dose (mg)			Dose (mg)						Dose
	20	30	40	50	100	150	200	250	300	0
Total Duration of Exposure (Wks)										
1	7 (7.5%)	24 (25.8%)	7 (7.5%)	91 (95.8%)	92 (96.8%)	79 (83.2%)	24 (25.3%)	23 (24.2%)	8 (8.4%)	2 (2.3%)
2	6 (6.5%)	12 (12.9%)	6 (6.5%)	4 (4.2%)	0 (0.0%)	2 (2.1%)	14 (14.7%)	4 (4.2%)	2 (2.1%)	6 (6.9%)
3	5 (5.4%)	6 (6.5%)	15 (16.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (6.3%)	10 (10.5%)	10 (10.5%)	3 (3.4%)
4	30 (32.3%)	8 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (9.5%)	1 (1.1%)	0 (0.0%)	2 (2.3%)
5	12 (12.9%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	23 (24.2%)	0 (0.0%)	0 (0.0%)	6 (6.9%)
7	33 (35.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	68 (78.2%)
Exposure (days)	**93**	**51**	**28**	**95**	**92**	**81**	**76**	**38**	**20**	**87**
Mean ± SE	**49.2 ± 1.92**			**48.8 ± 1.94**						**54.9 ± 1.88**
Median	**56**			**56**						**58**
Range	**1 - 73**			**8 - 77**						**9 - 79**

Source: Data Source Table 14.1 in Section 12; Patient Data Listing in Appendix B.16

6.2 Adverse Experiences

Overall, 245 patients (89.1%) had treatment-emergent adverse experiences: 86 patients (92.5%) in the paroxetine group, 90 patients (94.7%) in the imipramine group, and 69 patients (79.3%) in the placebo group.

The most commonly occurring emergent adverse experiences (i.e., those occurring in at least 5% of patients in any group) are shown in Table 42. These are presented by body system and preferred term.

The nature of the adverse events reported for the paroxetine group during the 8-week acute phase in this study is similar to that reported for adult depressed patients receiving paroxetine in controlled trials of comparable length[1]. In addition, the incidence of these common events as well as the attributable risk (i.e., the incidence in paroxetine group less the incidence in placebo) was similar to the incidence and the attributable risk reported in short term trials in adults.

The most common events (i.e. those occurring ≥ 15%) reported for the adolescent receiving paroxetine in the trial included headache (paroxetine = 34%, vs placebo = 39%), nausea (24% vs 20%), dry mouth (20% vs 14%), dizziness (24% vs 18%), somnolence (17% vs 3%), and insomnia (15% vs 5%).

The nature of the events occurring between 5% and 15% were generally comparable in the placebo and paroxetine groups, but for several events the rates were higher in the paroxetine group. Those events for which the incidence in the paroxetine patients was at least twice that of placebo, included tremors (paroxetine = 11% vs placebo = 2%), hostility (8% vs 0%), emotional lability (7% vs 1%) and tooth disorder (5% vs 2%). The tremor incidence and attributable risk are similar to those reported in adults. Hostility included events such as aggressiveness as well as behavior disturbances in school. The preferred term for emotional lability captured descriptions related to suicidal ideation and gestures as well as events such as overdose. These last two categories are described in more detail in the serious adverse events section of this report in Section 6.6.

The most common events (≥ 15%) in the imipramine group included dizziness (imipramine = 47% vs placebo = 18%), dry mouth (45% vs 14%), headache (40% vs 39%), nausea (24% vs 20%), and tachycardia (19% vs 1%).

Among those events reported to occur at a rate between 5% and 15% in the imipramine group and for which incidence was at least twice that of placebo, included tremor (imipramine = 15% vs placebo = 2%), postural hypotension (14%

vs 1%), vasodilation (6% vs 2%), chest pain (5% vs 2%), hostility (3% vs 0%), emotional liability (3% vs 1%), sweating (6% vs 1%), constipation (10% vs5%), insomnia (14% vs 5%), somnolence (14% vs 3%) and abnormal vision (7% vs 2%).

Table 42 Treatment-emergent Adverse Experiences Most Frequently Reported (by = or > 5% in Any Treatment Regimen), by Body System and Preferred Term (number (%) of patients)

Adverse Experience		Paroxetine N=93	Imipramine N=95	Placebo N=87
Patients with Adverse Experiences		86 (92.5%)	90 (94.7%)	69 (79.3%)
Body System	**Preferred Term**			
Body as a whole	Abdominal Pain	10 (10.8%)	7 (7.4%)	10 (11.5%)
	Asthenia	10 (10.8%)	7 (7.4%)	10 (11.5%)
	Back Pain	4 (4.3%)	2 (2.1%)	10 (11.5%)
	Chest Pain	2 (2.2%)	5 (5.3%)	2 (2.3%)
	Headache	32 (34.4%)	38 (40.0%)	34 (39.1%)
	Infection	10 (10.8%)	5 (5.3%)	9 (10.3%)
	Trauma	2 (2.2%)	3 (3.2%)	6 (6.9%)
Cardiovascular sytem	Postural Hypotension	1 (1.1%)	13 (13.7%)	1 (1.1%)
	Tachycardia	2 (2.2%)	18 (18.9%)	1 (1.1%)
	Vasodilatation	0 (0.0%)	6 (6.3%)	2 (2.3%)
Digestive system	Constipation	5 (5.4%)	9 (9.5%)	4 (4.6%)
	Decreased Appetite	7 (7.5%)	2 (2.1%)	4 (4.6%)
	Diarrhea	7 (7.5%)	3 (3.2%)	7 (8.0%)
	Dry Mouth	19 (20.4%)	43 (45.3%)	12 (13.8%)
	Dyspepsia	6 (6.5%)	9 (9.5%)	4 (4.6%)
	Nausea	22 (23.7%)	23 (24.2%)	17 (19.5%)
	Tooth Disorder	5 (5.4%)	2 (2.1%)	2 (2.3%)
	Vomiting	3 (3.2%)	8 (8.4%)	6 (6.9%)
Nervous system	Dizziness	22 (23.7%)	45 (47.4%)	16 (18.4%)
	Emotional Lability	6 (6.5%)	3 (3.2%)	1 (1.1%)
	Hostility	7 (7.5%)	3 (3.2%)	0 (0.0%)
	Insomnia	14 (15.1%)	13 (13.7%)	4 (4.6%)
	Nervousness	8 (8.6%)	6 (6.3%)	5 (5.7%)
	Somnolence	16 (17.2%)	13 (13.7%)	3 (3.4%)
	Tremor	10 (10.8%)	14 (14.7%)	2 (2.3%)
Respiratory system	Cough Increased	5 (5.4%)	3 (3.2%)	6 (6.9%)
	Pharyngitis	5 (5.4%)	12 (12.6%)	8 (9.2%)
	Respiratory Disorder	10 (10.8%)	7 (7.4%)	11 (12.6%)
	Rhinitis	7 (7.5%)	3 (3.2%)	5 (5.7%)
	Sinusitis	6 (6.5%)	2 (2.1%)	7 (8.0%)
Other	Sweating	1 (1.1%)	6 (6.3%)	1 (1.1%)
	Abnormal Vision	1 (1.1%)	7 (7.4%)	2 (2.3%)

Source: Data Source Table 14.2.1 in Section 12; Patient Data Listings in Appendix B.11 & B.12, D.1 & D.2

Analysis of Adverse Experiences by Age

Adverse experiences were also tabulated by patient age groups. Table 43 shows the most common emergent adverse events (i.e., > 5%) for patients under 15 years of age and for those 15 or older. The age of 15 was chosen as it provided a reasonable midpoint of the study population.

For most events reported in the paroxetine group, there is no clear pattern suggesting that the event is more likely to occur in one age group than the other. The exception to this is within the nervous system category in which some events tended to occur more often in the younger subset. As mentioned above, the term "hostility" included events such as conduct and behavioral disturbances.

In the imipramine group, the incidence of cardiovascular events including postural hypotension and tachycardia was reported more often in the older than younger group (18% vs 8% and 23% vs 13% respectively). Headache was also more often reported among the older adolescent.

In the placebo group, there were only a few events that appeared to cluster in one age group. As might be expected infections and respiratory events were more common in the younger subset.

Table 43 Number and Percent of Patients with Adverse Experiences by Age (by = or >5% in Any Group), by Body System, and Preferred Term (number (%) patients)

Adverse Experience (by Body System and Preferred Term)		Younger <15 yr	Older ≥ 15 yr
Paroxetine group			
Total Number of Patients		**39 (100%)**	**54 (100%)**
Patients With Adverse Experiences		**35 (89.7%)**	**51 (94.4%)**
Body as a whole	Abdominal Pain	6 (15.4%)	4 (7.4%)
	Asthenia	6 (15.4%)	4 (7.4%)
	Back Pain	3 (7.7%)	1 (1.9%)
	Headache	10 (25.6%)	22 (40.7%)
	Infection	5 (12.8%)	5 (9.3%)
Digestive	Constipation	1 (2.6%)	4 (7.4%)
	Decreased Appetite	5 (12.8%)	2 (3.7%)
	Diarrhea	3 (7.7%)	4 (7.4%)
	Dry Mouth	9 (23.1%)	10 (18.5%)
	Increased Appetite	2 (5.1%)	1 (1.9%)
	Nausea	9 (23.1%)	13 (24.1%)
	Tooth Disorder	2 (5.1%)	3 (5.6%)
	Vomiting	2 (5.1%)	1 (1.9%)
Nervous system	Depression	3 (7.7%)	1 (1.9%)
	Dizziness	11 (28.2%)	11 (20.4%)
	Emotional Lability	1 (2.6%)	5 (9.3%)
	Hostility	5 (12.8%)	2 (3.7%)
	Insomnia	9 (23.1%)	5 (9.3%)
	Manic Reaction	2 (5.1%)	0 (0.0%)
	Nervousness	4 (10.3%)	4 (7.4%)
	Somnolence	9 (23.1%)	7 (13.0%)
	Tremor	4 (10.3%)	6 (11.1%)
Respiratory system	Cough Increased	2 (5.1%)	3 (5.6%)
	Pharyngitis	4 (10.3%)	1 (1.9%)
	Respiratory Disorder	5 (12.8%)	5 (9.3%)
	Rhinitis	2 (5.1%)	5 (9.3%)
	Sinusitis	2 (5.1%)	4 (7.4%)
Other	Rash	2 (5.1%)	2 (3.7%)
	Urine Abnormality	2 (5.1%)	0 (0.0%)
	Myalgia	0 (0.0%)	3 (5.6%)

Table 43 (Continued)

Imipramine group			
Total Number of Patients		**38 (100%)**	**57 (100%)**
Patients With Adverse Experiences		**34 (89.5%)**	**56 (98.2%)**
Body as a whole	Abdominal Pain	5 (13.2%)	2 (3.5%)
	Asthenia	3 (7.9%)	4 (7.0%)
	Chest Pain	4 (10.5%)	1 (1.8%)
	Headache	11 (28.9%)	27 (47.4%)
	Infection	1 (2.6%)	4 (7.0%)
	Trauma	0 (0.0%)	3 (5.3%)
CV system	AV Block	2 (5.3%)	0 (0.0%)
	Postural Hypotension	3 (7.9%)	10 (17.5%)
	Syncope	1 (2.6%)	3 (5.3%)
	Tachycardia	5 (13.2%)	13 (22.8%)
	Vasodilatation	3 (7.9%)	3 (5.3%)
Digestive system	Constipation	3 (7.9%)	6 (10.5%)
	Diarrhea	0 (0.0%)	3 (5.3%)
	Dry Mouth	12 (31.6%)	31 (54.4%)
	Dyspepsia	2 (5.3%)	7 (12.3%)
	Nausea	12 (31.6%)	11 (19.3%)
	Vomiting	3 (7.9%)	5 (8.8%)
Nervous system	Abnormal Dreams	3 (7.9%)	1 (1.8%)
	Agitation	2 (5.3%)	0 (0.0%)
	Dizziness	16 (42.1%)	29 (50.9%)
	Emotional Lability	2 (5.3%)	1 (1.8%)
	Hostility	2 (5.3%)	1 (1.8%)
	Insomnia	4 (10.5%)	9 (15.8%)
	Nervousness	1 (2.6%)	5 (8.8%)
	Somnolence	9 (23.7%)	4 (7.0%)
	Thinking Abnormal	2 (5.3%)	0 (0.0%)
	Tremor	2 (5.3%)	12 (21.1%)
Respiratory system	Dyspnea	1 (2.6%)	3 (5.3%)
	Pharyngitis	1 (2.6%)	11 (19.3%)
	Respiratory Disorder	2 (5.3%)	5 (8.8%)
	Rhinitis	2 (5.3%)	1 (1.8%)
Other	Sweating	2 (5.3%)	4 (7.0%)
	Abnormal Vision	2 (5.3%)	5 (8.8%)
	Urination Impaired	2 (5.3%)	1 (1.8%)

Table 43 (Continued)

Placebo group			
Total Number of Patients		**33 (100%)**	**54 (100%)**
Patients With Adverse Experiences		**27 (81.8%)**	**42 (77.8%)**
Body as a whole	Abdominal Pain	2 (6.1%)	8 (14.8%)
	Allergic Reaction	0 (0.0%)	3 (5.6%)
	Asthenia	4 (12.1%)	6 (11.1%)
	Back Pain	2 (6.1%)	8 (14.8%)
	Fever	3 (9.1%)	1 (1.9%)
	Headache	12 (36.4%)	22 (40.7%)
	Infection	5 (15.2%)	4 (7.4%)
	Trauma	3 (9.1%)	3 (5.6%)
CV system	Vasodilatation	2 (6.1%)	0 (0.0%)
Digestive system	Constipation	1 (3.0%)	3 (5.6%)
	Decreased Appetite	2 (6.1%)	3 (5.6%)
	Diarrhea	2 (6.1%)	5 (9.3%)
	Dry Mouth	3 (9.1%)	9 (16.7%)
	Dyspepsia	2 (6.1%)	2 (3.7%)
	Nausea	6 (18.2%)	11 (20.4%)
	Vomiting	1 (3.0%)	5 (9.3%)
Nervous system	Dizziness	8 (24.2%)	8 (14.8%)
	Insomnia	1 (3.0%)	3 (5.6%)
	Nervousness	2 (6.1%)	3 (5.6%)
Respiratory system	Bronchitis	0 (0.0%)	4 (7.4%)
	Cough Increased	3 (9.1%)	3 (5.6%)
	Pharyngitis	5 (15.2%)	3 (5.6%)
	Respiratory Disorder	4 (12.1%)	7 (13.0%)
	Rhinitis	3 (9.1%)	2 (3.7%)
	Sinusitis	2 (6.1%)	5 (9.3%)
Other	Arthralgia	1 (3.0%)	3 (5.6%)

Source: Data Source Table 14.10.1 in Section 12

Male and Female - Specific Adverse Experiences

There were no male-specific adverse experiences. Female-specific adverse experiences were related to the urogenital system and consisted of amenorrhea, breast enlargement, dysmenorrhea, and female genital disorders (Data Source Table 14.2.3 in Section 12). There was a higher incidence of dysmenorrhea in the imipramine group among older patients (13.2%) than in the placebo group (5.6%) (Data Source Table 14.10.3 in Section 12). One unintended pregnancy occurred in the imipramine group in a 17 year-old patient and is reported as a withdrawal due to adverse event in Section 6.7.

6.2.1 Adverse Experiences by Severity

Most adverse experiences were mild to moderate in severity. Severe treatment emergent events were reported by a total of 66 patients: 27 (29%) in the paroxetine group, 24 (25%) in the imipramine group, and 15 (17%) in the placebo group. Those severe events that occurred in more than one patient in any one treatment regimen are presented in Table 44. A complete list of all severe events can be found in supporting tables 14.3.1 and 14.3.3 in Section 12.

Headache was the most common of the severe adverse events occurring in 15 patients, 8 of whom received imipramine. Two paroxetine and one imipramine patient were withdrawn for headaches. In two cases (one paroxetine and one imipramine) the headaches were accompanied by severe nausea. Severe infections were reported for 9 patients, and in no cases did the event result in stopping study medication. Within the nervous system category, worsening depression, including suicidal ideation/gestures and hostility were the most commonly reported severe events. These events also met the criteria for a serious event (requiring hospitalization) and are discussed in section 6.6 of this report.

Table 44 Severe Treatment-emergent Adverse Experience and those Occurring in More Than One Patient in any Group (number (%) of patients)

Severe Adverse Experience (by Body System and Preferred Term)		**Treatment Group**		
		Paroxetine N=93	**Imipramine N=95**	**Placebo N=87**
Number of Patients with at least one severe AE		**27 (29.0%)**	**24 (25.3%)**	**15 (17.2%)**
Body as a whole	Asthenia	2 (2.2%)	1 (1.1%)	1 (1.1%)
	Headache	3 (3.2%)	8 (8.4%)	4 (4.6%)
	Infection	4 (4.3%)	2 (2.1%)	3 (3.4%)
Digestive system	Constipation	0 (0%)	2 (2.1%)	0 (0%)
	Diarrhea	2 (2.2%)	1 (1.1%)	0 (0%)
	Vomiting	1 (1.1%)	3 (3.2%)	0 (0%)
	Nausea	2 (2.2%)	2 (2.1%)	0 (0%)
Nervous system	Worsening Depression	3 (3.2%)	0 (0%)	2 (2.3%)
	Emotional lability	4 (4.3%)	0 (0%)	1 (1.1%)
	Insomnia	2 (2.2%)	0 (0%)	0 (0%)
	Hostility	3 (3.2%)	2 (2.1%)	0 (0%)
	Somnolence	3 (3.2%)	0 (0%)	0 (0%)
	Tremor	1 (1.1%)	2 (2.1%)	0 (0%)
Respiratory System	Sinusitis	0 (0%)	0 (0%)	3 (3.4%)

Source: Data Source Table 14.3.1 in Section 12; Patient Data Listings in Appendix D.1 & D.2

6.2.2 Adverse Experiences by Time of First Occurrence

An analysis of the time of when adverse experiences first occurred is presented in source tables 14.4.1 and 14.4.3 in Section 12. Table 45 derived from Source Table 14.4.1 shows the time to first occurrence of the four most common events in each of the treatment regimens. The incidence of each event is expressed as a percentage of the overall number of patients in that group with the event.

In general the pattern seen with the four most commonly reported events supports that the onset of these events occurs during the first week of treatment. This includes the imipramine group in which patients were titrated over a four week period. For less common events, a pattern of early onset is also apparent, however, any interpretation is limited because there are fewer number of events occurring over the eight week period.

Table 45 Number (%) of Patients of the Four Most Frequently Reported Treatment-emergent Adverse Experiences by the Time of First Occurrence

Adverse Experience	No. of pts with event	Time of First Occurrence							
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Paroxetine group									
Headache[a]	32	14 (43.8%)	3 (9.4%)	3 (9.4%)	0 (0.0%)	2 (6.3%)	3 (9.4%)	0 (0.0%)	7 (21.9%)
Nausea	22	12 (54.5%)	2 (9.1%)	1 (4.5%)	2 (9.1%)	1 (4.5%)	3 (13.6%)	1 (4.5%)	0 (0.0%)
Dry Mouth	19	12 (63.2%)	4 (21.1%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	1 (5.3%)	1 (5.3%)	0 (0.0%)
Dizziness	22	12 (54.5%)	1 (4.5%)	2 (9.1%)	2 (9.1%)	0 (0.0%)	2 (9.1%)	1 (4.5%)	2 (9.1%)
Imipramine group									
Headache[b]	38	19 (50.0%)	1 (2.6%)	6 (15.8%)	3 (7.9%)	3 (7.9%)	2 (5.3%)	3 (7.9%)	1 (2.6%)
Nausea[c]	23	11 (47.8%)	2 (8.7%)	1 (4.3%)	1 (4.3%)	3 (13.0%)	3 (13.0%)	1 (4.3%)	1 (4.3%)
Dry Mouth[d]	43	20 (46.5%)	7 (16.3%)	8 (18.6%)	3 (7.0%)	3 (7.0%)	1 (2.3%)	0 (0.0%)	1 (2.3%)
Dizziness	45	21 (46.7%)	7 (15.6%)	8 (17.8%)	1 (2.2%)	5 (11.1%)	2 (4.4%)	1 (2.2%)	0 (0.0%)
Placebo group									
Headache	34	8 (23.5%)	7 (20.6%)	7 (20.6%)	3 (8.8%)	5 (14.7%)	0 (0.0%)	3 (8.8%)	1 (2.9%)
Nausea	17	7 (41.2%)	2 (11.8%)	4 (23.5%)	2 (11.8%)	1 (5.9%)	1 (5.9%)	0 (0.0%)	0 (0.0%)
Dizziness	16	5 (31.3%)	1 (6.3%)	4 (25.0%)	0 (0.0%)	4 (25.0%)	0 (0.0%)	2 (12.5%)	0 (0.0%)
Dry Mouth	12	5 (41.7%)	1 (8.3%)	0 (0.0%)	1 (8.3%)	1 (8.3%)	2 (16.7%)	1 (8.3%)	1 (8.3%)

Source: Data Source Table 14.4.1 in Section 12; Patient Data Listings in Appendix D.1 & D.2

[a] Patient 329.005.00116 experienced a headache on day 65

[b] Patients 329.007.00270 and 329.007.00307 experienced a headache on days 47 and 50 respectively

[c] Patient 329.004.00215 experienced nausea on day 42

[d] Patients 329.003.00082 and 329.012.00221 experienced dry mouth on days 38 and 67 respectively

6.3 Dose Reductions for Adverse Experiences

Overall, adverse experiences led to a dose reduction in 19 patients; (8 paroxetine, 9 imipramine, and 2 placebo). All patients with a treatment-emergent adverse experience that led to a dose reduction are listed in Table 46. In the paroxetine group, sleepiness, insomnia, and restlessness were the most common events that led to a dose reduction. For the imipramine group, the most common events were gastrointestinal complaints and hand tremors. In all cases the events were non-serious and the patients remained in the study following dose reduction.

Table 46 Treatment-emergent Adverse Experiences That Led to Dose Reductions

Patient number	Adverse Experience (verbatim)	Investigator's Attribution
	Paroxetine Group	
329.003.00075	Anorgasmia (female) Drowsiness	Related Possibly related
329.003.00250	Sleepiness	Possibly related
329.004.00017	Anxiety, insomnia, nausea	Related
329.004.00214	Dizziness, upset stomach, headache, headache, nausea	Possibly related, Related, Related, possibility related
329.005.00008	Extreme sleepiness/fatigue	Related
329.008.00271	Lightheadedness; cold, clammy, shakiness	Possibly related
329.009.00170	Loss of appetite	Possibly related
329.009.00173	Restlessness	Possibly related
	Imipramine Group	
329.002.00098	Constipation, dry mouth, headaches, shaking	Possibly related
329.003.00090	Constipation, indigestion, headache, bad taste	Possibly related
329.003.00247	Nervousness (irritable, edgy, burned self with cigarette)	Possibly related
329.005.00007	Hand tremors	Related
329.005.00009	Hand tremors	Related
329.005.00255	Blurred vision, hand tremors	Related
329.005.00335	EKG change (abnormal)	Related
329.008.00192	Lightheadedness, dry mouth, heartburn, drowsiness	Probably unrelated, probably unrelated, possibly related, probably unrelated
329.012.00221	Euphoria (mild elation and disinhibition)	Possibly related
	Placebo Group	
329.003.00252	Shortness of breath, headache, irritability	Possibly related
329.005.00331	Depersonalization ("spaced out" feeling)	Possibly related

Source: Data Source Table 14.5.1, 14.5.3 in Section 12; Patient Data Listings in Appendix B.16 & D.2

6.4 Adverse Experiences Requiring Corrective Treatment

Table 47 shows the number of adverse experiences in each treatment group (≥ 5%) that required corrective treatment regardless of attribution to study medication. In the paroxetine group, a total of 46 adverse experiences required corrective treatment, in the imipramine group, a total of 42 adverse experiences required corrective treatment, and in the placebo group, a total of 46 adverse

experiences required corrective treatment. The more common events that required treatment were headaches and symptoms of respiratory infections. The incidence of these events were comparable between treatment regimens.

Table 47 Adverse Experiences That Required Corrective Treatment (≥ 5%), Regardless of Attribution to Study Medication

Adverse Experiences	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Headache	20 (21.5%)	20 (21.1%)	23 (26.4%)
Respiratory Disorder	8 (8.6%)	5 (5.3%)	7 (8.0%)
Rhinitis	6 (6.5%)	3 (3.2%)	3 (3.4%)
Pharyngitis	4 (4.3%)	9 (9.5%)	5 (5.7%)
Infection	4 (4.3%)	2 (2.1%)	7 (8.0%)
Sinusitis	4 (4.3%)	1 (1.1%)	6 (6.9%)
Back Pain	4 (4.3%)	1 (1.1%)	5 (5.7%)

Source: Data Source Table 14.6.1 in Section 12; Patient Data Listings in Appendix D.1 & D.2

There were no male specific adverse experiences that required corrective treatment. Female specific adverse experiences are tabulated in Data Source Table 14.6.3 in Section 12. Of all females, a total of 10 patients (5.8%) had adverse experiences that required corrective treatment: 2 patients (3.4%) in the paroxetine group, 3 patients (5.4%) in the imipramine group, and 4 patients (7.0%) in the placebo group had dysmenorrhea; 1 patient (0.6%) in the imipramine group had vaginal moniliasis. The incidence of dysmenorrhea was incidental to study drug.

6.5 Deaths

There were no deaths reported during the acute phase of this study or for the 30 days following each patient's completion.

6.6 Serious Non-fatal Adverse Experiences

Serious adverse experiences (SAEs) were defined as those that were 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 48 shows the number of patients in each treatment group with serious non-fatal adverse experiences. Eighteen (18) patients in the intent-to-treat population had a total of 30 serious adverse experiences. Individual narratives for patients listed in Table 48 are provided in Section 12, Table 14.8a.

During the acute phase of the trial, eleven paroxetine patients were reported to have had a serious adverse event. One patient, a 14 year old girl, experienced discontinuation symptoms consisting of migraine headaches during a down titration phase after she completed 8 weeks of paroxetine treatment. She had been receiving a daily dose of 30 mg at the time of the adverse event. For the remaining ten patients, the serious events were psychiatric in nature including worsening depression (2 patients) emotional lability (5 patients), hostility or conduct problems (2 patients) and mania (one patient).

Of the two patients with worsening depression, one (329.001.00065) had the event early in treatment and it was accompanied by acts of anger.

The term emotional lability captures events such as suicidal ideation/gestures as well as overdoses and events such as hallucinations. Of the five paroxetine patients categorized under this term, two (329.002.00245 and 329.006.00038) were patients who took a undefined number of acetominophen pills and other various drugs. In both cases the act appeared to be impulsive and reactive to parental confrontation and were considered by the investigators to be unrelated to drug treatment. For patient 329.006.00038, the investigator indicated the patient had had significant improvement in her depression. Of the remaining three, one (329.003.00250) took more study medication tablets than prescribed, one (329.005.00333) was hospitalized for suicidal ideation, and one (329.003.00313) had auditory hallucination and displayed threats of self mutilation. Again, these events were considered by investigators to be either unrelated or probably unrelated to drug treatment.

The two events of hostility involved one patient (329.001.00065) who exhibited anger and aggression against self, and a second patient (329.002.00106) who became combative after parental confrontation. Both were hospitalized to control their hostility. Both events were considered by the investigator to be probably unrelated to drug treatment.

Manic and aggressive behavior resulted in hospitalization for female paroxetine patient 329.003.00089. She exhibited motor hyperactivity, impulsive and sexual provocative behavior. During a clinical visit, there were threats from the mother of punishment in an attempt to control the behavior. The patient reacted with agitation and threats of suicide. The investigator judged these events to be possible related to the study medication and possibly related to undiagnosed mania secondary to family discord.

In the imipramine group there were five patients with serious events, one patient (329.007.00307) developed a maculopapular rash, one patient (329.007.00270) experienced dyspnea and chest pain, and three patients had serious psychiatric symptoms including hostility (329.002.00321), emotional lability (329.012.00223), and one patient reported visual hallucinations accompanied by abnormal dreams (329.004.00215).

In the placebo group there were two patients with serious events, both were worsening depression (329.001.00123 and 329.012.00217).

Table 48 Serious Non-fatal Adverse Experiences

Patient number	Adverse experience (Preferred Term)	Investigator relationship	Outcome	Comments
		Paroxetine Group		
329.001.00065	Worsening of Depression, Hostility	Possibly related, Probably unrelated	Ongoing	Hospitalized, Withdrawn
329.002.00106	Hositlity	Probably unrelated	Resolved	Hospitalized, Withdrawn
329.002.00245	Emotional Lability (Overdose with Tylenol)	Unrelated	Resolved	Withdrawn
329.003.00089	Euphoria (elation and expansive mood)	Possibly related	Ongoing	Hospitalized
329.003.00248	Withdrawal Syndrome (Migraine headache)	Related	Resolved	Occurred during down titration
329.003.00250	Emotional Lability (Overdose: Exceeded Compliance)	Unrelated	Resolved	Patient continued in study
329.003.00313	Emotional Lability (superficial cuts, risk to self), hallucinations (auditory)	Probably unrelated	Resolved	Hospitalized, Withdrawn
329.005.00333	Emotional Lability (Suicidal ideation)	Unrelated	Resolved	Occurred 4 days after stopping study medication due to lack of efficacy
329.006.00038	Emotional Lability (suicide attempt with overdose)	Unrelated	Resolved	Multiple drugs, withdrawn
329.009.00201	Agitation, hostility, paranoid reaction	Possibly related	Treated	Hospitalized
329.009.00240	Worsening of depression, Insomnia	Unrelated, Possibly related	Ongoing	Hospitalized, Withdrawn
		Imipramine Group		
329.002.00321	Hostility	Unrelated	Unknown	Hospitalized, Withdrawn
329.004.00215	Hallucinations, nervousness, dizziness, abnormal dreams	Related	Resolved	Disabling per investigator, Withdrawn
329.007.00270	Chest pain, dyspnea	Possibly related	Resolved	Significant side effect per investigator, Withdrawn
329.007.00307	Maculopapular rash	Related	Resolved	Significant hazard per investigator, Withdrawn
329.012.00223	Hypertension, worsening of depression, emotional lability (self mutilation)	Unrelated	Ongoing	Hospitalized, Withdrawn
		Placebo Group		
329.001.00123	Emotional Lability (suicidal thoughts), worsening of depression	Related	Unknown	Life threatening per investigator, Withdrawn
329.012.00217	Worsening of depression on withdrawal	Unrelated	Ongoing	Patient withdrawn 5 days prior due to Flu

Source: Data Source Table 14.8 in Section 12; Patient Data Listings in Appendix D.1 & D.2

6.7 Withdrawals for Adverse Experiences

There were 45 patients (16.4%) withdrawn due to adverse experiences: 9 (9.7%) in the paroxetine, 30 (31.6%) in the imipramine group, and 6 (6.9%) in the placebo group. Adverse experiences related to the nervous system led to the withdrawal of more patients in the paroxetine group than any other body system. In the imipramine and placebo groups, adverse experiences related to the cardiovascular system led to the largest number of withdrawals. The events leading to withdrawal are summarized in Table 49. Table 50 lists individual patients who were withdrawn and the reason for withdrawal. Individual patient narratives for patients listed in Table 50 are provided in Section 12, Table 14.9.1a (unless discussed in a narrative for a serious adverse experience). For five patients in Table 49, the withdrawal occurred in the continutation phase following completion of the acute phase (see Table 49 footnotes).

Nervous system events were the most common occurrences leading to withdrawal in the paroxetine group. Many of these events have been discussed under the section describing the serious adverse experiences. Non-serious events leading to withdrawal of paroxetine patients included headache and various gastrointestinal complaints.

For the imipramine group, cardiovascular events commonly lead to stoppage of treatment, with tachycardia occurring the most frequent.

No particular pattern of withdrawals was observed in the placebo group.

Table 49 Treatment-emergent Adverse Experiences, Regardless of Attribution, Leading to Withdrawal (number (%) of patients)

Body system* preferred term	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Body as a whole	**2 (2.2%)**	**7 (7.4%)**	**1 (1.1%)**
Abnormal Laboratory value	0 (0.0%)	1 (1.1%)[a]	0 (0.0%)
Asthenia	0 (0.0%)	2 (2.1%)	0 (0.0%)
Chest Pain	0 (0.0%)	2 (2.1%)	0 (0.0%)
Headache	2 (2.2%)	1 (1.1%)	0 (0.0%)
Infection	0 (0.0%)	0 (0.0%)	1 (1.1%)
Trauma	0 (0.0%)	2 (2.1%)	0 (0.0%)
Cardiovascular System	**1 (1.1%)**	**13 (13.7%)**	**2 (2.3%)**
Arrhythmia	0 (0.0%)	1 (1.1%)	1 (1.1%)[f]
AV Block	1 (1.1%)	1 (1.1%)	0 (0.0%)
Bundle Branch Block	0 (0.0%)	0 (0.0%)	1 (1.1%)
Electrocardiogram Abnormal	0 (0.0%)	1 (1.1%)	0 (0.0%)
Extrasystoles	0 (0.0%)	1 (1.1%)	0 (0.0%)
Hypertension	0 (0.0%)	1 (1.1%)	0 (0.0%)
Postural Hypotension	0 (0.0%)	2 (2.1%)	0 (0.0%)
QT Interval Prolonged	0 (0.0%)	2 (2.1%)	0 (0.0%)
Tachycardia	0 (0.0%)	8 (8.4%)	1 (1.1%)
Digestive System	**2 (2.2%)**	**8 (8.4%)**	**1 (1.1%)**
Constipation	1 (1.1%)	1 (1.1%)	0 (0.0%)
Diarrhea	1 (1.1%)	0 (0.0%)	0 (0.0%)
Dry Mouth	0 (0.0%)	1 (1.1%)	0 (0.0%)
Dyspepsia	0 (0.0%)	1 (1.1%)	0 (0.0%)
Gastroenteritis	0 (0.0%)	1 (1.1%)	0 (0.0%)
Nausea	1 (1.1%)	5 (5.3%)[b]	1 (1.1%)
Ulcerative Stomatitis	0 (0.0%)	1 (1.1%)	0 (0.0%)
Vomiting	1 (1.1%)	3 (3.2%)	1 (1.1%)
Musculoskeletal System	**1 (1.1%)**	**1 (1.1%)**	**0 (0.0%)**
Arthralgia	0 (0.0%)	1 (1.1%)	0 (0,.0%)
Myalgia	1 (1.1%)	0 (0.0%)	0 (0.0%)
Myasthenia	1 (1.1%)	0 (0.0%)	0 (0.0%)
Nervous System	**8 (8.6%)**	**7 (7.4%)**	**2 (2.3%)**
Abnormal Dreams	0 (0.0%)	1 (1.1%)	0 (0.0%)
Agitation	1 (1.1%)[c]	0 (0.0%)	0 (0.0%)
Depression	2 (2.2%)	0 (0.0%)	0 (0.0%)
Dizziness	1 (1.1%)	5 (5.3%)	1 (1.1%)
Emotional Lability	3 (3.2%)	1 (1.1%)	0 (0.0%)
Hallucinations	1 (1.1%)	1 (1.1%)	0 (0.0%)
Hostility	2 (2.2%)[c]	1 (1.1%)	0 (0.0%)
Manic Reaction	2 (2.2%)	0 (0.0%)	1 (1.1%)[e]
Nervousness	0 (0.0%)	2 (2.1%)	0 (0.0%)
Paranoid Reaction	1 (1.1%)[c]	0 (0.0%)	0 (0.0%)
Somnolence	0 (0.0%)	1 (1.1%)	0 (0.0%)

Table 49 (Continued)

Respiratory System	**0 (0.0%)**	**2 (2.1%)**	**0 (0.0%)**
Dyspnea	0 (0.0%)	2 (2.1%)	0 (0.0%)
Skin and Appendages	**0 (0.0%)**	**4 (4.2%)**	**1 (1.1%)**
Acne	0 (0.0%)	1 (1.1%)	0 (0.0%)
Maculopapular Rash	0 (0.0%)	2 (2.1%)	1 (1.1%)
Rash	0 (0.0%)	1 (1.1%)d	0 (0.0%)
Special Senses	**0 (0.0%)**	**1 (1.1%)**	**0 (0.0%)**
Mydriasis	0 (0.0%)	1 (1.1%)	0 (0.0%)
Urogenital System	**0 (0.0%)**	**3 (3.2%)**	**0 (0.0%)**
Urinary Retention	0 (0.0%)	2 (2.1%)	0 (0.0%)
Urination Impaired	0 (0.0%)	1 (1.1%)	0 (0.0%)
Unintented Pregnancy	0 (0.0%)	1 (1.8%)g	0 (0.0%)

Source: Data Source Tables 14.9.1, 14.9.2 and 14.9.3 in Section 12; Patient Data Listings in Appendix D.1 & D.2

* The number of patients within a body system are not additive, since a patient can have more than one reason for withdrawal within a body system.

a Patient 329.011.00208 had a toxic imipramine level in the acute phase, however, was not withdrawn until the continuation phase.

b Patient 329.009.00194 developed nausea in the acute phase, however, was not withdrawn until the continuation phase.

c Patient 329.009.00201 completed the acute phase, however, did not participate in continuation phase due to ongoing serious adverse events.

d Patient 329.005.00007 developed a rash in the acute phase, however, was not withdrawn until the continuation phase.

e Patient 329.009.00169 completed acute phase, however, withdrew in continuation phase.

f Patient 329.009.00302 experienced an adverse experience of nodal arrhythmia for which the investigator indicated that the patient was withdrawn from the study, however, the action taken with respect to study drug was erroneously marked "none."

g Percent adjusted for gender.

Table 50 Adverse Experiences Leading to Withdrawal

Patient number	Adverse experience (preferred term)	Investigator relationship
	Paroxetine	
329.001.00063	Manic Reaction	Possibly Related
329.001.00065	Worsening Depression*, Hostility*	Possibly Related, Probably Unrelated
329.001.00205	Manic Reaction	Possibly Related
329.002.00245	Emotional Lability*	Unrelated
329.003.00313	Hallucination*, Emotional Lability*	Probably Unrelated
329.005.00152	Diarrhea, Headache, Nausea, Vomiting	Related
329.006.00038	Myasthenia, Emotional Lability*, Dizziness, Myalgia, Constipation, Headache	Unrelated
329.009.00240	Worsening Depression*	Unrelated
329.012.00226	AV Block	Possibly Related
	Imipramine	
329.001.00061	QT Interval Prolonged	Related
329.001.00066	Tachycardia	Related
329.001.00067	Postural hypotension, Dizziness	Possibly Related
329.001.00070	Tachycardia	Related
329.002.00050	Tachycardia, Urination Impaired, Postural Hypotension	Possibly Related
329.002.00056	Tachycardia	Possibly Related
329.002.00243	Trauma (fell)	Possibly Related
329.002.00321	Hostility*	Unrelated
329.002.00322	Arrythmia, Dizziness	Possibly Related
329.003.00073	Vomiting	Possibly Related
329.003.00088	Urinary Retention	Related
329.003.00290	Tachycardia, Hypertension	Possibly Related
329.004.00014	Nausea	Possibly Related
329.004.00211	Ulcerative Stomatitis, Dry Mouth, Gastroenteritis, Trauma	Related, Related, Unrelated, Related
329.004.00215	Vomiting, Nervousness*, Hallucinations*, Dizziness*, Arthralgia, Nausea, Headache, Asthenia, Abnormal Dreams*	Related
329.005.00003	Tachycardia	Related
329.005.00110	Pregnancy	Unrelated
329.005.00113	Emotional Lability	Unrelated
329.006.00040	Tachycardia, Dyspepsia, Dizziness, Nervousness, Mydriasis, Urinary Retention, Constipation, Asthenia	Related, Possibly related, Related. Related, Related, Related, Related, Related
329.007.00139	Dyspnea, Chest Pain	Possibly Related
329.007.00143	Acne	Possibly Related
329.007.00269	Tachycardia, ECG Abnormal	Related
329.007.00270	Dyspnea*, Chest Pain*	Possibly Related
329.007.00307	Maculopapular rash*	Related

Table 50 (Continued)

329.009.00127	Nausea	Related
329.009.00171	Maculopapular rash	Probably Unrelated
329.009.00195	Extrasystoles	Related
329.009.00203	QT Interval Prolonged, AV Block	Related
329.009.00236	Dizziness, Somnolence	Related
329.011.00163	Nausea, Vomiting	Possibly Related
	Placebo	
329.005.00005	Tachycardia	Possibly Related
329.007.00141	Angina Pectoris[1]	Probably Unrelated
329.009.00128	Bundle Branch Block	Possibly Related
329.009.00302	Maculopapular rash, Nodal Arrhythmia[2]	Possibly Related
329.009.00330	Nausea, Dizziness, Vomiting	Related, Related, Possibly Related
329.012.00217	Infection	Unrelated

Source: Patient Data Listings in Appendix D.1 & D.2.

* Also listed as a serious advese event in Table 48.

1 Pre-existing condition

2 Patient 329.009.00302 experienced an adverse experience of nodal arrhythmia for which the investigator indicated that the patient was withdrawn from the study, however, the action taken with respect to study drug was erroneously marked "none."

6.8 Vital Signs and Body Weight

Table 51 presents the group mean values for baseline, final treatment values and change from baseline for the systolic and diastolic blood pressure, pulse rate, and body weight. The number of patients with values of potential clinical concern at any time during treatment are shown in Table 52. Individual patient narratives for vital signs and body weights of potential clinical concern are in Section 12, Table 14.12a unless discussed in a narrative for a serious adverse experiences or an adverse experience withdrawal.

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

In the imipramine group there was a marked increase in mean sitting and standing pulse rates. The pulse rates tended to increase by over 15 beats/min. for measures taken sitting and standing. The blood pressure also increased in the imipramine group but to a lesser degree than pulse rate. Diastolic pressure increased by an average of 2.5 and 3.5 for standing and sitting diastolic pressure respectively.

Table 52 shows that the number of paroxetine patients with vital signs of potential clinical concern were few and comparable to placebo. In the imipramine group, however, nearly 20% of patients had significantly elevated standing pulse rates.

Table 51 Vital Signs and Body Weight at Screening, Baseline and at Endpoint (mean +/- SD)

Vital sign parameter	Treatment Group					
	Paroxetine	**n**	**Imipramine**	**n**	**Placebo**	**n**
Sitting systolic BP (mmHg)						
Screening	112.29 ± 12.24	87	110.74 ± 12.49	90	112.30 ± 11.45	84
Baseline	110.45 ± 13.67	88	109.38 ± 14.20	89	109.19 ± 12.88	80
Endpoint	110.38 ± 12.47	90	111.27 ± 14.34	94	110.32 ± 11.04	87
Change	-0.52 ± 12.06	90	1.81 ± 12.28	94	0.68 ± 10.88	87
Sitting diastolic BP (mmHg)						
Screening	68.54 ± 7.69	87	67.69 ± 8.36	90	68.26 ± 9.91	84
Baseline	67.74 ± 8.68	88	66.88 ± 9.98	89	67.10 ± 10.71	80
Endpoint	67.52 ± 7.80	90	70.48 ± 8.94	94	66.85 ± 9.94	87
Change	-0.54 ± 9.01	90	3.59 ± 9.26	94	-0.85 ± 10.40	87
Standing systolic BP (mmHg)						
Screening	110.75 ± 12.68	85	110.93 ± 13.09	88	110.04 ± 11.19	80
Baseline	109.42 ± 15.11	88	106.26 ± 13.90	88	107.66 ± 12.76	76
Endpoint	110.18 ± 13.48	90	105.80 ± 15.15	93	108.32 ± 12.75	87
Change	0.44 ± 12.63	90	-0.44 ± 13.32	93	-0.24 ± 13.26	86
Standing diastolic BP (mmHg)						
Screening	71.16 ± 7.98	85	69.14 ± 8.75	88	70.40 ± 9.66	80
Baseline	69.89 ± 8.91	88	67.49 ± 9.67	88	66.74 ± 9.64	76
Endpoint	70.04 ± 8.58	90	69.76 ± 11.30	93	67.32 ± 10.22	87
Change	0.13 ± 10.08	90	2.53 ± 10.24	93	0.22 ± 10.43	86
Sitting pulse (bpm)						
Screening	74.78 ± 13.98	86	74.53 ± 10.95	89	75.44 ± 11.08	82
Baseline	76.91 ± 10.28	87	76.61 ± 10.51	89	79.32 ± 10.61	79
Endpoint	78.12 ± 12.93	90	92.10 ± 13.43	94	78.57 ± 11.62	87
Change	0.86 ± 12.26	90	15.39 ± 13.41	94	0.14 ± 13.00	87
Standing pulse (bpm)						
Screening	81.47 ± 13.78	85	82.82 ± 13.01	88	83.24 ± 13.38	80
Baseline	84.55 ± 13.72	88	83.41 ± 11.31	88	87.07 ± 11.97	75
Endpoint	85.83 ± 13.62	90	101.22 ± 17.26	93	86.72 ± 14.01	87
Change	1.07 ± 14.63	90	17.68 ± 17.19	93	0.49 ± 15.99	86
Body weight (lb)						
Screening	146.27 ± 38.91	88	139.41 ± 36.72	91	145.30 ± 40.76	84
Baseline	146.49 ± 38.79	87	141.19 ± 37.14	87	144.93 ± 41.31	77
Endpoint	146.88 ± 38.16	90	138.46 ± 36.76	93	147.09 ± 41.15	87
Change	-0.23 ± 4.56	90	-0.99 ± 4.52	93	1.19 ± 3.95	87

Source: Data Source Table 14.11 in Section 12; Patient Data Listing in Appendix E.1

N.B.: Change is calculated using the baseline value. In the absence of a baseline value the screening value is substituted.

Table 52 Number (%) of Patients with Vital Sign or Body Weight Values of Potential Clinical Concern at Any Time During Treatment

Vital Sign Parameter of Clinical Concern	Treatment Group		
	Paroxetine (N=93)	Imipramine (N=95)	Placebo (N=87)
Sitting systolic BP (mmHg)			
HI (>180 and increase ≥ 40)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LO (<90 and decrease ≥30)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sitting diastolic BP (mmHg)			
HI (>105 and increase ≥30)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LO (<50 and decrease ≥20)	1 (1.1%)	0 (0.0%)	2 (2.3%)
Standing systolic BP (mmHg)			
HI (>180 and increase ≥40)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LO (<90 and decrease ≥30)	3 (3.2%)	2 (2.1%)	3 (3.4%)
Standing diastolic BP (mmHg)			
HI (>105 and increase ≥30)	0 (0.0%)	0 (0.0%)	0 (0.0%)
LO (<50 and decrease ≥20)	1 (1.1%)	1 (1.1%)	1 (1.1%)
Sitting pulse (bpm)			
HI (>120 and increase ≥30)	0 (0.0%)	4 (4.2%)	0 (0.0%)
LO (<50 and decrease ≥30)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Standing pulse (bpm)			
HI (>120 and increase ≥30)	1 (1.1%)	17 (17.9%)	1 (1.1%)
LO (<50 and decrease ≥30)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Body weight (lbs)			
HI (increase ≥7%)	2 (2.2%)	0 (0.0%)	3 (3.4%)
LO (decrease ≥7%)	2 (2.2%)	3 (3.2%)	1 (1.1%)

Note: The number of patients is not additive, since an individual patient may have had more than one value of clinical concern.
Source: Data Source Table 14.12 in Section 12; Patient Data Listing in Appendix E.2

6.9 Other Safety Data

Serum Concentrations of Imipramine and Desipramine

One patient (329.011.00208) was reported as having an imipramine level of 592 ng/mL during treatment. This was recorded at the week 8 visit during the acute phase of which the patient completed. There were no adverse events or abnormal vital signs reported in association with this event, however, the patient was withdrawn from the study shortly after starting in the continuation phase. Serum drug levels will be reported separately.

Serum Pregnancy Tests

One patient in the imipramine group (329.005.00110) was found to be pregnant upon retest of serum HCG shortly after starting study medication (day 11). She was withdrawn from the trial.

6.10 Laboratory Tests

Change from Baseline in Laboratory Values at Endpoint

Clinical laboratory studies were performed for each patient prior to the start of study medication (screening/baseline) and at the patient's final visit. These laboratory parameters were summarized using descriptive statistics. Review of the mean values pre and post treatment 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 14.13 in Section 12. All laboratory data by patient can be found in appendix G.

Laboratory Values of Potential Clinical Concern

In addition to reviewing the mean laboratory data, each lab 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 Table 53. Values above or below these extended ranges were considered to be of potential clinical concern.

Table 53 Criteria for Flagging of Selected Laboratory Parameters

Laboratory Tests		Units	Reference Range	Sponsor-defined Values of Clinical Concern
Hematology				
Hemoglobin	M	g/dL	12-15.6	≤11.5
Hemoglobin	F	g/dL		≤9.5
Hematocrit	M	%	35-46	≤37.0
Hematocrit	F	%		≤32.0
WBC count		THOU/mcL	3.8-10.1	≤2.8 or ≥16.0
Neutrophils (segs)		%	40-75	≤15
Lymphocytes		%	18-47	≥75
Monocytes		%	0-12	≥15
Eosinophils		%	0-7	≥10
Basophils		%	0-2	≥10
Platelet count		$x\ 10^9/L$	130-400	≤75 or ≥700
Liver Function				
AST (SGOT)		U/L	0-42	≥150
ALT (SGPT)		U/L	0-48	≥165
Alkaline phosphatase		U/L	15-110	≥390
Total bilirubin		mg/dL	0.3-1.3	≥2.0
Renal Function				
Serum creatinine		mg/dL	0.8-1.5	≥2.0
BUN		mg/dL	7-25	≥30.0
Urinalysis				
Proteinuria		-	0	≥4+
Glucosuria		-	0	≥4+
RBC	M	/hpf	0	>8
RBC	F			>10
WBC		/hpf	0	>10

The number of patients with laboratory values considered to be of potential clinical concern is shown in Table 54. A total of 26 patients were identified as having one or more laboratory value(s) of potential clinical concern during the study: 12 patients (12.9%) in the paroxetine group, 7 patients (7.4%) in the imipramine group, and 7 patients (8.0%) in the placebo group.

Seven patients had an abnormal platelet count (4 paroxetine, 2 imipramine, 1 placebo). For the imipramine and paroxetine patients, all were low counts and were due to in vitro clumping of the sample and not of clinical significance. The placebo patient (329.003.00316) entered the study with an elevated platelet count at 606,000 per cubic millimeter. By week 8, the patient's platelet count increased to 771,000 at which time the investigator reported an adverse experience of thrombocythemia of mild intensity, probably unrelated to study drug. No treatment was required and the patient continued in the study.

There were five patients who were identified as having a low hematocrit level of potential clinical concern (2 paroxetine, 3 imipramine, 0 placebo). None of these, however, were reported as adverse events by the investigators and all five patients completed the acute phase of the study.

Two patients in the paroxetine group had high white blood cell counts at levels of potential clinical concern. One patient's sample was reported to be hemolyzed. Neither was reported as an adverse event by the investigator. Both patients completed the acute phase of the study.

There were eight patients who had red blood cells in their urine which were considered to be a potential clinical concern (5 paroxetine, 1 imipramine, 2 placebo). All but one patient was female and in no case was the abnormal lab reported as an adverse experience by the investigator.

Other laboratory values identified as potential concern occurred in small numbers and none were reported as adverse experiences by the investigator.

Table 54 Number of Patients with Laboratory Values Considered to Be of Clinical Concern

	Treatment Group		
Laboratory Tests*	**Paroxetine**	**Imipramine**	**Placebo**
Hematology			
Hematocrit (M)	2	2	0
Hematocrit (F)	0	1	0
WBC count	2	0	0
Neutrophils (segs)	0	0	1
Eosinophils	0	0	3
Platelet count	4	2	1
Liver Function			
Alkaline phosphatase	0	0	1
Urinalysis			
RBC (M)	1	0	0
RBC (F)	4	1	2
WBC	1	1	0

Source: Data Source Table 14.14 in Section 12; Patient Data Listing in Appendix F.2.

* The number of patients is not additive, since a patient may have had more than one abnormal laboratory value.

Individual patient narratives for patients listed in Table 54 are provided in Section 12, Table 14.14a (unless discussed in a narrative for serious adverse events, adverse experience withdrawal, or vital sign of potential of clinical concern).

7 Discussion

The results of this double blind placebo controlled trial support that paroxetine is beneficial in treating adolescents with major depression. This support is derived from the analyses of eight prospectively defined measures of depression. For each of these measures, the analysis of the week 8 endpoint using the LOCF dataset shows that the response in the paroxetine group was numerically superior to the placebo group. The protocol defined primary endpoints did not achieve statistical significance (the change in HAM-D total score, p=0.133; and the responders analysis, p=0.112), but significance was achieved for four secondary measures (depression item of the HAM-D, p=0.001; the depression item of the K-SADS-L, p=0.049; percentage of responders based on a CGI rating of "very much" or "much improved," p=0.020; and the analysis of patients in remission based on a score of 8 or less at the endpoint HAM-D, p=0.019). The analysis of the OC dataset generally paralleled the analysis of the LOCF dataset, and statistical significance was achieved in 6 of the 8 measures of depression.

Are these results clinically meaningful? The difference in the paroxetine response relative to placebo in the change in HAM-D scores was less than 2 points. This is not as large as the difference reported from placebo controlled trials in adults in which the difference between paroxetine and placebo has been 3 points or more. The HAM-D, of course, is the gold standard in depression trials in the adult, but its use in the adolescent has not been fully accepted. The 9-item K-SADS-L which was developed to use language targeted at adolescents showed a slightly better differential between paroxetine and placebo than the HAM-D, and the difference was nearly statistically significant (p=0.065).

In favor of a meaningful clinical benefit is the change in the depressed mood item of both the HAM-D and the K-SADS-L. Here paroxetine was statistically significant to placebo and the differential is similar to that reported for adults. Other measures that support clinical benefit are the number of paroxetine patients in remission that was statistically superior to placebo, as well as the number of patients rated to have a moderate or marked improvement. Both these measures are attractive to the clinician as they have more meaning than an average change in a composite score such as the HAM-D, but these measures were not identified as primary. It is of interest, however, that the percent of placebo patients who met the definition of remission was nearly 50%. The reason for a high response rate among the placebo group is unclear, but it may be a result of the weekly 45-minute "supportive" therapy sessions allowed by the protocol.

The study employed a flexible dose design. The starting dose of paroxetine was 20 mg/day and dose increases in 10 mg increments up to 40 mg/day were permitted during weeks 4 through 8 of treatment. Over half the paroxetine patients in the trial were up-titrated to doses above 20 mg/day and the average daily dose at endpoint was 28 mg/day. This is similar to seen in flexible dose trials in adults with major depression.[17] [18] [19] [20] [21] [22]

Three behavioral/functional scales were used in the study; the parent-completed autonomous functional checklist (AFC) which measures behavioral functioning of the adolescent, the self perception profile (SPP) which measures patients' self-esteem and the sickness impact profile (SIP) which measures impact of illness on the patients daily activities. There were no significant advantages of paroxetine over placebo in any of these scales, although there were modest trends in the AFC and SPP instruments. It is possible that a longer treatment period is required to show benefits of therapy. In addition, the 1988 version of the SSP used in the present study was revised in 1995 [23] to simplify the confusing format of having the patient chose between two adolescents with opposite characteristics. The newer version employs one statement for each item and has been reported to have a higher reliability.

There was little evidence to support the benefit of imipramine in treating adolescents with depression, although there were some trends in the global assessments. This is in agreement with the smaller trials with TCAs which also failed to support antidepressant effects.[7]

The nature and incidence of adverse events reported for the paroxetine group were similar to that reported for adult depressed patients receiving paroxetine in controlled trials of comparable duration[1] and as described in the Paxil prescribing information. As in the adult, adverse events were more likely to occur during the initial weeks of treatment. Analysis by age suggests that events associated with the nervous system (dizziness, sleep problems and conduct disorders) were more likely to occur in younger subset (<15 yrs).

There were no deaths during the trial. Serious adverse events occurred in 18 patients, 11 in the paroxetine group, 5 in the imipramine group, and 2 in the placebo group. One of the paroxetine patients experienced migraine headache during the down titration after completing 8 weeks of treatment. For the remaining patients the events were psychiatric in nature and included worsening depression, suicidal ideation/gestures, and conduct disorders. In the imipramine group, one patient developed a maculopapular rash, one had dyspnea associated with chest pain, one reported hallucinations, and two were reported to have

serious conduct problems. In the placebo group, the two serious events were worsening depression.

Clinical laboratory abnormalities of concern were few in number and none were identified by investigators as related to the study drug. For placebo and paroxetine patients, there were no changes in vital signs of clinical significance. For the imipramine group, 17 patients were identified as having significant increases in the pulse rate.

8 Conclusions

This study supports that paroxetine is beneficial in treating adolescents with major depression although the support is derived mainly from secondary measures. The superiority of the paroxetine response over placebo appears less than seen in adults; this may be a result of the weekly supportive psychotherapy sessions allowed by the protocol producing a large "placebo" response. The safety profile of paroxetine in the adolescent appears similar to that reported in adults. The study provided little support for the benefit of imipramine in treating adolescent depression.

9 References

1. BOYER WF. BLUMHARDT CL. 1992. The safety profile of paroxetine. *J. Clin. Psychiatry*, **53 (2) Suppl,** 61-66.

2 . CONNERS CK. 1992. Methodology of antidepressant trials for treating depression in adolescents. *J Child Adolescent Psychopharmacol*, **2,** 11-22.

3. EMSLIE GJ, RUSH J, WEINBERG WA, KOWATCH RA, HUGHS CW, CARMODY T, RINELMANN J. 1997. A double-blind,randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Archive General Psychiatry,* **54,** 1031-1037.

4 . STROBER M. 1992. The pharmacotherapy of depressive illness in adolescence: III. Diagnostic and conceptual issues in studies of tricyclic antidepressants. *J Child Adolescent Psychopharmacol,* **2,** 23-29.

5 . JENSEN PS ET AL. 1992. Psychopharmacology of child and adolescent major depression: Present status and future directions. *J Child Adolescent Psychopharmacol,* **2,** 31-45.

6 . STROBER M, FREEMAN R, RIGALI J. 1990. The pharmacotherapy of depressive illness in adolescence: I. An open label trial of imipramine. *Psychopharmacol Bull,* **26,** 80-84.

7. KYE C, RYAN N. 1995. Pharmacologic treatment of child and adolescent depression. *Pediatric Psychopharmacology II,* **4 (2),** 261-281.

8. HAMILTON M. 1967. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol,* **6,** 278-296.

9 . AMERICAN PSYCHIATRIC ASSOCIATION. 1987. *DSM-III-Revised: Diagnostic and Statistical Manual of Mental Disorders,* Washington, DC: American Psychiatric Association.

10 . FAWCETT J, EPSTEIN P, FIESTER SJ, ELKIN I, AUTRY JH. 1987. Clinical management - imipramine/placebo administration manual. *Psychopharmacol Bull,* **23,** 309-324.

11 . ENDICOTT J, SPITZER RL. 1978. A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry,* **35,** 837-844.

12 . CHAMBERS W, PUIG-ANTICH J, HIRSCH M ET AL. 1985. The assessment of affective disorders in children and adolescents by semistuctured interview: Test-retest reliability of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present Episode Version. *Arch Gen Psychiatry,* **42,** 696-702.

13 . SIGAFOOS AD, FEINSTEIN CB, DAMOND M, REISS D. 1988. The measurement of behavioral autonomy in adolescence: The autonomous functioning checklist. *Adolesc Psychiatry,* **15,** 432-462.

14 . HARTER S. 1988. *Manual for the Self Perception Profile for Adolescents,* Denver, CO: University of Denver.

15 . BERGNER M, BOBBITT RA, CARTER WB, GILSON BS. 1981. The Sickness Impact Profile: Development and final revision of a health status measure. *Med Care,* **19,** 787-805.

16 . NATIONAL INSTITUTE OF MENTAL HEALTH. 1985. Special feature: Rating scales and assessment instruments for use in pediatric psychopharmacology research. *Psychopharmacol Bull,* **21,** 839-844.

17. CLAGHORN J. 1992. The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients. *Journal of Clinical Psychiatry,* **53,** 33-35.

18. SMITH WT, GLAUDIN V. 1992. A placebo-controlled trial of paroxetine in the treatment of major depression. *Journal of Clinical Psychiatry,* **53,** 36-39.

19. FABRE LF. 1992. A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients. *Journal of Clinical Psychiatry,* **53,** 40-43.

20. FEIGHNER JP, BOYER WF. 1992. Paroxetine in the treatment of depression: a comparison with imipramine and placebo. *Journal of Clinical Psychiatry,* **53,** 44-47.

21. SHRIVASTAVA RK, SHRIVASTAVA SHP, OVERWEG N, BLUMHARDT CL. 1992. A double-blind comparison of paroxetine, imipramine, and placebo in major depression. *Journal of Clinical Psychiatry,* **53,** 48-51.

22. COHN JB, WILCOX CS. 1992. Paroxetine in major depression: a double-blind trial with imipramine and placebo. *Journal of Clinical Psychiatry,* **53,** 52-56.

23. WICHSTROM L. 1995. Harter's self-perception profile for adolescents: reliability, validity, and evaluation of the question format. *Journal of Personality Assessment,* **65 (1),** 100-116.

10 Data Source Tables: Study Population

PAROXETINE - PROTOCOL 329

Table 12.1

Summary of Patient Distribution by Investigator by Treatment
Intent-to-Treat Population

Investigator	Center Number	PAROXETINE	IMIPRAMINE	PLACEBO	TOTAL
	001	7	5	6	18
	002	9	11	10	30
	003	10	14	11	35
	004	5	4	4	13
	005	16	15	14	45
	006	4	2	3	9
	007	9	7	5	21
	008	5	6	3	14
	009	17	18	18	53
	010	3	2	4	9
	011	2	5	4	11
	012	6	6	5	17
	TOTAL	93	95	87	275

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

PAROXETINE - PROTOCOL 329

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

PAROXETINE - PROTOCOL 329

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

PAROXETINE - PROTOCOL 329

Table 12.5.1

Summary of Demographic Data
Intent-to-Treat Population

		TREATMENT GROUP							
		PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL PATIENTS	
		N	%	N	%	N	%	N	%
RACE	Black	5	5.4	3	3.2	6	6.9	14	5.1
	Caucasian	77	82.8	83	87.4	70	80.5	230	83.6
	Oriental	1	1.1	2	2.1	2	2.3	5	1.8
	Other	10	10.8	7	7.4	9	10.3	26	9.5
SEX	Female	58	62.4	56	58.9	57	65.5	171	62.2
	Male	35	37.6	39	41.1	30	34.5	104	37.8
AGE (YRS)	12 - 13	19	20.4	24	25.3	18	20.7	61	22.2
	14 - 15	38	40.9	35	36.8	27	31.0	100	36.4
	16 - 17	32	34.4	31	32.6	39	44.8	102	37.1
	< 12	1	1.1	0	0	0	0	1	0.4
	>= 18	3	3.2	5	5.3	3	3.4	11	4.0
TOTAL PATIENTS		93	100.0	95	100.0	87	100.0	275	100.0

PAROXETINE - PROTOCOL 329

Table 12.5.1

Summary of Demographic Data
Intent-to-Treat Population

		TREATMENT GROUP			
		PAROXETINE	IMIPRAMINE	PLACEBO	TOTAL PATIENTS
AGE (YRS)	MEAN	14.8	14.9	15.1	14.9
	MINIMUM	11.0	12.0	12.0	11.0
	MAXIMUM	18.0	18.0	18.0	18.0
	STD DEV	1.6	1.7	1.6	1.7

PAROXETINE - PROTOCOL 329

Table 12.5.2

Summary of Height and Weight at Screening/Baseline
Intent-to-Treat Population

	PAROXETINE					IMIPRAMINE					PLACEBO				
	n	mean	s.d.	minimum	maximum	n	mean	s.d.	minimum	maximum	n	mean	s.d.	minimum	maximum
Height (in)	88	65.4	3.51	54.0	76.0	91	64.6	4.81	52.0	80.0	84	65.1	4.11	56.0	75.0
Weight (lbs)	88	146.3	38.9	74.0	308.3	91	139.4	36.7	76.0	261.0	84	145.3	40.8	80.9	287.6

Paroxetine - Protocol 329
Table 12.6
Summary of Child Global Assessment Scale (Scores at Screening)
Intent to Treat Population

		PAROXETINE	IMIPRAMINE	PLACEBO
CURRENT EPISODE	N	93	93	87
	Mean	43.03	42.78	43.28
	Median	41	41	36
	Std Dev	9.94	8.89	8.94
	Minimum	21	21	21
	Maximum	81	71	61
LAST TWO WEEKS	N	93	93	87
	Mean	42.71	42.53	42.79
	Median	41	41	36
	Std Dev	7.45	7.39	8.19
	Minimum	31	31	21
	Maximum	61	61	61

Paroxetine - Protocol 329
Table 12.7
Summary of Kiddie-SADS-Lifetime Diagnostic Criteria at Screening
Intent to Treat Population

Treatment = PAROXETINE

	Past n/N	Past %	Continuing n/N	Continuing %	Both n/N	Both %
Major Depressive Episode	0 /89	(0.0)	72 /89	(80.9)	16 /89	(18.0)
Hypomanic Episode	0 /89	(0.0)	1 /89	(1.1)	0 /89	(0.0)
Manic Episode	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Anorexia Nervosa	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Bulimia Nervosa	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Specific Phobia	2 /89	(2.2)	8 /89	(9.0)	0 /89	(0.0)
Separation anxiety disorder	2 /89	(2.2)	0 /89	(0.0)	0 /89	(0.0)
Panic disorder(w/o agorophobia)	2 /89	(2.2)	0 /89	(0.0)	0 /89	(0.0)
Panic disorder(w/ agorophobia)	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Agorophobia (no panic)	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Social Phobia	1 /89	(1.1)	3 /89	(3.4)	0 /89	(0.0)
Obsessive Compulsive disorder	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Generalized anxiety disorder	0 /89	(0.0)	11 /89	(12.4)	0 /89	(0.0)
Post-traumatic stress disorder	2 /89	(2.2)	0 /89	(0.0)	0 /89	(0.0)
Attention-deficit/hyperactivity	2 /89	(2.2)	5 /89	(5.6)	1 /89	(1.1)
Conduct disorder	2 /89	(2.2)	7 /89	(7.9)	0 /89	(0.0)
Antisocial personality disorder	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Oppositional Defiant disorder	2 /89	(2.2)	11 /89	(12.4)	0 /89	(0.0)

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

Paroxetine - Protocol 329
Table 12.7
Summary of Kiddie-SADS-Lifetime Diagnostic Criteria at Screening
Intent to Treat Population

Treatment = PAROXETINE

	Past n/N	Past %	Continuing n/N	Continuing %	Both n/N	Both %
Alcohol Dependence	1 /89	(1.1)	0 /89	(0.0)	0 /89	(0.0)
Alcohol Abuse	1 /89	(1.1)	0 /89	(0.0)	0 /89	(0.0)
Substance dependence	1 /89	(1.1)	0 /89	(0.0)	0 /89	(0.0)
Substance abuse	1 /89	(1.1)	0 /89	(0.0)	0 /89	(0.0)
Tic disorders	2 /89	(2.2)	0 /89	(0.0)	0 /89	(0.0)
Schizophrenia	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Schizoaffective disorder	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Brief psychotic disorder	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)
Delusional disorder	0 /89	(0.0)	0 /89	(0.0)	0 /89	(0.0)

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

Paroxetine - Protocol 329
Table 12.7
Summary of Kiddie-SADS-Lifetime Diagnostic Criteria at Screening
Intent to Treat Population

Treatment = IMIPRAMINE

	Past		Continuing		Both	
	n/N	%	n/N	%	n/N	%
Major Depressive Episode	3 /93	(3.2)	75 /93	(80.6)	15 /93	(16.1)
Hypomanic Episode	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Manic Episode	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Anorexia Nervosa	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Bulimia Nervosa	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Specific Phobia	1 /93	(1.1)	4 /93	(4.3)	1 /93	(1.1)
Separation anxiety disorder	2 /93	(2.2)	1 /93	(1.1)	1 /93	(1.1)
Panic disorder(w/o agorophobia)	2 /93	(2.2)	2 /93	(2.2)	0 /93	(0.0)
Panic disorder(w/ agorophobia)	0 /93	(0.0)	1 /93	(1.1)	0 /93	(0.0)
Agorophobia (no panic)	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Social Phobia	1 /93	(1.1)	8 /93	(8.6)	0 /93	(0.0)
Obsessive Compulsive disorder	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Generalized anxiety disorder	1 /93	(1.1)	12 /93	(12.9)	1 /93	(1.1)
Post-traumatic stress disorder	1 /93	(1.1)	0 /93	(0.0)	0 /93	(0.0)
Attention-deficit/hyperactivity	2 /93	(2.2)	14 /93	(15.1)	0 /93	(0.0)
Conduct disorder	1 /93	(1.1)	5 /93	(5.4)	0 /93	(0.0)
Antisocial personality disorder	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Oppositional Defiant disorder	2 /93	(2.2)	8 /93	(8.6)	0 /93	(0.0)

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

Paroxetine - Protocol 329
Table 12.7
Summary of Kiddie-SADS-Lifetime Diagnostic Criteria at Screening
Intent to Treat Population

Treatment = IMIPRAMINE

	Past		Continuing		Both	
	n/N	%	n/N	%	n/N	%
Alcohol Dependence	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Alcohol Abuse	2 /93	(2.2)	0 /93	(0.0)	0 /93	(0.0)
Substance dependence	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Substance abuse	1 /93	(1.1)	0 /93	(0.0)	0 /93	(0.0)
Tic disorders	1 /93	(1.1)	1 /93	(1.1)	0 /93	(0.0)
Schizophrenia	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Schizoaffective disorder	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Brief psychotic disorder	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)
Delusional disorder	0 /93	(0.0)	0 /93	(0.0)	0 /93	(0.0)

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

Paroxetine - Protocol 329
Table 12.7
Summary of Kiddie-SADS-Lifetime Diagnostic Criteria at Screening
Intent to Treat Population

	Treatment = PLACEBO					
	Past		Continuing		Both	
	n/N	%	n/N	%	n/N	%
Major Depressive Episode	3 /86	(3.5)	66 /86	(76.7)	17 /86	(19.8)
Hypomanic Episode	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Manic Episode	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Anorexia Nervosa	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Bulimia Nervosa	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Specific Phobia	3 /86	(3.5)	6 /86	(7.0)	0 /86	(0.0)
Separation anxiety disorder	3 /86	(3.5)	2 /86	(2.3)	0 /86	(0.0)
Panic disorder(w/o agorophobia)	1 /86	(1.2)	3 /86	(3.5)	0 /86	(0.0)
Panic disorder(w/ agorophobia)	0 /86	(0.0)	1 /86	(1.2)	0 /86	(0.0)
Agorophobia (no panic)	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Social Phobia	0 /86	(0.0)	10 /86	(11.6)	0 /86	(0.0)
Obsessive Compulsive disorder	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Generalized anxiety disorder	0 /86	(0.0)	17 /86	(19.8)	0 /86	(0.0)
Post-traumatic stress disorder	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Attention-deficit/hyperactivity	5 /86	(5.8)	3 /86	(3.5)	0 /86	(0.0)
Conduct disorder	2 /86	(2.3)	3 /86	(3.5)	0 /86	(0.0)
Antisocial personality disorder	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Oppositional Defiant disorder	1 /86	(1.2)	8 /86	(9.3)	1 /86	(1.2)

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

Paroxetine - Protocol 329
Table 12.7
Summary of Kiddie-SADS-Lifetime Diagnostic Criteria at Screening
Intent to Treat Population

Treatment = PLACEBO

	Past n/N	Past %	Continuing n/N	Continuing %	Both n/N	Both %
Alcohol Dependence	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Alcohol Abuse	1 /86	(1.2)	0 /86	(0.0)	0 /86	(0.0)
Substance dependence	1 /86	(1.2)	0 /86	(0.0)	0 /86	(0.0)
Substance abuse	1 /86	(1.2)	0 /86	(0.0)	0 /86	(0.0)
Tic disorders	1 /86	(1.2)	0 /86	(0.0)	0 /86	(0.0)
Schizophrenia	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Schizoaffective disorder	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Brief psychotic disorder	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)
Delusional disorder	0 /86	(0.0)	0 /86	(0.0)	0 /86	(0.0)

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

PAROXETINE - PROTOCOL 329

Table 12.8

Summary of Personal History
Intent-to-Treat Population

		PAROXETINE N = 93		IMIPRAMINE N = 95		PLACEBO N = 87	
		n	%	n	%	n	%
Highest Level of Education for Father	Graduated JHS	5	5.4	8	8.4	5	5.7
	Graduated HS (do not count G.E.D.)	27	29.0	29	30.5	38	43.7
	Graduated Junior College (A.A.)	12	12.9	10	10.5	4	4.6
	Graduated Senior College (B.A., B.S., B.F.A., etc)	18	19.4	15	15.8	13	14.9
	Completed Masters Degree (M.A., M.S., M.S.W., etc.)	4	4.3	7	7.4	5	5.7
	Completed Doctoral, Medical, Law or Comparable Degree	5	5.4	4	4.2	4	4.6
	Dropped out of JHS	3	3.2	2	2.1	2	2.3
	Dropped out of HS	5	5.4	3	3.2	1	1.1
	Dropped out of College	7	7.5	8	8.4	8	9.2
	Received G.E.D.	2	2.2	4	4.2	4	4.6
Highest Level of Education for Mother	Graduated JHS	5	5.4	5	5.3	5	5.7
	Graduated HS (do not count G.E.D.)	24	25.8	34	35.8	29	33.3
	Graduated Junior College (A.A.)	12	12.9	13	13.7	18	20.7
	Graduated Senior College (B.A., B.S., B.F.A., etc)	17	18.3	23	24.2	9	10.3
	Completed Masters Degree (M.A., M.S., M.S.W., etc.)	10	10.8	5	5.3	7	8.0
	Completed Doctoral, Medical, Law or Comparable Degree	2	2.2	1	1.1	1	1.1
	Dropped out of JHS	3	3.2	0	0.0	2	2.3
	Dropped out of HS	6	6.5	2	2.1	3	3.4
	Dropped out of College	9	9.7	11	11.6	8	9.2
	Received G.E.D.	3	3.2	0	0.0	3	3.4
Occupation for Father	Higher executive, proprietors of large concerns, major professionals	7	7.5	6	6.3	6	6.9
	Business managers in large concerns, proprietors of medium-sized businesses	14	15.1	10	10.5	9	10.3
	Administrative personnel, owners of small independent businesses	14	15.1	21	22.1	18	20.7
	Clerical and sales workers, technicians, owners of little businesses	12	12.9	16	16.8	14	16.1
	Skilled manual employees	18	19.4	17	17.9	26	29.9
	Machine operators, semi-skilled employees	8	8.6	6	6.3	5	5.7
	Unskilled employees	9	9.7	9	9.5	3	3.4
	Not relevant (e.g., was never employed)	7	7.5	4	4.2	5	5.7
Occupation for Mother	Higher executive, proprietors of large concerns, major professionals	7	7.5	2	2.1	1	1.1
	Business managers in large concerns, proprietors of medium-sized businesses	9	9.7	13	13.7	5	5.7

Table 12.8

Summary of Personal History
Intent-to-Treat Population

		PAROXETINE N = 93 n	%	IMIPRAMINE N = 95 n	%	PLACEBO N = 87 n	%
Occupation for Mother	Administrative personnel, owners of small independent businesses	23	24.7	30	31.6	19	21.8
	Clerical and sales workers, technicians, owners of little businesses	24	25.8	24	25.3	33	37.9
	Skilled manual employees	5	5.4	3	3.2	5	5.7
	Machine operators, semi-skilled employees	6	6.5	2	2.1	7	8.0
	Unskilled employees	8	8.6	10	10.5	2	2.3
	Not relevant (e.g., was never employed)	10	10.8	10	10.5	13	14.9
Family Composition	2 parent home	42	45.2	38	40.0	42	48.3
	Single parent alone	34	36.6	33	34.7	24	27.6
	1 parent & 1 step-parent	7	7.5	15	15.8	13	14.9
	1 parent & 1 common-law parent	2	2.2	2	2.1	2	2.3
	Other relative(s) is (are) caregiver(s)	5	5.4	3	3.2	4	4.6
	Parent & other relative(s) are caregiver(s)	1	1.1	3	3.2	1	1.1
Number of People in Household	Mean (S.D.)	3.9 (1.36)		3.9 (1.22)		4.0 (1.35)	
Offspring	Adopted	4	4.3	5	5.3	1	1.1
	Natural offspring	88	94.6	89	93.7	85	97.7
School Placement	Regular education	85	91.4	82	86.3	79	90.8
	Special education	7	7.5	11	11.6	6	6.9

PAROXETINE - PROTOCOL 329

Table 12.9

Summary of Medical/Surgical History
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH CONDITIONS :	33	35.5%	42	44.2%	38	43.7%	113	41.1%
DISEASE CODE LEVEL 1 : PREFERRED TERM	N	%	N	%	N	%	N	%
ANOMALIES:	0	0.0	3	3.2	1	1.1	4	1.5
CONG ANOM, GU	0	0.0	1	1.1	0	0.0	1	0.4
CONG ANOM, MUSCULOSKEL	0	0.0	2	2.1	1	1.1	3	1.1
CONGEN ANOM, HEAD/NECK	0	0.0	0	0.0	1	1.1	1	0.4
CIRCULATORY SYST:	0	0.0	0	0.0	2	2.3	2	0.7
BRADYCARDIA	0	0.0	0	0.0	1	1.1	1	0.4
HYPERTENSION	0	0.0	0	0.0	1	1.1	1	0.4
COMPLIC OF PREGNANCY/BIRTH:	0	0.0	3	3.2	1	1.1	4	1.5
PREGNANCY, COMPLICATIONS	0	0.0	3	3.2	1	1.1	4	1.5
DIGESTIVE SYST:	2	2.2	1	1.1	2	2.3	5	1.8
APPENDICITIS	0	0.0	0	0.0	2	2.3	2	0.7
HERNIA, ABDOMINAL	1	1.1	0	0.0	0	0.0	1	0.4
LIVER DISORD	0	0.0	1	1.1	0	0.0	1	0.4
PANCREATITIS	1	1.1	0	0.0	0	0.0	1	0.4
ENDOCR/METAB/IMMUNITY DISORD:	0	0.0	0	0.0	2	2.3	2	0.7
CHOLEST/TRIGLYCERIDE, ELEVATED	0	0.0	0	0.0	1	1.1	1	0.4
HYPOTHYROIDISM	0	0.0	0	0.0	1	1.1	1	0.4
EXT CAUSES OF INJURY/POISONING:	0	0.0	2	2.1	0	0.0	2	0.7
ADVERSE EFF/ANTIBIOTIC	0	0.0	1	1.1	0	0.0	1	0.4
RAPE	0	0.0	1	1.1	0	0.0	1	0.4
SUICIDE	0	0.0	1	1.1	0	0.0	1	0.4
FAMILY/PERSONAL HISTORY:	0	0.0	2	2.1	2	2.3	4	1.5
ALCOHOL INGESTION, OTHER	0	0.0	0	0.0	1	1.1	1	0.4
PREGNANCY	0	0.0	2	2.1	1	1.1	3	1.1
GENITOURINARY SYST DIS:	1	1.1	4	4.2	0	0.0	5	1.8
CYSTITIS	1	1.1	0	0.0	0	0.0	1	0.4
GENITAL FEMALE DISORD, OTHER	0	0.0	1	1.1	0	0.0	1	0.4
KIDNEY DISORD	0	0.0	1	1.1	0	0.0	1	0.4
KIDNEY INFECT	0	0.0	1	1.1	0	0.0	1	0.4
URINARY TRACT INFECTION	0	0.0	2	2.1	0	0.0	2	0.7

The conditions listed in this table were indicated as being past or past and current.

Table 12.9

Summary of Medical/Surgical History
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH CONDITIONS :	33	35.5%	42	44.2%	38	43.7%	113	41.1%
DISEASE CODE LEVEL 1 : PREFERRED TERM	N	%	N	%	N	%	N	%
INFECTIOUS/PARASITIC DIS:	4	4.3	5	5.3	6	6.9	15	5.5
ARTHROPOD-BORNE DIS, OTHER	0	0.0	0	0.0	2	2.3	2	0.7
BACT DIS, OTHER	0	0.0	1	1.1	0	0.0	1	0.4
INFECT/PARASIT DIS, OTHER	0	0.0	0	0.0	1	1.1	1	0.4
INFECTION, BACTERIAL	1	1.1	1	1.1	0	0.0	2	0.7
TUBERCULOSIS	1	1.1	0	0.0	0	0.0	1	0.4
VIRAL DIS/EXANTHEM	1	1.1	1	1.1	0	0.0	2	0.7
VIRUS/CHLAMYD DIS, OTHER	1	1.1	2	2.1	3	3.4	6	2.2
INJURY/POISONING:	6	6.5	8	8.4	9	10.3	23	8.4
COMPLIC OF MED CARE	1	1.1	1	1.1	0	0.0	2	0.7
CONTUSION	0	0.0	1	1.1	0	0.0	1	0.4
FRACTURE, LOWER LIMB	1	1.1	1	1.1	2	2.3	4	1.5
FRACTURE, SKULL	0	0.0	0	0.0	1	1.1	1	0.4
FRACTURE, UPPER LIMB	2	2.2	2	2.1	4	4.6	8	2.9
INJURY, INTRACRANIAL	0	0.0	1	1.1	2	2.3	3	1.1
OPEN WOUND	2	2.2	0	0.0	0	0.0	2	0.7
SPRAINS/STRAINS	0	0.0	3	3.2	4	4.6	7	2.5
TRAUMA/INJURIES, UNSPEC	0	0.0	0	0.0	1	1.1	1	0.4
MENTAL DISORD:	2	2.2	2	2.1	1	1.1	5	1.8
CONDUCT DISORD	1	1.1	1	1.1	0	0.0	2	0.7
DEPRESSION	0	0.0	1	1.1	0	0.0	1	0.4
DRUG ABUSE	0	0.0	0	0.0	1	1.1	1	0.4
NEUROSES	1	1.1	0	0.0	0	0.0	1	0.4
TICS	1	1.1	0	0.0	0	0.0	1	0.4
MUSCULOSKEL/CONNECT TISSUE DIS:	4	4.3	1	1.1	2	2.3	7	2.5
BACK PAIN	1	1.1	0	0.0	0	0.0	1	0.4
BONE/CARTIL DISORD, OTHER	1	1.1	0	0.0	0	0.0	1	0.4
DEFORMITY, ACQUIRED	1	1.1	0	0.0	0	0.0	1	0.4
JOINT DISORD, OTHER	0	0.0	0	0.0	1	1.1	1	0.4
OSTEOCHONDROPATHIES	1	1.1	1	1.1	0	0.0	2	0.7
RHEUMATIC DISORD	0	0.0	0	0.0	1	1.1	1	0.4
NERVOUS SYST/SENSE ORGAN DIS:	1	1.1	8	8.4	3	3.4	12	4.4
EYE DISORD, OTHER	0	0.0	1	1.1	0	0.0	1	0.4
HEARING LOSS	0	0.0	1	1.1	0	0.0	1	0.4

The conditions listed in this table were indicated as being past or past and current.

Table 12.9

Summary of Medical/Surgical History
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH CONDITIONS :	33	35.5%	42	44.2%	38	43.7%	113	41.1%
DISEASE CODE LEVEL 1 : PREFERRED TERM	N	%	N	%	N	%	N	%
MENINGITIS	1	1.1	1	1.1	2	2.3	4	1.5
MIGRAINE	0	0.0	1	1.1	0	0.0	1	0.4
OTITIS MEDIA	0	0.0	4	4.2	1	1.1	5	1.8
VISUAL DISTURB	0	0.0	1	1.1	0	0.0	1	0.4
OPERATIONS:	11	11.8	11	11.6	13	14.9	35	12.7
OPERATION, BONE/JOINT	1	1.1	1	1.1	1	1.1	3	1.1
OPERATION, BREAST	0	0.0	0	0.0	1	1.1	1	0.4
OPERATION, EAR	1	1.1	3	3.2	4	4.6	8	2.9
OPERATION, ENDOCR	0	0.0	0	0.0	1	1.1	1	0.4
OPERATION, EYE	1	1.1	1	1.1	0	0.0	2	0.7
OPERATION, HERNIA REPAIR	1	1.1	3	3.2	2	2.3	6	2.2
OPERATION, LYMPH	1	1.1	0	0.0	0	0.0	1	0.4
OPERATION, NOSE/MOUTH	3	3.2	4	4.2	3	3.4	10	3.6
OPERATION, OTHER ABDOM	0	0.0	0	0.0	1	1.1	1	0.4
OPERATION, OTHER URINARY	1	1.1	0	0.0	0	0.0	1	0.4
OPERATION, SKIN/SUBCUT	2	2.2	1	1.1	0	0.0	3	1.1
OPERATION, SOFT TISSUE	0	0.0	1	1.1	0	0.0	1	0.4
PERINATAL COND:	0	0.0	2	2.1	0	0.0	2	0.7
CONDITIONS, PERINATAL	0	0.0	2	2.1	0	0.0	2	0.7
PROCEDURES:	0	0.0	2	2.1	0	0.0	2	0.7
THERAPY, REHAB	0	0.0	2	2.1	0	0.0	2	0.7
RESPIRATORY SYST DIS:	6	6.5	13	13.7	10	11.5	29	10.5
ASTHMA	3	3.2	5	5.3	4	4.6	12	4.4
BRONCHITIS, OTHER	0	0.0	0	0.0	1	1.1	1	0.4
EPIGLOTTITIS, ACUTE	1	1.1	0	0.0	0	0.0	1	0.4
INFLUENZA	1	1.1	0	0.0	1	1.1	2	0.7
LARYNGITIS/TRACH, ACUTE	0	0.0	1	1.1	0	0.0	1	0.4
NASOPHARYNGITIS, ACUTE	0	0.0	1	1.1	3	3.4	4	1.5
PHARYNGITIS, ACUTE	1	1.1	2	2.1	0	0.0	3	1.1
PNEUMONIA, OTHER	0	0.0	0	0.0	2	2.3	2	0.7
RHINITIS, ALLERGIC	0	0.0	2	2.1	0	0.0	2	0.7
SINUSITIS,NOS	0	0.0	2	2.1	1	1.1	3	1.1
TONSILS/ADENOIDS DIS	0	0.0	1	1.1	0	0.0	1	0.4

The conditions listed in this table were indicated as being past or past and current.

Table 12.9

Summary of Medical/Surgical History
Intent-to-Treat Population

TREATMENT GROUP		PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS	:	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH CONDITIONS	:	33	35.5%	42	44.2%	38	43.7%	113	41.1%
DISEASE CODE LEVEL 1 : PREFERRED TERM		N	%	N	%	N	%	N	%
SIGNS,SYMPTOMS,ILL-DEFINED CON:		8	8.6	6	6.3	7	8.0	21	7.6
BLOOD PRESSURE, ELEVATED		0	0.0	1	1.1	0	0.0	1	0.4
CARDIAC MURMURS		1	1.1	2	2.1	1	1.1	4	1.5
COMA AND STUPOR		1	1.1	0	0.0	0	0.0	1	0.4
CONDITIONS, OTHER, ABN		1	1.1	0	0.0	0	0.0	1	0.4
CONVULSIONS		0	0.0	0	0.0	1	1.1	1	0.4
HEADACHE		0	0.0	1	1.1	2	2.3	3	1.1
INCONTINENCE, URINARY		2	2.2	0	0.0	0	0.0	2	0.7
MENTAL STATUS, IMPAIRED		1	1.1	0	0.0	1	1.1	2	0.7
NAUSEA		0	0.0	1	1.1	0	0.0	1	0.4
PAIN, ABDOMINO-PELVIC		0	0.0	0	0.0	1	1.1	1	0.4
PYREXIA		1	1.1	0	0.0	1	1.1	2	0.7
SUDDEN INFANT DEATH SYNDROME		0	0.0	0	0.0	1	1.1	1	0.4
WEIGHT GAIN		1	1.1	0	0.0	0	0.0	1	0.4
WEIGHT LOSS		0	0.0	1	1.1	0	0.0	1	0.4
SKIN/SUBCUTANEOUS TISSUE DIS:		1	1.1	2	2.1	1	1.1	4	1.5
CELLULITIS/ABSCESS		0	0.0	1	1.1	0	0.0	1	0.4
LYMPHADENITIS, ACUTE		1	1.1	0	0.0	0	0.0	1	0.4
SCARRING		0	0.0	1	1.1	0	0.0	1	0.4
SKIN/SUBCUT DISORD, OTHER		0	0.0	0	0.0	1	1.1	1	0.4

The conditions listed in this table were indicated as being past or past and current.

PAROXETINE - PROTOCOL 329

Table 12.10

Summary of Presenting Conditions
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH CONDITIONS :	67	72.0%	67	70.5%	62	71.3%	196	71.3%
DISEASE CODE LEVEL 1 : PREFERRED TERM	N	%	N	%	N	%	N	%
BLOOD/BLOOD FORMING ORGAN DIS:	4	4.3	4	4.2	2	2.3	10	3.6
ANEMIA, OTHER	2	2.2	0	0.0	2	2.3	4	1.5
LEUCOCYTOSIS	0	0.0	1	1.1	0	0.0	1	0.4
LEUKOPENIA	2	2.2	2	2.1	0	0.0	4	1.5
LYMPHOCYTOSIS	0	0.0	1	1.1	0	0.0	1	0.4
LYMPHOPENIA	0	0.0	1	1.1	0	0.0	1	0.4
MONOCYTOSIS	1	1.1	0	0.0	0	0.0	1	0.4
CIRCULATORY SYST:	2	2.2	1	1.1	6	6.9	9	3.3
ANGINA PECTORIS	0	0.0	0	0.0	1	1.1	1	0.4
ARRHYTHMIA	0	0.0	1	1.1	2	2.3	3	1.1
BRADYCARDIA	1	1.1	1	1.1	2	2.3	4	1.5
CARDIOMEGALY	1	1.1	0	0.0	1	1.1	2	0.7
EXTRASYSTOLES, ATRIAL	0	0.0	0	0.0	1	1.1	1	0.4
MITRAL VALVE DISORD	0	0.0	0	0.0	1	1.1	1	0.4
DIGESTIVE SYST:	2	2.2	7	7.4	4	4.6	13	4.7
DENTOFACIAL ANOM	0	0.0	2	2.1	1	1.1	3	1.1
DIGESTIVE DISORD, OTHER	0	0.0	1	1.1	0	0.0	1	0.4
DYSPEPSIA	1	1.1	2	2.1	1	1.1	4	1.5
ENTERITIS/COLITIS	0	0.0	1	1.1	0	0.0	1	0.4
ESOPHAGITIS	0	0.0	0	0.0	1	1.1	1	0.4
STOMACH/DUODENUM DISORD	1	1.1	1	1.1	0	0.0	2	0.7
ULCER, GASTRIC	0	0.0	0	0.0	1	1.1	1	0.4
ENDOCR/METAB/IMMUNITY DISORD:	4	4.3	2	2.1	6	6.9	12	4.4
HYPOGLYCEMIA	0	0.0	1	1.1	0	0.0	1	0.4
HYPOTHYROIDISM	0	0.0	0	0.0	1	1.1	1	0.4
OBESITY	3	3.2	1	1.1	5	5.7	9	3.3
OVARIAN DYSFUNC	1	1.1	0	0.0	0	0.0	1	0.4
EXT CAUSES OF INJURY/POISONING:	2	2.2	4	4.2	4	4.6	10	3.6
ADVERSE EFF ON AUTONOMIC NS	1	1.1	0	0.0	0	0.0	1	0.4
ADVERSE EFF/ANALGESIC	1	1.1	0	0.0	1	1.1	2	0.7
ADVERSE EFF/ANTI-INFECT	1	1.1	0	0.0	1	1.1	2	0.7
ADVERSE EFF/ANTIBIOTIC	0	0.0	2	2.1	2	2.3	4	1.5
ADVERSE EFF/OTHER DRUG	0	0.0	1	1.1	0	0.0	1	0.4
ADVERSE EFF/PSYCHOTROPICS	0	0.0	1	1.1	0	0.0	1	0.4

The conditions listed in this table were indicated as being current or past and current.

Table 12.10

Summary of Presenting Conditions
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH CONDITIONS :	67	72.0%	67	70.5%	62	71.3%	196	71.3%
DISEASE CODE LEVEL 1 : PREFERRED TERM	N	%	N	%	N	%	N	%
FAMILY/PERSONAL HISTORY:	1	1.1	0	0.0	0	0.0	1	0.4
POSTPARTUM CARE	1	1.1	0	0.0	0	0.0	1	0.4
GENITOURINARY SYST DIS:	6	6.5	14	14.7	9	10.3	29	10.5
AMENORRHEA	1	1.1	0	0.0	0	0.0	1	0.4
GENITAL FEMALE DISORD, OTHER	4	4.3	12	12.6	7	8.0	23	8.4
GYNECOMASTIA	0	0.0	1	1.1	0	0.0	1	0.4
HEMATURIA	1	1.1	0	0.0	2	2.3	3	1.1
URINARY TRACT INFECTION	0	0.0	1	1.1	1	1.1	2	0.7
VAGINITIS	0	0.0	0	0.0	1	1.1	1	0.4
INFECTIOUS/PARASITIC DIS:	3	3.2	3	3.2	0	0.0	6	2.2
INFECTION, BACTERIAL	1	1.1	1	1.1	0	0.0	2	0.7
MYCOSES	1	1.1	2	2.1	0	0.0	3	1.1
VIRAL DIS/EXANTHEM	1	1.1	0	0.0	0	0.0	1	0.4
VIRUS/CHLAMYD DIS, OTHER	0	0.0	1	1.1	0	0.0	1	0.4
INJURY/POISONING:	7	7.5	10	10.5	2	2.3	19	6.9
ALLERGIC REACTION, FOOD	0	0.0	3	3.2	0	0.0	3	1.1
ALLERGY, NEC	5	5.4	5	5.3	0	0.0	10	3.6
FRACTURE, UPPER LIMB	0	0.0	1	1.1	0	0.0	1	0.4
INJURY, SUPERFICIAL	0	0.0	0	0.0	1	1.1	1	0.4
OPEN WOUND	0	0.0	0	0.0	1	1.1	1	0.4
SPRAINS/STRAINS	1	1.1	1	1.1	0	0.0	2	0.7
TOXIC EFFECTS, VENOM	1	1.1	0	0.0	0	0.0	1	0.4
MENTAL DISORD:	3	3.2	4	4.2	6	6.9	13	4.7
ANXIETY	0	0.0	0	0.0	2	2.3	2	0.7
CONDUCT DISORD	2	2.2	0	0.0	1	1.1	3	1.1
DEPRESSION	0	0.0	1	1.1	0	0.0	1	0.4
DRUG ABUSE	1	1.1	0	0.0	1	1.1	2	0.7
DRUG DEPEND	0	0.0	0	0.0	1	1.1	1	0.4
NEUROSES	0	0.0	0	0.0	1	1.1	1	0.4
PSYCHOGENIC PHYSIOL DYSFUNC	0	0.0	1	1.1	0	0.0	1	0.4
STRESS REACTION	0	0.0	1	1.1	0	0.0	1	0.4
TOBACCO USE	0	0.0	1	1.1	0	0.0	1	0.4
MUSCULOSKEL/CONNECT TISSUE DIS:	5	5.4	4	4.2	4	4.6	13	4.7

The conditions listed in this table were indicated as being current or past and current.

Table 12.10

Summary of Presenting Conditions
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH CONDITIONS :	67	72.0%	67	70.5%	62	71.3%	196	71.3%
DISEASE CODE LEVEL 1 : PREFERRED TERM	N	%	N	%	N	%	N	%
BACK PAIN	2	2.2	0	0.0	3	3.4	5	1.8
DEFORMITY, ACQUIRED	1	1.1	0	0.0	0	0.0	1	0.4
JOINT DISORD, OTHER	0	0.0	0	0.0	1	1.1	1	0.4
MYALGIA	1	1.1	2	2.1	0	0.0	3	1.1
OSTEOCHONDROPATHIES	0	0.0	1	1.1	0	0.0	1	0.4
PAIN, JOINT	1	1.1	1	1.1	0	0.0	2	0.7
PAIN, LIMB	1	1.1	0	0.0	1	1.1	2	0.7
SWELLING, LIMB	0	0.0	1	1.1	0	0.0	1	0.4
NEOPLASMS:	0	0.0	1	1.1	0	0.0	1	0.4
NEOPLASMS BENIGN	0	0.0	1	1.1	0	0.0	1	0.4
NERVOUS SYST/SENSE ORGAN DIS:	1	1.1	6	6.3	5	5.7	12	4.4
EAR/MASTOID DISORD	0	0.0	0	0.0	1	1.1	1	0.4
EYE DISORD, OTHER	0	0.0	1	1.1	0	0.0	1	0.4
HEARING LOSS	0	0.0	0	0.0	1	1.1	1	0.4
MIGRAINE	1	1.1	2	2.1	0	0.0	3	1.1
OTITIS MEDIA	0	0.0	1	1.1	4	4.6	5	1.8
VISUAL DISTURB	0	0.0	2	2.1	0	0.0	2	0.7
OPERATIONS:	0	0.0	1	1.1	2	2.3	3	1.1
OPERATION, BONE/JOINT	0	0.0	0	0.0	1	1.1	1	0.4
OPERATION, EAR	0	0.0	0	0.0	1	1.1	1	0.4
OPERATION, MUSCLE/TENDON	0	0.0	1	1.1	0	0.0	1	0.4
RESPIRATORY SYST DIS:	17	18.3	21	22.1	21	24.1	59	21.5
ASTHMA	6	6.5	9	9.5	3	3.4	18	6.5
BRONCHITIS, OTHER	0	0.0	0	0.0	2	2.3	2	0.7
INFLUENZA	0	0.0	1	1.1	1	1.1	2	0.7
NASOPHARYNGITIS, ACUTE	1	1.1	4	4.2	0	0.0	5	1.8
PHARYNGITIS, ACUTE	0	0.0	0	0.0	1	1.1	1	0.4
RESP DIS, OTHER	0	0.0	1	1.1	0	0.0	1	0.4
RHINITIS, ALLERGIC	6	6.5	8	8.4	9	10.3	23	8.4
SINUSITIS, OTHER	0	0.0	1	1.1	0	0.0	1	0.4
SINUSITIS,NOS	2	2.2	1	1.1	3	3.4	6	2.2
TONSILLITIS, ACUTE	0	0.0	1	1.1	0	0.0	1	0.4
UPPER RESP DISORD, OTHER	2	2.2	0	0.0	3	3.4	5	1.8
UPPER RESP INFECT, ACUTE	1	1.1	0	0.0	2	2.3	3	1.1

The conditions listed in this table were indicated as being current or past and current.

Table 12.10

Summary of Presenting Conditions
Intent-to-Treat Population

TREATMENT GROUP		PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS	:	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH CONDITIONS	:	67	72.0%	67	70.5%	62	71.3%	196	71.3%
DISEASE CODE LEVEL 1 : PREFERRED TERM		N	%	N	%	N	%	N	%
SIGNS,SYMPTOMS,ILL-DEFINED CON:		46	49.5	44	46.3	39	44.8	129	46.9
CARDIAC MURMURS		0	0.0	0	0.0	1	1.1	1	0.4
CARDIOVAS FUNCTIONS/ECG, ABN		1	1.1	2	2.1	2	2.3	5	1.8
CREATININE, INCREASED		0	0.0	0	0.0	1	1.1	1	0.4
DIARRHEA		0	0.0	1	1.1	0	0.0	1	0.4
DISTURBANCE, SLEEP, UNSPEC		1	1.1	0	0.0	0	0.0	1	0.4
DIZZINESS AND GIDDINESS		0	0.0	0	0.0	2	2.3	2	0.7
DIZZINESS, POSTURAL		1	1.1	0	0.0	0	0.0	1	0.4
DYSPNEA, OTHER		0	0.0	0	0.0	1	1.1	1	0.4
GASTROINTEST PROB, NEC		0	0.0	0	0.0	1	1.1	1	0.4
HEADACHE		41	44.1	34	35.8	28	32.2	103	37.5
HEARTBURN		1	1.1	1	1.1	0	0.0	2	0.7
HYPERHIDROSIS		0	0.0	2	2.1	0	0.0	2	0.7
INSOMNIA		1	1.1	3	3.2	1	1.1	5	1.8
LYMPHADENOPATHY		1	1.1	1	1.1	0	0.0	2	0.7
MALAISE AND FATIGUE		0	0.0	1	1.1	2	2.3	3	1.1
NAUSEA		3	3.2	1	1.1	0	0.0	4	1.5
NERVOUSNESS		0	0.0	1	1.1	0	0.0	1	0.4
PAIN, ABDOMINO-PELVIC		6	6.5	5	5.3	5	5.7	16	5.8
PAIN, GENERAL		0	0.0	1	1.1	0	0.0	1	0.4
PROTEINURIA		2	2.2	2	2.1	2	2.3	6	2.2
PYREXIA		1	1.1	0	0.0	0	0.0	1	0.4
RASH/OTHER SKIN ERUPTION		1	1.1	0	0.0	0	0.0	1	0.4
SWELLING, MASS, LOCALIZED		0	0.0	1	1.1	0	0.0	1	0.4
SYNCOPE AND COLLAPSE		0	0.0	0	0.0	1	1.1	1	0.4
TACHYCARDIA, UNSPEC		0	0.0	0	0.0	1	1.1	1	0.4
THYROID FUNCTION, ABN		0	0.0	1	1.1	0	0.0	1	0.4
TREMOR		1	1.1	1	1.1	0	0.0	2	0.7
URINARY CASTS/WBC'S		0	0.0	0	0.0	1	1.1	1	0.4
URINE, ABN, OTHER		0	0.0	0	0.0	1	1.1	1	0.4
WEIGHT GAIN		1	1.1	0	0.0	1	1.1	2	0.7
SKIN/SUBCUTANEOUS TISSUE DIS:		9	9.7	6	6.3	7	8.0	22	8.0
INFLAM SKIN/SUBCUT		2	2.2	0	0.0	1	1.1	3	1.1
SKIN/SUBCUT DISORD, OTHER		7	7.5	6	6.3	6	6.9	19	6.9

The conditions listed in this table were indicated as being current or past and current.

Table 12.11

Summary of Prior Medications by WHO ATC Classification
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	54	58.1%	65	68.4%	53	60.9%	172	62.5%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
ALIMENTARY TRACT/METAB:	6	6.5	9	9.5	5	5.7	20	7.3
ALUMINIUM HYDROXIDE	0	0.0	0	0.0	2	2.3	2	0.7
APPETITE SUPPRESSANT	1	1.1	0	0.0	0	0.0	1	0.4
ASCORBIC ACID	0	0.0	3	3.2	0	0.0	3	1.1
ATROPINE SULFATE	1	1.1	0	0.0	0	0.0	1	0.4
BISMUTH SUBSALICYLATE	0	0.0	1	1.1	0	0.0	1	0.4
CALCIUM CARBONATE	1	1.1	0	0.0	0	0.0	1	0.4
CALCIUM PANTOTHENATE	0	0.0	1	1.1	0	0.0	1	0.4
DICYCLOVERINE	0	0.0	0	0.0	1	1.1	1	0.4
DIHYDROXYALUMINUM SODIUM CARBONATE	1	1.1	0	0.0	0	0.0	1	0.4
DIMETICONE, ACTIVATED	0	0.0	0	0.0	2	2.3	2	0.7
FAMOTIDINE	0	0.0	2	2.1	2	2.3	4	1.5
HYOSCINE HYDROBROMIDE	1	1.1	0	0.0	0	0.0	1	0.4
HYOSCYAMINE SULFATE	1	1.1	1	1.1	0	0.0	2	0.7
LOPERAMIDE HYDROCHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
MAGNESIUM HYDROXIDE	0	0.0	0	0.0	2	2.3	2	0.7
MINERALS NOS	0	0.0	1	1.1	0	0.0	1	0.4
NICOTINAMIDE	0	0.0	1	1.1	0	0.0	1	0.4
PHENOBARBITAL	1	1.1	0	0.0	0	0.0	1	0.4
PYRIDOXINE HYDROCHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
RANITIDINE HYDROCHLORIDE	1	1.1	1	1.1	2	2.3	4	1.5
RIBOFLAVIN	0	0.0	1	1.1	0	0.0	1	0.4
THIAMINE HYDROCHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
VITAMINS NOS	2	2.2	1	1.1	0	0.0	3	1.1
ANTIINFECTIVES,SYSTEMIC:	6	6.5	10	10.5	12	13.8	28	10.2
AMOXICILLIN	0	0.0	2	2.1	4	4.6	6	2.2
AMOXICILLIN TRIHYDRATE	2	2.2	0	0.0	1	1.1	3	1.1
AZITHROMYCIN	0	0.0	0	0.0	1	1.1	1	0.4
CLARITHROMYCIN	1	1.1	0	0.0	0	0.0	1	0.4
CLAVULANIC ACID	1	1.1	0	0.0	1	1.1	2	0.7
CLINDAMYCIN HYDROCHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
ERYTHROMYCIN	0	0.0	1	1.1	2	2.3	3	1.1
HEPATITIS B VACCINE	1	1.1	0	0.0	0	0.0	1	0.4
KETOCONAZOLE	0	0.0	1	1.1	0	0.0	1	0.4
METACYCLINE	0	0.0	0	0.0	1	1.1	1	0.4
MINOCYCLINE	1	1.1	3	3.2	1	1.1	5	1.8
PHENOXYMETHYLPENICILLIN POTASSIUM	0	0.0	1	1.1	0	0.0	1	0.4
SULFAMETHOXAZOLE	0	0.0	1	1.1	1	1.1	2	0.7
TETRACYCLINE	1	1.1	1	1.1	1	1.1	3	1.1

Table 12.11

Summary of Prior Medications by WHO ATC Classification
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	54	58.1%	65	68.4%	53	60.9%	172	62.5%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
TETRACYCLINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
TRIMETHOPRIM	0	0.0	1	1.1	1	1.1	2	0.7
ANTINEOPLASTIC & IMMUNOSUP:	1	1.1	0	0.0	1	1.1	2	0.7
DIETHYLSTILBESTROL DIPROPIONATE	1	1.1	0	0.0	1	1.1	2	0.7
BLOOD/BLOOD FORM ORGANS:	1	1.1	1	1.1	0	0.0	2	0.7
CYANOCOBALAMIN	0	0.0	1	1.1	0	0.0	1	0.4
FERROUS SULFATE	1	1.1	0	0.0	0	0.0	1	0.4
CARDIOVASCULAR:	1	1.1	1	1.1	0	0.0	2	0.7
BENZOCAINE	1	1.1	0	0.0	0	0.0	1	0.4
THEOPHYLLINE	0	0.0	1	1.1	0	0.0	1	0.4
CENTRAL NERVOUS SYSTEM:	37	39.8	43	45.3	34	39.1	114	41.5
ACETYLSALICYLIC ACID	6	6.5	8	8.4	5	5.7	19	6.9
AMITRIPTYLINE HYDROCHLORIDE	0	0.0	0	0.0	1	1.1	1	0.4
ANALGESICS	1	1.1	1	1.1	1	1.1	3	1.1
BUTALBITAL	0	0.0	1	1.1	0	0.0	1	0.4
CAFFEINE	3	3.2	6	6.3	3	3.4	12	4.4
CANNABIS	1	1.1	1	1.1	0	0.0	2	0.7
CHLORPHENAMINE MALEATE	3	3.2	1	1.1	1	1.1	5	1.8
CINNAMEDRINE HYDROCHLORIDE	1	1.1	3	3.2	2	2.3	6	2.2
CITRIC ACID	0	0.0	2	2.1	0	0.0	2	0.7
CLONAZEPAM	0	0.0	0	0.0	1	1.1	1	0.4
CODEINE PHOSPHATE	1	1.1	1	1.1	0	0.0	2	0.7
DEXTROMETHORPHAN HYDROBROMIDE	3	3.2	1	1.1	1	1.1	5	1.8
DIAZEPAM	0	0.0	0	0.0	1	1.1	1	0.4
DIPHENHYDRAMINE CITRATE	0	0.0	1	1.1	0	0.0	1	0.4
DIPHENHYDRAMINE HYDROCHLORIDE	0	0.0	0	0.0	1	1.1	1	0.4
FLUOXETINE	1	1.1	0	0.0	0	0.0	1	0.4
MEPYRAMINE MALEATE	0	0.0	1	1.1	2	2.3	3	1.1
METHYLPHENIDATE HYDROCHLORIDE	3	3.2	1	1.1	0	0.0	4	1.5
PAIN RELIEVER	1	1.1	0	0.0	0	0.0	1	0.4
PAMABROM	0	0.0	1	1.1	2	2.3	3	1.1
PARACETAMOL	31	33.3	37	38.9	26	29.9	94	34.2
PEMOLINE MAGNESIUM	0	0.0	0	0.0	1	1.1	1	0.4
PHENACETIN	1	1.1	0	0.0	0	0.0	1	0.4
PHENYLPROPANOLAMINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
PHENYLTOLOXAMINE CITRATE	1	1.1	0	0.0	0	0.0	1	0.4

Table 12.11

Summary of Prior Medications by WHO ATC Classification
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	54	58.1%	65	68.4%	53	60.9%	172	62.5%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
PSEUDOEPHEDRINE HYDROCHLORIDE	4	4.3	1	1.1	2	2.3	7	2.5
SALICYLAMIDE	0	0.0	1	1.1	0	0.0	1	0.4
SERTRALINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
SODIUM BICARBONATE	0	0.0	2	2.1	0	0.0	2	0.7
VENLAFAXINE HYDROCHLORIDE	0	0.0	0	0.0	1	1.1	1	0.4
DERMATOLOGICALS:	8	8.6	9	9.5	9	10.3	26	9.5
BENZOCAINE	1	1.1	0	0.0	0	0.0	1	0.4
BUDESONIDE	1	1.1	0	0.0	0	0.0	1	0.4
CLOTRIMAZOLE	0	0.0	1	1.1	0	0.0	1	0.4
DERMATOLOGICALS NOS	0	0.0	0	0.0	1	1.1	1	0.4
DIPHENHYDRAMINE CITRATE	0	0.0	1	1.1	0	0.0	1	0.4
DIPHENHYDRAMINE HYDROCHLORIDE	3	3.2	3	3.2	3	3.4	9	3.3
ERYTHROMYCIN	0	0.0	1	1.1	2	2.3	3	1.1
FLUTICASONE PROPIONATE	0	0.0	1	1.1	0	0.0	1	0.4
ISOTRETINOIN	1	1.1	0	0.0	1	1.1	2	0.7
KETOCONAZOLE	0	0.0	1	1.1	0	0.0	1	0.4
PARACETAMOL	0	0.0	1	1.1	0	0.0	1	0.4
TETRACYCLINE	1	1.1	1	1.1	1	1.1	3	1.1
TETRACYCLINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
TRETINOIN	0	0.0	0	0.0	1	1.1	1	0.4
GU SYSTEM/SEX HORMONES:	3	3.2	6	6.3	7	8.0	16	5.8
CLOTRIMAZOLE	0	0.0	1	1.1	0	0.0	1	0.4
DESOGESTREL	0	0.0	1	1.1	0	0.0	1	0.4
DIETHYLSTILBESTROL DIPROPIONATE	1	1.1	0	0.0	1	1.1	2	0.7
ETHINYLESTRADIOL	1	1.1	4	4.2	3	3.4	8	2.9
INJECTABLE CONTRACEPTIVE, NOS	0	0.0	0	0.0	1	1.1	1	0.4
LEVONORGESTREL	0	0.0	1	1.1	2	2.3	3	1.1
MESTRANOL	0	0.0	0	0.0	1	1.1	1	0.4
NORETHISTERONE	1	1.1	1	1.1	2	2.3	4	1.5
NORETHISTERONE ACETATE	0	0.0	1	1.1	0	0.0	1	0.4
ORAL CONTRACEPTIVE	1	1.1	1	1.1	1	1.1	3	1.1
MUSCULO-SKELETAL:	14	15.1	18	18.9	10	11.5	42	15.3
BACLOFEN	0	0.0	1	1.1	0	0.0	1	0.4
FLURBIPROFEN	0	0.0	1	1.1	0	0.0	1	0.4
IBUPROFEN	13	14.0	13	13.7	6	6.9	32	11.6
KETOPROFEN	0	0.0	1	1.1	0	0.0	1	0.4
NAPROXEN	0	0.0	1	1.1	0	0.0	1	0.4

Table 12.11

Summary of Prior Medications by WHO ATC Classification
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	54	58.1%	65	68.4%	53	60.9%	172	62.5%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
NAPROXEN SODIUM	2	2.2	3	3.2	3	3.4	8	2.9
OXAPROZIN	0	0.0	0	0.0	1	1.1	1	0.4
PSEUDOEPHEDRINE HYDROCHLORIDE	0	0.0	1	1.1	1	1.1	2	0.7
RESPIRATORY:	19	20.4	21	22.1	22	25.3	62	22.5
AMINOACETIC ACID	0	0.0	0	0.0	1	1.1	1	0.4
ANTIASTHMATIC, NOS	0	0.0	1	1.1	0	0.0	1	0.4
ANTIHISTAMINE, NOS	1	1.1	0	0.0	0	0.0	1	0.4
BECLOMETASONE DIPROPIONATE	0	0.0	1	1.1	1	1.1	2	0.7
BENZALKONIUM CHLORIDE	0	0.0	0	0.0	1	1.1	1	0.4
BENZOCAINE	1	1.1	0	0.0	0	0.0	1	0.4
BROMPHENIRAMINE MALEATE	1	1.1	0	0.0	2	2.3	3	1.1
BUDESONIDE	1	1.1	0	0.0	0	0.0	1	0.4
CARBINOXAMINE MALEATE	0	0.0	1	1.1	0	0.0	1	0.4
CETIRIZINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
CHLORPHENAMINE MALEATE	4	4.3	1	1.1	4	4.6	9	3.3
CLEMASTINE FUMARATE	1	1.1	0	0.0	0	0.0	1	0.4
CODEINE	0	0.0	0	0.0	1	1.1	1	0.4
CODEINE PHOSPHATE	0	0.0	1	1.1	1	1.1	2	0.7
CROMOGLICATE SODIUM	0	0.0	1	1.1	1	1.1	2	0.7
DECONGESTANT NOS	0	0.0	0	0.0	1	1.1	1	0.4
DEXBROMPHENIRAMINE MALEATE	0	0.0	1	1.1	2	2.3	3	1.1
DEXTROMETHORPHAN HYDROBROMIDE	3	3.2	2	2.1	1	1.1	6	2.2
DIPHENHYDRAMINE CITRATE	0	0.0	1	1.1	0	0.0	1	0.4
DIPHENHYDRAMINE HYDROCHLORIDE	3	3.2	3	3.2	4	4.6	10	3.6
DOXYLAMINE SUCCINATE	0	0.0	1	1.1	1	1.1	2	0.7
FEXOFENADINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
FLUTICASONE PROPIONATE	0	0.0	1	1.1	0	0.0	1	0.4
GUAIFENESIN	0	0.0	1	1.1	3	3.4	4	1.5
HYDROCODONE BITARTRATE	0	0.0	1	1.1	0	0.0	1	0.4
IBUPROFEN	0	0.0	1	1.1	1	1.1	2	0.7
IODINATED GLYCEROL	0	0.0	1	1.1	0	0.0	1	0.4
LORATADINE	1	1.1	1	1.1	1	1.1	3	1.1
MEPYRAMINE MALEATE	0	0.0	1	1.1	0	0.0	1	0.4
ORCIPRENALINE SULFATE	0	0.0	1	1.1	0	0.0	1	0.4
OXYMETAZOLINE HYDROCHLORIDE	0	0.0	0	0.0	1	1.1	1	0.4
PARACETAMOL	4	4.3	3	3.2	5	5.7	12	4.4
PHENIRAMINE MALEATE	0	0.0	0	0.0	1	1.1	1	0.4
PHENYLEPHRINE HYDROCHLORIDE	1	1.1	2	2.1	4	4.6	7	2.5
PHENYLMERCURIC ACETATE	0	0.0	0	0.0	1	1.1	1	0.4

Table 12.11

Summary of Prior Medications by WHO ATC Classification
Intent-to-Treat Population

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	54	58.1%	65	68.4%	53	60.9%	172	62.5%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
PHENYLPROPANOLAMINE HYDROCHLORIDE	3	3.2	1	1.1	4	4.6	8	2.9
PHENYLTOLOXAMINE CITRATE	0	0.0	1	1.1	0	0.0	1	0.4
PROMETHAZINE HYDROCHLORIDE	0	0.0	0	0.0	1	1.1	1	0.4
PSEUDOEPHEDRINE	0	0.0	1	1.1	0	0.0	1	0.4
PSEUDOEPHEDRINE HYDROCHLORIDE	6	6.5	4	4.2	5	5.7	15	5.5
PSEUDOEPHEDRINE SULFATE	0	0.0	1	1.1	2	2.3	3	1.1
SALBUTAMOL	5	5.4	7	7.4	5	5.7	17	6.2
SALBUTAMOL SULFATE	0	0.0	0	0.0	1	1.1	1	0.4
SORBITOL	0	0.0	0	0.0	1	1.1	1	0.4
THEOPHYLLINE	0	0.0	1	1.1	0	0.0	1	0.4
TRIPROLIDINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
SENSORY ORGANS:	3	3.2	3	3.2	3	3.4	9	3.3
BETAMETHASONE SODIUM PHOSPHATE	0	0.0	0	0.0	1	1.1	1	0.4
ERYTHROMYCIN	0	0.0	1	1.1	2	2.3	3	1.1
GENTAMICIN SULFATE	0	0.0	0	0.0	1	1.1	1	0.4
GRAMICIDIN	1	1.1	0	0.0	0	0.0	1	0.4
POLYMYXIN B SULFATE	1	1.1	0	0.0	0	0.0	1	0.4
SULFACETAMIDE SODIUM	0	0.0	1	1.1	0	0.0	1	0.4
TETRACYCLINE	1	1.1	1	1.1	1	1.1	3	1.1
TETRACYCLINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
SYSTEMIC HORMONAL:	0	0.0	0	0.0	1	1.1	1	0.4
LEVOTHYROXINE SODIUM	0	0.0	0	0.0	1	1.1	1	0.4
VARIOUS:	1	1.1	3	3.2	0	0.0	4	1.5
ALLERGENIC EXTRACT, NOS	0	0.0	2	2.1	0	0.0	2	0.7
HERBAL MEDICATION	0	0.0	1	1.1	0	0.0	1	0.4
LYSINE	1	1.1	0	0.0	0	0.0	1	0.4

PAROXETINE - PROTOCOL 329

Table 12.12

Summary of Concomitant Medications by WHO ATC Classification
Screening Failures Only

	TOTAL	
TOTAL NUMBER OF PATIENTS	21	100.0%
PATIENTS WITH MEDICATIONS	3	14.3%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%
ANTIINFECTIVES,SYSTEMIC:	1	4.8
CLARITHROMYCIN	1	4.8
CENTRAL NERVOUS SYSTEM:	1	4.8
CHLORPHENAMINE MALEATE	1	4.8
DEXTROMETHORPHAN HYDROBROMIDE	1	4.8
PARACETAMOL	1	4.8
PSEUDOEPHEDRINE HYDROCHLORIDE	1	4.8
MUSCULO-SKELETAL:	2	9.5
IBUPROFEN	2	9.5
RESPIRATORY:	2	9.5
BECLOMETASONE DIPROPIONATE	1	4.8
CHLORPHENAMINE MALEATE	1	4.8
DEXTROMETHORPHAN HYDROBROMIDE	1	4.8
GUAIFENESIN	1	4.8
MEPYRAMINE MALEATE	1	4.8
PARACETAMOL	1	4.8
PHENIRAMINE MALEATE	1	4.8
PHENYLPROPANOLAMINE HYDROCHLORIDE	1	4.8
PHENYLTOLOXAMINE CITRATE	1	4.8
PSEUDOEPHEDRINE HYDROCHLORIDE	2	9.5

PAROXETINE - PROTOCOL 329

Table 12.14

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	53	57.0%	53	55.8%	51	58.6%	157	57.1%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
ALIMENTARY TRACT/METAB:	10	10.8	10	10.5	6	6.9	26	9.5
ALUMINIUM HYDROXIDE	0	0.0	1	1.1	0	0.0	1	0.4
ANTIEMETICS & ANTINAUSEANTS NOS	0	0.0	1	1.1	0	0.0	1	0.4
ASCORBIC ACID	2	2.2	1	1.1	0	0.0	3	1.1
BISACODYL	0	0.0	0	0.0	1	1.1	1	0.4
BISMUTH SUBSALICYLATE	2	2.2	1	1.1	2	2.3	5	1.8
CAFFEINE	0	0.0	1	1.1	0	0.0	1	0.4
CALCIUM CARBONATE	1	1.1	2	2.1	0	0.0	3	1.1
CALCIUM PANTOTHENATE	1	1.1	1	1.1	0	0.0	2	0.7
CIMETIDINE	0	0.0	2	2.1	0	0.0	2	0.7
CISAPRIDE	0	0.0	1	1.1	0	0.0	1	0.4
DICYCLOVERINE HYDROCHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
DIHYDROXYALUMINUM SODIUM CARBONATE	1	1.1	0	0.0	0	0.0	1	0.4
DIMETICONE, ACTIVATED	0	0.0	1	1.1	0	0.0	1	0.4
DOCUSATE SODIUM	1	1.1	0	0.0	0	0.0	1	0.4
ENEMA, NOS	0	0.0	1	1.1	0	0.0	1	0.4
FAMOTIDINE	1	1.1	1	1.1	0	0.0	2	0.7
HYOSCINE BUTYLBROMIDE	0	0.0	0	0.0	1	1.1	1	0.4
LOPERAMIDE HYDROCHLORIDE	1	1.1	1	1.1	1	1.1	3	1.1
MAGNESIUM HYDROXIDE	0	0.0	1	1.1	0	0.0	1	0.4
MINERALS NOS	1	1.1	0	0.0	0	0.0	1	0.4
NICOTINAMIDE	1	1.1	1	1.1	0	0.0	2	0.7
OMEPRAZOLE	0	0.0	0	0.0	1	1.1	1	0.4
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
PYRIDOXINE HYDROCHLORIDE	1	1.1	1	1.1	0	0.0	2	0.7
RIBOFLAVIN	1	1.1	1	1.1	0	0.0	2	0.7
SENNA FRUIT	0	0.0	1	1.1	0	0.0	1	0.4
THIAMINE HYDROCHLORIDE	1	1.1	1	1.1	0	0.0	2	0.7
TRIAMCINOLONE	1	1.1	0	0.0	0	0.0	1	0.4
VITAMINS NOS	1	1.1	0	0.0	0	0.0	1	0.4
YELLOW PHENOLPHTHALEIN	1	1.1	0	0.0	0	0.0	1	0.4
ANTIINFECTIVES,SYSTEMIC:	15	16.1	8	8.4	14	16.1	37	13.5
AMOXICILLIN	3	3.2	2	2.1	4	4.6	9	3.3
AMOXICILLIN TRIHYDRATE	5	5.4	1	1.1	1	1.1	7	2.5
ANTIBIOTIC NOS	1	1.1	0	0.0	1	1.1	2	0.7
AZITHROMYCIN	0	0.0	0	0.0	1	1.1	1	0.4
CEFACLOR	2	2.2	1	1.1	0	0.0	3	1.1
CEFALEXIN MONOHYDRATE	1	1.1	0	0.0	1	1.1	2	0.7
CEFIXIME	1	1.1	0	0.0	0	0.0	1	0.4

Table 12.14

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	53	57.0%	53	55.8%	51	58.6%	157	57.1%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
CLARITHROMYCIN	1	1.1	1	1.1	1	1.1	3	1.1
CLAVULANIC ACID	2	2.2	0	0.0	1	1.1	3	1.1
DOXYCYCLINE	1	1.1	0	0.0	2	2.3	3	1.1
ERYTHROMYCIN	1	1.1	0	0.0	0	0.0	1	0.4
HEPATITIS B VACCINE	1	1.1	1	1.1	0	0.0	2	0.7
PHENOXYMETHYLPENICILLIN	0	0.0	1	1.1	0	0.0	1	0.4
PHENOXYMETHYLPENICILLIN POTASSIUM	0	0.0	1	1.1	0	0.0	1	0.4
SULFAMETHOXAZOLE	0	0.0	1	1.1	2	2.3	3	1.1
TETANUS TOXOID	0	0.0	0	0.0	1	1.1	1	0.4
TETRACYCLINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
TRIMETHOPRIM	0	0.0	1	1.1	2	2.3	3	1.1
ANTINEOPLASTIC & IMMUNOSUP:	0	0.0	0	0.0	1	1.1	1	0.4
MEDROXYPROGESTERONE ACETATE	0	0.0	0	0.0	1	1.1	1	0.4
BLOOD/BLOOD FORM ORGANS:	0	0.0	1	1.1	1	1.1	2	0.7
FERROUS SULFATE	0	0.0	0	0.0	1	1.1	1	0.4
I.V. FLUIDS	0	0.0	1	1.1	0	0.0	1	0.4
CARDIOVASCULAR:	2	2.2	0	0.0	0	0.0	2	0.7
BETAMETHASONE	1	1.1	0	0.0	0	0.0	1	0.4
THEOPHYLLINE	1	1.1	0	0.0	0	0.0	1	0.4
CENTRAL NERVOUS SYSTEM:	32	34.4	34	35.8	34	39.1	100	36.4
ACETYLSALICYLIC ACID	8	8.6	5	5.3	8	9.2	21	7.6
ALUMINIUM GLYCINATE	0	0.0	0	0.0	1	1.1	1	0.4
ANALGESICS	0	0.0	1	1.1	1	1.1	2	0.7
BUTALBITAL	1	1.1	0	0.0	0	0.0	1	0.4
CAFFEINE	6	6.5	3	3.2	2	2.3	11	4.0
CANNABIS	0	0.0	2	2.1	0	0.0	2	0.7
CHLORAL HYDRATE	0	0.0	1	1.1	0	0.0	1	0.4
CHLORPHENAMINE MALEATE	0	0.0	0	0.0	1	1.1	1	0.4
CINNAMEDRINE HYDROCHLORIDE	1	1.1	2	2.1	1	1.1	4	1.5
CODEINE PHOSPHATE	0	0.0	2	2.1	0	0.0	2	0.7
CYCLOBENZAPRINE	0	0.0	1	1.1	0	0.0	1	0.4
DEXTROMETHORPHAN HYDROBROMIDE	0	0.0	0	0.0	1	1.1	1	0.4
DIAZEPAM	0	0.0	0	0.0	1	1.1	1	0.4
HYDROCODONE BITARTRATE	0	0.0	0	0.0	1	1.1	1	0.4
LORAZEPAM	0	0.0	0	0.0	1	1.1	1	0.4
MAGNESIUM CARBONATE	0	0.0	0	0.0	1	1.1	1	0.4

Table 12.14

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	53	57.0%	53	55.8%	51	58.6%	157	57.1%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
MEPYRAMINE MALEATE	0	0.0	1	1.1	1	1.1	2	0.7
OXYCODONE HYDROCHLORIDE	1	1.1	1	1.1	0	0.0	2	0.7
OXYCODONE TEREPHTHALATE	1	1.1	1	1.1	0	0.0	2	0.7
PAMABROM	0	0.0	1	1.1	1	1.1	2	0.7
PARACETAMOL	30	32.3	27	28.4	28	32.2	85	30.9
PAROXETINE	0	0.0	0	0.0	1	1.1	1	0.4
PHENACETIN	1	1.1	0	0.0	3	3.4	4	1.5
PHENYLPROPANOLAMINE HYDROCHLORIDE	0	0.0	0	0.0	3	3.4	3	1.1
PHENYLTOLOXAMINE CITRATE	0	0.0	0	0.0	3	3.4	3	1.1
PSEUDOEPHEDRINE HYDROCHLORIDE	1	1.1	1	1.1	1	1.1	3	1.1
SLEEPING PILL	0	0.0	1	1.1	0	0.0	1	0.4
TRAMADOL HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
TRANQUILIZER	1	1.1	0	0.0	0	0.0	1	0.4
DERMATOLOGICALS:	12	12.9	13	13.7	6	6.9	31	11.3
BENTONITE	0	0.0	1	1.1	0	0.0	1	0.4
BETAMETHASONE	1	1.1	0	0.0	0	0.0	1	0.4
BUTOCONAZOLE NITRATE	0	0.0	1	1.1	0	0.0	1	0.4
CALAMINE	0	0.0	3	3.2	0	0.0	3	1.1
CAMPHOR	0	0.0	2	2.1	0	0.0	2	0.7
CLOTRIMAZOLE	1	1.1	0	0.0	0	0.0	1	0.4
DERMATOLOGICALS NOS	0	0.0	0	0.0	1	1.1	1	0.4
DIPHENHYDRAMINE HYDROCHLORIDE	6	6.5	8	8.4	0	0.0	14	5.1
DOFAMIUM CHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
ERYTHROMYCIN	1	1.1	0	0.0	0	0.0	1	0.4
FLUTICASONE PROPIONATE	1	1.1	0	0.0	1	1.1	2	0.7
GLYCEROL	0	0.0	3	3.2	0	0.0	3	1.1
GRISEOFULVIN	1	1.1	0	0.0	0	0.0	1	0.4
ISOTRETINOIN	0	0.0	1	1.1	1	1.1	2	0.7
METHYLPREDNISOLONE	0	0.0	0	0.0	1	1.1	1	0.4
METHYLPREDNISOLONE SODIUM SUCCINATE	0	0.0	1	1.1	0	0.0	1	0.4
PERMETHRIN	0	0.0	0	0.0	1	1.1	1	0.4
PHENOL	0	0.0	1	1.1	0	0.0	1	0.4
PHENOL, LIQUEFIED	0	0.0	1	1.1	0	0.0	1	0.4
PROMETHAZINE HYDROCHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
SODIUM CITRATE	0	0.0	1	1.1	0	0.0	1	0.4
SULFUR	1	1.1	0	0.0	0	0.0	1	0.4
TERCONAZOLE	0	0.0	1	1.1	0	0.0	1	0.4
TETRACYCLINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
TOPICAL ANTIFUNGAL NOS	0	0.0	1	1.1	0	0.0	1	0.4

Table 12.14

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	53	57.0%	53	55.8%	51	58.6%	157	57.1%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
TRETINOIN	0	0.0	0	0.0	1	1.1	1	0.4
TRIAMCINOLONE	1	1.1	0	0.0	0	0.0	1	0.4
TRICLOSAN	1	1.1	0	0.0	0	0.0	1	0.4
ZINC OXIDE	0	0.0	1	1.1	0	0.0	1	0.4
GU SYSTEM/SEX HORMONES:	4	4.3	3	3.2	3	3.4	10	3.6
BUTOCONAZOLE NITRATE	0	0.0	1	1.1	0	0.0	1	0.4
CLOTRIMAZOLE	1	1.1	0	0.0	0	0.0	1	0.4
DESOGESTREL	1	1.1	0	0.0	1	1.1	2	0.7
ETHINYLESTRADIOL	3	3.2	2	2.1	2	2.3	7	2.5
LEVONORGESTREL	0	0.0	2	2.1	0	0.0	2	0.7
MEDROXYPROGESTERONE ACETATE	0	0.0	0	0.0	1	1.1	1	0.4
NORETHISTERONE	1	1.1	0	0.0	0	0.0	1	0.4
NORGESTIMATE	1	1.1	0	0.0	1	1.1	2	0.7
MUSCULO-SKELETAL:	14	15.1	11	11.6	14	16.1	39	14.2
CYCLOBENZAPRINE	0	0.0	1	1.1	0	0.0	1	0.4
ETODOLAC	1	1.1	0	0.0	0	0.0	1	0.4
EUCALYPTUS OIL	1	1.1	0	0.0	0	0.0	1	0.4
IBUPROFEN	12	12.9	9	9.5	12	13.8	33	12.0
KETOPROFEN	1	1.1	0	0.0	0	0.0	1	0.4
MENTHOL	2	2.2	0	0.0	0	0.0	2	0.7
METAXALONE	1	1.1	0	0.0	0	0.0	1	0.4
NAPROXEN	0	0.0	0	0.0	1	1.1	1	0.4
NAPROXEN SODIUM	2	2.2	1	1.1	2	2.3	5	1.8
RESPIRATORY:	22	23.7	21	22.1	15	17.2	58	21.1
ACRIVASTINE	1	1.1	0	0.0	0	0.0	1	0.4
AMINOACETIC ACID	1	1.1	0	0.0	0	0.0	1	0.4
BECLOMETASONE DIPROPIONATE	0	0.0	0	0.0	1	1.1	1	0.4
BENZALKONIUM CHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
CARBINOXAMINE MALEATE	2	2.2	1	1.1	0	0.0	3	1.1
CETIRIZINE HYDROCHLORIDE	0	0.0	0	0.0	1	1.1	1	0.4
CHLORPHENAMINE MALEATE	2	2.2	1	1.1	1	1.1	4	1.5
CHLORPHENAMINE TANNATE	1	1.1	0	0.0	0	0.0	1	0.4
CLEMASTINE FUMARATE	0	0.0	0	0.0	1	1.1	1	0.4
CODEINE PHOSPHATE	0	0.0	1	1.1	0	0.0	1	0.4
COUGH COLD PREPARATIONS NOS	0	0.0	2	2.1	0	0.0	2	0.7
COUGH SYRUP/MED	1	1.1	1	1.1	0	0.0	2	0.7
CROMOGLICATE SODIUM	0	0.0	0	0.0	1	1.1	1	0.4

Table 12.14

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	53	57.0%	53	55.8%	51	58.6%	157	57.1%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
DEXBROMPHENIRAMINE MALEATE	2	2.2	0	0.0	0	0.0	2	0.7
DEXTROMETHORPHAN HYDROBROMIDE	4	4.3	3	3.2	1	1.1	8	2.9
DIMENHYDRINATE	1	1.1	1	1.1	0	0.0	2	0.7
DIPHENHYDRAMINE HYDROCHLORIDE	6	6.5	7	7.4	0	0.0	13	4.7
DOXYLAMINE SUCCINATE	2	2.2	1	1.1	0	0.0	3	1.1
ETHANOL	1	1.1	0	0.0	0	0.0	1	0.4
EUCALYPTUS OIL	1	1.1	0	0.0	0	0.0	1	0.4
FLUTICASONE PROPIONATE	1	1.1	0	0.0	1	1.1	2	0.7
GUAIFENESIN	4	4.3	3	3.2	7	8.0	14	5.1
HYDROCODONE BITARTRATE	2	2.2	0	0.0	1	1.1	3	1.1
IODINATED GLYCEROL	0	0.0	1	1.1	0	0.0	1	0.4
LORATADINE	0	0.0	0	0.0	2	2.3	2	0.7
MENTHOL	2	2.2	0	0.0	0	0.0	2	0.7
MEPYRAMINE MALEATE	1	1.1	0	0.0	0	0.0	1	0.4
MEPYRAMINE TANNATE	1	1.1	0	0.0	0	0.0	1	0.4
OXYMETAZOLINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
PARACETAMOL	4	4.3	4	4.2	3	3.4	11	4.0
PHENIRAMINE MALEATE	0	0.0	0	0.0	1	1.1	1	0.4
PHENYLEPHRINE HYDROCHLORIDE	5	5.4	1	1.1	2	2.3	8	2.9
PHENYLEPHRINE TANNATE	1	1.1	0	0.0	0	0.0	1	0.4
PHENYLMERCURIC ACETATE	1	1.1	0	0.0	0	0.0	1	0.4
PHENYLPROPANOLAMINE HYDROCHLORIDE	2	2.2	2	2.1	3	3.4	7	2.5
PHENYLTOLOXAMINE CITRATE	1	1.1	1	1.1	0	0.0	2	0.7
PREDNISONE	1	1.1	0	0.0	0	0.0	1	0.4
PROMETHAZINE HYDROCHLORIDE	0	0.0	1	1.1	0	0.0	1	0.4
PSEUDOEPHEDRINE	2	2.2	0	0.0	0	0.0	2	0.7
PSEUDOEPHEDRINE HYDROCHLORIDE	3	3.2	7	7.4	4	4.6	14	5.1
PSEUDOEPHEDRINE SULFATE	2	2.2	0	0.0	0	0.0	2	0.7
SALBUTAMOL	4	4.3	0	0.0	1	1.1	5	1.8
SORBITOL	1	1.1	0	0.0	0	0.0	1	0.4
THEOPHYLLINE	1	1.1	0	0.0	0	0.0	1	0.4
TRIPROLIDINE HYDROCHLORIDE	0	0.0	1	1.1	1	1.1	2	0.7
SENSORY ORGANS:	6	6.5	1	1.1	1	1.1	8	2.9
BETAMETHASONE	1	1.1	0	0.0	0	0.0	1	0.4
EAR MEDICATION, NOS	1	1.1	0	0.0	0	0.0	1	0.4
ERYTHROMYCIN	1	1.1	0	0.0	0	0.0	1	0.4
GRAMICIDIN	1	1.1	0	0.0	0	0.0	1	0.4
METHYLPREDNISOLONE	0	0.0	0	0.0	1	1.1	1	0.4
METHYLPREDNISOLONE SODIUM SUCCINATE	0	0.0	1	1.1	0	0.0	1	0.4

Table 12.14

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH MEDICATIONS :	53	57.0%	53	55.8%	51	58.6%	157	57.1%
ATC CLASSIFICATION LEVEL 1 : GENERIC TERM	N	%	N	%	N	%	N	%
POLYMYXIN B SULFATE	1	1.1	0	0.0	0	0.0	1	0.4
TETRACYCLINE HYDROCHLORIDE	1	1.1	0	0.0	0	0.0	1	0.4
TRIAMCINOLONE	1	1.1	0	0.0	0	0.0	1	0.4
SYSTEMIC HORMONAL:	3	3.2	2	2.1	1	1.1	6	2.2
BETAMETHASONE	1	1.1	0	0.0	0	0.0	1	0.4
MELATONIN	0	0.0	1	1.1	0	0.0	1	0.4
METHYLPREDNISOLONE	0	0.0	0	0.0	1	1.1	1	0.4
METHYLPREDNISOLONE SODIUM SUCCINATE	0	0.0	1	1.1	0	0.0	1	0.4
PREDNISONE	1	1.1	0	0.0	0	0.0	1	0.4
TRIAMCINOLONE	1	1.1	0	0.0	0	0.0	1	0.4
VARIOUS:	0	0.0	1	1.1	0	0.0	1	0.4
HOMEOPATHIC PREPARATIONS	0	0.0	1	1.1	0	0.0	1	0.4

PAROXETINE - PROTOCOL 329

Table 12.16

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

	PAROXETINE N = 93		IMIPRAMINE N = 95		PLACEBO N = 87	
	n	%	n	%	n	%
Unknown	5	5.4	2	2.1	1	1.1
< 80 %	3	3.2	8	8.4	5	5.7
80 - 120 %	85	91.4	85	89.5	81	93.1
Mean compliance	94.8		93.1		93.5	

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 12.18

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

	PAROXETINE N = 93 Dose Level						IMIPRAMINE N = 95 Dose Level						PLACEBO N = 87 Dose Level					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Week 1	9	82	2	0	0	0	6	88	1	0	0	0	5	81	1	0	0	0
Week 2	1	5	78	2	0	0	1	13	76	1	0	0	0	7	78	0	0	0
Week 3	0	0	5	75	0	0	0	0	10	70	0	0	0	0	8	71	0	0
Week 4	0	0	0	43	34	0	0	0	0	56	19	0	0	0	0	43	33	0
Week 5	0	0	0	33	26	17	0	0	0	40	18	11	0	0	0	30	23	21
Week 6	0	0	1	25	23	25	0	0	0	33	14	16	0	0	0	25	16	27
Week 7	0	0	0	24	20	27	0	0	0	29	14	15	0	0	0	23	9	35
Week 8	0	0	0	23	20	22	0	0	0	26	12	15	0	0	0	20	11	35
Endpoint	8	3	3	31	22	26	3	11	5	45	15	16	2	3	5	27	14	36
Maximum	8	3	3	28	23	28	3	11	5	38	18	20	2	3	5	26	15	36

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

PAROXETINE - PROTOCOL 329

Table 12.18

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

	PAROXETINE N = 93			IMIPRAMINE N = 95			PLACEBO N = 87		
	n	mean	s.d.	n	mean	s.d.	n	mean	s.d.
Mean Dose (mg) at Endpoint	93	28.0	8.54	95	205.8	63.94	87	0.0	0.00

Paroxetine - Protocol 329
Table 12.20
Summary of Duration of Current Episode (mo)
Intent to Treat Population

PAROXETINE					IMIPRAMINE					PLACEBO				
n	mean	std dev	min	max	n	mean	std dev	min	max	n	mean	std dev	min	max
92	14.4	17.5	1.8	81.5	93	14.2	17.9	0.9	122.6	85	12.5	16.6	0.7	96.1

Paroxetine - Protocol 329
Table 12.21
Summary of Number of Depressive Episodes
Intent to Treat Population

	PAROXETINE n/N	(%)	IMIPRAMINE n/N	(%)	PLACEBO n/N	(%)
0	2/93	(2.2)	0/95	(0.0)	0/87	(0.0)
1	73/93	(78.5)	75/95	(78.9)	67/87	(77.0)
2	11/93	(11.8)	13/95	(13.7)	12/87	(13.8)
>= 3	6/93	(6.5)	6/95	(6.3)	7/87	(8.0)
Missing	1/93	(1.1)	1/95	(1.1)	1/87	(1.1)

Paroxetine - Protocol 329
Table 12.21
Summary of Number of Depressive Episodes
Intent to Treat Population

PAROXETINE					IMIPRAMINE					PLACEBO				
n	mean	std dev	min	max	n	mean	std dev	min	max	n	mean	std dev	min	max
92	1.2	0.6	0	4	94	1.3	0.9	1	7	86	1.3	0.7	1	4

Paroxetine - Protocol 329
Table 12.22
Summary of Age at Onset of First Episode (yr)
Intent to Treat Population

PAROXETINE					IMIPRAMINE					PLACEBO				
n	mean	std dev	min	max	n	mean	std dev	min	max	n	mean	std dev	min	max
91	13.1	2.7	7	18	94	13.1	2.7	6	18	86	13.5	2.3	6	18

Paroxetine - Protocol 329
Table 12.23
Summary of Melancholic/Endogenous Depression
Intent to Treat Population

	PAROXETINE		IMIPRAMINE		PLACEBO	
	n/N	(%)	n/N	(%)	n/N	(%)
Yes	34/93	(36.6)	33/95	(34.7)	35/87	(40.2)
No	58/93	(62.4)	61/95	(64.2)	51/87	(58.6)
Missing	1/93	(1.1)	1/95	(1.1)	1/87	(1.1)

Melancholic/Endogeneous Depression is defined as at least one of: loss of pleasure, lack of reactivity and three or more of: distinct quality of mood, morning mood worsening, early morning awakening, psychomotor retardation or psychomotor agitation, significant anorexia or weight loss, excessive guilt

Paroxetine - Protocol 329
Table 12.24
Summary of Atypical Depression
Intent to Treat Population

	PAROXETINE		IMIPRAMINE		PLACEBO	
	n/N	(%)	n/N	(%)	n/N	(%)
Yes	23/93	(24.7)	15/95	(15.8)	8/87	(9.2)
No	69/93	(74.2)	78/95	(82.1)	78/87	(89.7)
Missing	1/93	(1.1)	2/95	(2.1)	1/87	(1.1)

Atypical Depression is defined as mood reactivity plus one or more of: lack of energy, rejection sensitivity, hypersomnia, increased appetite or weight gain greater than or equal to 10 pounds plus lack of qualification for melancholic subtype of depression

Paroxetine - Protocol 329
Table 12.25
Summary of Family History of Major Depression
Intent to Treat Population

	PAROXETINE		IMIPRAMINE		PLACEBO	
	n/N	(%)	n/N	(%)	n/N	(%)
Yes	80/93	(86.0)	85/95	(89.5)	83/87	(95.4)
No	5/93	(5.4)	4/95	(4.2)	3/87	(3.4)
Missing	8/93	(8.6)	6/95	(6.3)	1/87	(1.1)

Family members include biologic mother, biologic father, and siblings

Paroxetine - Protocol 329
Table 12.26
Summary of Any Concomitant Diagnosis
Intent to Treat Population

	PAROXETINE		IMIPRAMINE		PLACEBO	
	n/N	(%)	n/N	(%)	n/N	(%)
Yes	38/93	(40.9)	47/95	(49.5)	39/87	(44.8)
No	54/93	(58.1)	47/95	(49.5)	47/87	(54.0)
Missing	1/93	(1.1)	1/95	(1.1)	1/87	(1.1)

Concomitant diagnoses are defined as any K-SADS-L diagnostic criteria at screening other than major depressive episode

Paroxetine - Protocol 329
Table 12.27
Summary of Anxiety Disorder
Intent to Treat Population

	PAROXETINE		IMIPRAMINE		PLACEBO	
	n/N	(%)	n/N	(%)	n/N	(%)
Yes	18/93	(19.4)	25/95	(26.3)	24/87	(27.6)
No	74/93	(79.6)	69/95	(72.6)	62/87	(71.3)
Missing	1/93	(1.1)	1/95	(1.1)	1/87	(1.1)

Anxiety disorder is defined as at least one of: separation anxiety disorder, panic disorder (without agorophobia), panic disorder (with agorophobia), agorophobia (no panic), social phobia, generalized anxiety disorder

Paroxetine - Protocol 329
Table 12.28
Summary of Externalizing Disorder
Intent to Treat Population

	PAROXETINE		IMIPRAMINE		PLACEBO	
	n/N	(%)	n/N	(%)	n/N	(%)
Yes	23/93	(24.7)	25/95	(26.3)	17/87	(19.5)
No	69/93	(74.2)	69/95	(72.6)	69/87	(79.3)
Missing	1/93	(1.1)	1/95	(1.1)	1/87	(1.1)

Externalizing Disorder is defined as at least one of: attention-deficit/hyperactivity, conduct disorder, oppositional defiant disorder

11 Data Source Tables: Efficacy Results

Paroxetine - Protocol 329
Table 13.1
Baseline Mean and Mean Change from Baseline at Weekly Intervals--HAMD Scale
Acute 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	90	18.98	(0.43)	94	18.11	(0.43)	87	18.97	(0.44)	0.985	0.137
Week 1	88	-3.75	(0.47)	91	-3.35	(0.47)	84	-3.23	(0.48)	0.416	0.851
Week 2	81	-6.08	(0.62)	88	-5.49	(0.60)	80	-5.34	(0.62)	0.373	0.857
Week 3	76	-8.74	(0.75)	77	-6.98	(0.76)	75	-6.77	(0.75)	0.051	0.834
Week 4	76	-9.20	(0.71)	69	-8.09	(0.77)	73	-7.84	(0.72)	0.159	0.806
Week 5	72	-9.52	(0.81)	67	-9.23	(0.85)	70	-9.43	(0.85)	0.927	0.862
Week 6	72	-10.68	(0.81)	62	-9.18	(0.87)	66	-10.17	(0.84)	0.640	0.383
Week 7	67	-11.98	(0.84)	54	-9.83	(0.95)	63	-10.49	(0.86)	0.185	0.581
Week 8	67	-12.18	(0.88)	56	-10.59	(0.97)	66	-10.51	(0.88)	0.153	0.945
Endpoint	90	-10.74	(0.81)	94	-8.91	(0.81)	87	-9.09	(0.83)	0.133	0.873

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 13.1.1
Baseline Mean and Mean Change from Baseline at Weekly Intervals--HAMD Scale
Acute Phase
Per Protocol 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	77	18.99	(0.47)	84	18.29	(0.47)	80	19.23	(0.48)	0.702	0.130
Week 1	75	-3.25	(0.50)	81	-3.22	(0.49)	77	-2.98	(0.51)	0.688	0.724
Week 2	68	-5.54	(0.65)	79	-5.63	(0.62)	74	-5.24	(0.64)	0.731	0.638
Week 3	63	-8.31	(0.81)	69	-6.95	(0.82)	71	-6.50	(0.79)	0.092	0.664
Week 4	63	-8.90	(0.78)	61	-8.55	(0.85)	67	-7.83	(0.79)	0.310	0.498
Week 5	60	-9.15	(0.90)	58	-9.37	(0.96)	65	-9.38	(0.92)	0.853	0.997
Week 6	59	-10.55	(0.88)	54	-9.41	(0.94)	61	-10.13	(0.88)	0.723	0.542
Week 7	54	-11.92	(0.93)	47	-9.99	(1.05)	58	-10.51	(0.92)	0.254	0.686
Week 8	55	-12.00	(0.97)	47	-10.95	(1.10)	61	-10.41	(0.96)	0.219	0.685
Endpoint	77	-10.23	(0.88)	84	-8.89	(0.88)	80	-9.16	(0.89)	0.369	0.818

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 13.2
Baseline Mean and Mean Change from Baseline at Weekly Intervals-- K-SADS-L Depression 9-Item Scale
Acute 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	83	28.25	(0.52)	88	27.54	(0.51)	85	28.84	(0.52)	0.399	0.058
Week 2	77	-5.51	(0.67)	82	-5.53	(0.65)	76	-6.26	(0.67)	0.405	0.408
Week 4	70	-9.01	(0.83)	60	-8.55	(0.91)	66	-8.17	(0.85)	0.455	0.748
Week 6	67	-11.00	(0.89)	50	-11.02	(1.02)	54	-11.22	(1.01)	0.860	0.883
Week 8	67	-12.03	(0.93)	56	-10.68	(1.02)	65	-10.87	(0.93)	0.348	0.883
Endpoint	83	-11.66	(0.84)	88	-9.55	(0.83)	85	-9.57	(0.83)	0.065	0.984

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 13.2.1
Baseline Mean and Mean Change from Baseline at Weekly Intervals-- K-SADS-L Depression 9-Item Scale
Acute Phase
Per Protocol 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	70	28.42	(0.56)	79	27.76	(0.55)	79	28.97	(0.55)	0.464	0.095
Week 2	64	-4.86	(0.73)	74	-5.52	(0.69)	70	-6.11	(0.72)	0.197	0.524
Week 4	57	-8.34	(0.94)	54	-8.67	(1.00)	61	-7.96	(0.93)	0.758	0.576
Week 6	54	-10.61	(0.96)	44	-11.55	(1.08)	49	-10.86	(1.05)	0.849	0.617
Week 8	55	-11.80	(1.02)	48	-10.64	(1.15)	60	-10.40	(1.01)	0.305	0.866
Endpoint	70	-11.26	(0.92)	79	-9.48	(0.90)	79	-9.13	(0.90)	0.085	0.772

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 13.3
Number (%) of Patients Responding to Treatment
Acute Phase
Intent to Treat Population

	PAROXETINE n/N	%	IMIPRAMINE n/N	%	PLACEBO n/N	%	-- Pairwise Comparisons --- Par vs Pla		Imp vs Pla
Week 1	13 /88	(14.8)	10 /91	(11.0)	6 /84	(7.1)	0.211		0.521
Week 2	29 /81	(35.8)	24 /88	(27.3)	19 /80	(23.8)	0.146		0.786
Week 3	40 /76	(52.6)	33 /77	(42.9)	26 /75	(34.7)	0.024	*	0.196
Week 4	43 /76	(56.6)	35 /69	(50.7)	39 /73	(53.4)	0.715		0.652
Week 5	47 /72	(65.3)	37 /67	(55.2)	38 /70	(54.3)	0.244		0.687
Week 6	48 /72	(66.7)	37 /62	(59.7)	44 /66	(66.7)	0.994		0.388
Week 7	48 /67	(71.6)	39 /54	(72.2)	39 /63	(61.9)	0.176		0.199
Week 8	54 /67	(80.6)	41 /56	(73.2)	43 /66	(65.2)	0.051		0.363
Endpoint	60 /90	(66.7)	55 /94	(58.5)	48 /87	(55.2)	0.112		0.612

Only patients with one or more on-therapy evaluations are included.
* - significantly different from placebo for alpha = 0.05
Response is defined as a HAMD total score less than or equal to 8 or a decrease from baseline in HAMD total score of 50% or greater.
Treatment p-value obtained from categorical analysis using a model with effects for treatment and investigator.

Paroxetine - Protocol 329
Table 13.3.1
Number (%) of Patients Responding to Treatment
Acute Phase
Per Protocol Population

	PAROXETINE n/N	%	IMIPRAMINE n/N	%	PLACEBO n/N	%	-- Pairwise Comparisons --- Par vs Pla		Imp vs Pla
Week 1	8 /75	(10.7)	7 /81	(8.6)	4 /77	(5.2)	0.260		0.452
Week 2	19 /68	(27.9)	22 /79	(27.8)	17 /74	(23.0)	0.515		0.577
Week 3	32 /63	(50.8)	29 /69	(42.0)	24 /71	(33.8)	0.026	*	0.211
Week 4	33 /63	(52.4)	32 /61	(52.5)	36 /67	(53.7)	0.978		0.875
Week 5	37 /60	(61.7)	32 /58	(55.2)	34 /65	(52.3)	0.366		0.600
Week 6	39 /59	(66.1)	32 /54	(59.3)	40 /61	(65.6)	0.844		0.471
Week 7	38 /54	(70.4)	35 /47	(74.5)	36 /58	(62.1)	0.271		0.178
Week 8	44 /55	(80.0)	36 /47	(76.6)	38 /61	(62.3)	0.053		0.135
Endpoint	49 /77	(63.6)	49 /84	(58.3)	43 /80	(53.8)	0.196		0.502

Only patients with one or more on-therapy evaluations are included.
* - significantly different from placebo for alpha = 0.05
Response is defined as a HAMD total score less than or equal to 8 or a decrease from baseline in HAMD total score of 50% or greater.
Treatment p-value obtained from categorical analysis using a model with effects for treatment and investigator.

Paroxetine - Protocol 329
Table 13.4
Mean at Weekly Intervals--CGI Global Improvement
Acute 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 1	88	3.52	(0.08)	90	3.58	(0.08)	84	3.52	(0.08)	0.975		0.546
Week 2	80	3.04	(0.11)	89	3.19	(0.10)	79	3.15	(0.11)	0.447		0.818
Week 3	76	2.68	(0.12)	78	2.91	(0.12)	75	2.90	(0.12)	0.165		0.920
Week 4	76	2.49	(0.13)	69	2.76	(0.14)	73	2.79	(0.13)	0.088		0.874
Week 5	72	2.55	(0.14)	67	2.49	(0.15)	70	2.73	(0.15)	0.336		0.220
Week 6	73	2.44	(0.15)	61	2.61	(0.17)	66	2.58	(0.16)	0.516		0.870
Week 7	66	2.20	(0.16)	53	2.38	(0.18)	63	2.41	(0.16)	0.319		0.915
Week 8	68	1.91	(0.15)	56	2.16	(0.17)	66	2.36	(0.16)	0.030	*	0.371
Endpoint	90	2.37	(0.16)	94	2.70	(0.15)	87	2.73	(0.16)	0.094		0.896

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 13.5
Distribution Of Patients in Each Class of CGI Global Improvement at Endpoint
Acute Phase
Intent to Treat Population

	PAROXETINE		IMIPRAMINE		PLACEBO	
	Endpoint		Endpoint		Endpoint	
	n/N	(%)	n/N	(%)	n/N	(%)
Very Much Improved (1)	32 /90	(35.6)	21 /94	(22.3)	20 /87	(23.0)
Much Improved (2)	27 /90	(30.0)	28 /94	(29.8)	22 /87	(25.3)
Minimally Improved (3)	12 /90	(13.3)	20 /94	(21.3)	17 /87	(19.5)
No Change (4)	13 /90	(14.4)	15 /94	(16.0)	22 /87	(25.3)
Minimally Worse (5)	1 /90	(1.1)	8 /94	(8.5)	4 /87	(4.6)
Much Worse (6)	3 /90	(3.3)	1 /94	(1.1)	2 /87	(2.3)
Very Much Worse (7)	2 /90	(2.2)	1 /94	(1.1)	0 /87	(0.0)

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

Paroxetine - Protocol 329
Table 13.6
Number (%) of Patients Withdrawing for Lack of Efficacy
Acute 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	4 /93	(4.3)	1 /95	(1.1)	6 /87	(6.9)	0.526	0.056

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

Paroxetine - Protocol 329
Table 13.7
Baseline Mean and Mean Change from Baseline at Weekly Intervals--HAMD Anxiety/Somatization Scale
Acute 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	90	5.82	(0.23)	94	5.29	(0.23)	87	5.60	(0.23)	0.477		0.312
Week 1	88	-1.37	(0.23)	91	-0.45	(0.23)	84	-0.92	(0.24)	0.159		0.130
Week 2	81	-1.75	(0.27)	88	-1.08	(0.26)	80	-1.33	(0.27)	0.239		0.480
Week 3	76	-2.85	(0.32)	77	-1.51	(0.32)	75	-1.66	(0.32)	0.005	*	0.714
Week 4	76	-2.73	(0.29)	69	-1.70	(0.32)	73	-2.11	(0.30)	0.124		0.319
Week 5	72	-2.99	(0.34)	67	-2.22	(0.36)	70	-2.46	(0.35)	0.241		0.603
Week 6	72	-3.53	(0.34)	62	-2.13	(0.37)	66	-3.03	(0.36)	0.281		0.064
Week 7	67	-4.00	(0.34)	54	-2.55	(0.39)	63	-2.97	(0.35)	0.026	*	0.392
Week 8	67	-3.79	(0.35)	56	-2.54	(0.39)	66	-2.88	(0.35)	0.051		0.491
Endpoint	90	-3.18	(0.33)	94	-2.07	(0.33)	87	-2.59	(0.33)	0.184		0.231

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 13.8
Baseline Mean and Mean Change from Baseline at Weekly Intervals--HAMD Sleep Scale
Acute 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	90	2.41	(0.19)	94	2.49	(0.19)	87	2.50	(0.20)	0.735	0.969
Week 1	88	0.01	(0.18)	91	-0.74	(0.18)	84	-0.47	(0.19)	0.059	0.267
Week 2	81	-0.88	(0.21)	88	-0.96	(0.21)	80	-0.69	(0.21)	0.513	0.345
Week 3	76	-0.95	(0.21)	77	-1.05	(0.22)	75	-0.95	(0.21)	0.981	0.724
Week 4	76	-1.22	(0.21)	69	-1.20	(0.23)	73	-0.76	(0.22)	0.111	0.143
Week 5	72	-1.15	(0.23)	67	-1.49	(0.25)	70	-1.14	(0.24)	0.979	0.272
Week 6	72	-1.45	(0.23)	62	-1.29	(0.25)	66	-1.45	(0.24)	0.997	0.610
Week 7	67	-1.41	(0.23)	54	-1.24	(0.26)	63	-1.33	(0.24)	0.795	0.781
Week 8	67	-1.41	(0.25)	56	-1.46	(0.27)	66	-1.35	(0.25)	0.852	0.767
Endpoint	90	-1.26	(0.21)	94	-1.20	(0.21)	87	-1.11	(0.22)	0.605	0.746

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 13.9
Baseline Mean and Mean Change from Baseline at Weekly Intervals--HAMD Cognitive Disturbance Scale
Acute 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	90	3.25	(0.20)	94	3.09	(0.20)	87	3.44	(0.20)	0.458	0.182
Week 1	88	-0.55	(0.22)	91	-0.74	(0.21)	84	-0.52	(0.22)	0.907	0.439
Week 2	81	-1.00	(0.21)	88	-1.20	(0.21)	80	-0.97	(0.21)	0.932	0.423
Week 3	76	-1.33	(0.23)	77	-1.42	(0.24)	75	-1.42	(0.23)	0.774	0.997
Week 4	76	-1.22	(0.25)	69	-1.62	(0.27)	73	-1.53	(0.26)	0.365	0.791
Week 5	72	-1.23	(0.26)	67	-1.39	(0.27)	70	-1.77	(0.27)	0.119	0.287
Week 6	72	-1.26	(0.26)	62	-1.75	(0.28)	66	-1.60	(0.27)	0.324	0.680
Week 7	67	-1.56	(0.27)	54	-1.75	(0.31)	63	-1.88	(0.28)	0.386	0.746
Week 8	67	-1.74	(0.26)	56	-2.28	(0.29)	66	-2.10	(0.26)	0.296	0.609
Endpoint	90	-1.71	(0.25)	94	-1.63	(0.25)	87	-1.71	(0.25)	0.989	0.827

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 13.10
Baseline Mean and Mean Change from Baseline at Weekly Intervals--HAMD Retardation Scale
Acute 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	90	7.32	(0.21)	94	6.84	(0.21)	87	7.12	(0.21)	0.479	0.367
Week 1	88	-1.77	(0.24)	91	-1.16	(0.24)	84	-1.23	(0.24)	0.111	0.842
Week 2	81	-2.53	(0.30)	88	-1.95	(0.29)	80	-2.42	(0.29)	0.797	0.262
Week 3	76	-3.62	(0.38)	77	-2.63	(0.39)	75	-2.73	(0.35)	0.086	0.852
Week 4	76	-3.81	(0.32)	69	-3.21	(0.40)	73	-3.24	(0.33)	0.220	0.949
Week 5	72	-3.95	(0.35)	67	-3.85	(0.42)	70	-3.76	(0.42)	0.722	0.876
Week 6	72	-4.29	(0.39)	62	-3.68	(0.44)	66	-4.15	(0.40)	0.797	0.430
Week 7	67	-4.77	(0.43)	54	-4.16	(0.55)	63	-4.16	(0.42)	0.309	0.994
Week 8	67	-4.82	(0.43)	56	-4.25	(0.54)	66	-4.09	(0.41)	0.221	0.821
Endpoint	90	-4.36	(0.34)	94	-3.76	(0.35)	87	-3.59	(0.34)	0.104	0.722

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

Retardation Scale includes items 1, 7, 8, 14

Paroxetine - Protocol 329
Table 13.10.1
Baseline Mean and Mean Change from Baseline at Weekly Intervals--HAMD Retardation Scale
Acute Phase Without Center 007
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	82	7.35	(0.19)	88	6.86	(0.19)	82	7.16	(0.19)	0.466		0.250
Week 1	81	-1.69	(0.22)	85	-1.26	(0.22)	79	-1.14	(0.23)	0.066		0.685
Week 2	73	-2.61	(0.28)	82	-2.05	(0.26)	76	-2.04	(0.27)	0.118		0.979
Week 3	70	-3.54	(0.33)	74	-2.78	(0.32)	71	-2.55	(0.32)	0.023	*	0.577
Week 4	70	-3.95	(0.31)	66	-3.19	(0.33)	69	-3.22	(0.32)	0.083		0.959
Week 5	66	-4.05	(0.33)	64	-3.65	(0.34)	66	-3.60	(0.34)	0.286		0.908
Week 6	65	-4.54	(0.34)	59	-3.79	(0.35)	62	-3.88	(0.34)	0.138		0.844
Week 7	64	-4.71	(0.36)	53	-3.96	(0.40)	60	-3.97	(0.37)	0.123		0.980
Week 8	62	-5.12	(0.38)	55	-4.00	(0.41)	62	-3.77	(0.38)	0.007	*	0.652
Endpoint	82	-4.59	(0.32)	88	-3.66	(0.31)	82	-3.33	(0.32)	0.003	*	0.427

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 13.11
Number (%) of Patients In Remission
Acute Phase
Intent to Treat Population

	PAROXETINE n/N	%	IMIPRAMINE n/N	%	PLACEBO n/N	%	-- Pairwise Comparisons --- Par vs Pla		Imp vs Pla
Week 1	12 /88	(13.6)	8 /91	(8.8)	5 /84	(6.0)	0.175		0.668
Week 2	24 /81	(29.6)	18 /88	(20.5)	15 /80	(18.8)	0.182		0.979
Week 3	33 /76	(43.4)	28 /77	(36.4)	23 /75	(30.7)	0.103		0.296
Week 4	36 /76	(47.4)	31 /69	(44.9)	33 /73	(45.2)	0.874		0.842
Week 5	40 /72	(55.6)	32 /67	(47.8)	31 /70	(44.3)	0.228		0.573
Week 6	40 /72	(55.6)	33 /62	(53.2)	39 /66	(59.1)	0.748		0.511
Week 7	45 /67	(67.2)	35 /54	(64.8)	38 /63	(60.3)	0.329		0.592
Week 8	51 /67	(76.1)	36 /56	(64.3)	38 /66	(57.6)	0.019	*	0.440
Endpoint	57 /90	(63.3)	47 /94	(50.0)	40 /87	(46.0)	0.019	*	0.574

Only patients with one or more on-therapy evaluations are included.
* - significantly different from placebo for alpha = 0.05
Remission is defined as a HAMD total score less than or equal to 8.
Treatment p-value obtained from categorical analysis using a model with effects for treatment and investigator.

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Paroxetine - Protocol 329
Table 13.12
Number (%) of Patients With Sustained Response
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)
Sustained Response	60 /90	66.7	29.5	32.0	55 /94	58.5	28.0	28.8	48 /87	55.2	29.0	30.3

Only patients with one or more on-therapy evaluations are included.
Median and Mean Time (days) to Sustained Response relative to start of acute phase.
Median and mean are not adjusted for censored data.
Sustained Response = HAMD Total Score less than or equal to 8 OR decrease from baseline of 50% or greater (lasting until endpoint).

Paroxetine - Protocol 329
Table 13.13
Baseline Mean and Mean Change from Baseline at Weekly Intervals--Self Perception Profile Scale
Acute 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	61	63.48	(2.58)	60	60.87	(2.67)	63	60.69	(2.52)	0.418	0.960
Week 8	60	12.93	(2.31)	55	13.25	(2.46)	60	12.66	(2.30)	0.930	0.853
Endpoint	61	13.25	(2.33)	60	13.07	(2.41)	63	11.36	(2.27)	0.542	0.586

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 13.14
Baseline Mean and Mean Change from Baseline at Weekly Intervals--Autonomous Functioning Scale
Acute 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	60	91.41	(3.80)	57	96.02	(3.97)	62	94.18	(3.74)	0.584	0.719
Week 8	58	14.37	(2.83)	52	13.37	(3.04)	60	9.32	(2.80)	0.184	0.297
Endpoint	60	14.70	(2.80)	57	11.57	(2.92)	62	9.30	(2.75)	0.148	0.546

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 13.15
Baseline Mean and Mean Change from Baseline at Weekly Intervals--Autonomous Functioning Scale:Self/Family Care Subscore
Acute 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	60	25.68	(1.37)	56	27.70	(1.44)	62	28.21	(1.35)	0.167	0.784
Week 8	58	3.78	(1.28)	51	3.67	(1.38)	60	1.10	(1.27)	0.119	0.145
Endpoint	60	3.68	(1.24)	56	3.31	(1.30)	62	1.23	(1.22)	0.138	0.213

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 13.16
Baseline Mean and Mean Change from Baseline at Weekly Intervals--Autonomous Functioning Scale:Management Subscore
Acute 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	60	36.71	(1.71)	57	38.31	(1.79)	62	37.40	(1.69)	0.762	0.691
Week 8	58	5.64	(1.23)	52	4.94	(1.32)	60	4.04	(1.22)	0.331	0.592
Endpoint	60	5.97	(1.22)	57	4.03	(1.28)	62	3.95	(1.20)	0.217	0.965

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 13.17
Baseline Mean and Mean Change from Baseline at Weekly Intervals--Autonomous Functioning Scale:Recreational Activity Subscore
Acute 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	60	22.00	(1.16)	57	23.51	(1.21)	62	21.96	(1.14)	0.979	0.320
Week 8	58	3.51	(0.90)	52	3.33	(0.97)	60	3.22	(0.89)	0.809	0.932
Endpoint	60	3.59	(0.89)	57	2.93	(0.93)	62	3.17	(0.88)	0.726	0.841

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 13.18
Baseline Mean and Mean Change from Baseline at Weekly Intervals--Autonomous Functioning Scale:Social/Vocational Activities Subscore
Acute 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	60	7.09	(0.46)	57	6.69	(0.48)	62	6.65	(0.45)	0.465	0.944
Week 8	58	1.46	(0.35)	52	1.15	(0.37)	60	1.04	(0.35)	0.362	0.819
Endpoint	60	1.49	(0.34)	57	1.04	(0.35)	62	1.03	(0.33)	0.309	0.980

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 13.19
Baseline Mean and Mean Change from Baseline at Weekly Intervals--Sickness Impact Profile Scale
Acute 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	63	30.90	(1.46)	60	30.38	(1.52)	65	32.17	(1.42)	0.511	0.363
Week 8	62	-11.19	(1.57)	55	-13.45	(1.70)	62	-10.61	(1.57)	0.786	0.193
Endpoint	63	-11.36	(1.55)	60	-12.92	(1.62)	65	-9.85	(1.51)	0.463	0.143

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 13.20
Baseline Mean and Mean Change from Baseline at Weekly Intervals--SIP Scale:Present Health Subscore
Acute 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	61	2.39	(0.12)	60	2.44	(0.12)	63	2.74	(0.11)	0.025	*	0.058
Week 8	60	-0.27	(0.12)	55	-0.22	(0.13)	60	-0.25	(0.12)	0.888		0.845
Endpoint	61	-0.28	(0.12)	60	-0.17	(0.12)	63	-0.25	(0.12)	0.812		0.622

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 13.21
Baseline Mean and Mean Change from Baseline at Weekly Intervals--SIP Scale:Present Quality of Life Subscore
Acute 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	61	3.38	(0.11)	60	3.40	(0.12)	63	3.52	(0.11)	0.343	0.414
Week 8	60	-0.66	(0.15)	55	-0.97	(0.16)	60	-0.69	(0.15)	0.913	0.165
Endpoint	61	-0.67	(0.15)	60	-0.96	(0.15)	63	-0.60	(0.14)	0.737	0.072

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 13.22
Baseline Mean and Mean Change from Baseline at Weekly Intervals--SIP Scale:Sleep/Rest Subscore
Acute 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	63	3.55	(0.26)	60	3.18	(0.27)	65	3.85	(0.26)	0.398	0.064
Week 8	62	-1.30	(0.29)	55	-1.52	(0.31)	62	-1.51	(0.29)	0.587	0.975
Endpoint	63	-1.30	(0.29)	60	-1.46	(0.30)	65	-1.34	(0.28)	0.921	0.746

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 13.23
Baseline Mean and Mean Change from Baseline at Weekly Intervals--SIP Scale:Home Maintenance Subscore
Acute 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	63	2.47	(0.23)	59	2.07	(0.24)	65	2.32	(0.22)	0.613	0.416
Week 8	62	-1.08	(0.24)	54	-0.84	(0.26)	62	-0.66	(0.24)	0.191	0.577
Endpoint	63	-1.08	(0.24)	59	-0.88	(0.25)	65	-0.55	(0.23)	0.098	0.310

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 13.24
Baseline Mean and Mean Change from Baseline at Weekly Intervals--SIP Scale:Social Interaction Subscore
Acute 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	63	7.65	(0.52)	60	7.69	(0.55)	65	7.97	(0.51)	0.640	0.689
Week 8	62	-3.00	(0.59)	55	-4.40	(0.63)	62	-3.07	(0.58)	0.930	0.104
Endpoint	63	-3.02	(0.58)	60	-4.19	(0.60)	65	-2.84	(0.56)	0.815	0.084

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 13.25
Baseline Mean and Mean Change from Baseline at Weekly Intervals--SIP Scale:Alertness Behavior Subscore
Acute 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	62	5.60	(0.39)	60	5.73	(0.41)	65	5.49	(0.38)	0.835	0.654	
Week 8	61	-2.19	(0.40)	55	-2.92	(0.43)	62	-1.82	(0.40)	0.487	0.047	*
Endpoint	62	-2.27	(0.39)	60	-2.77	(0.41)	65	-1.75	(0.38)	0.321	0.057	

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 13.26
Baseline Mean and Mean Change from Baseline at Weekly Intervals--SIP Scale:Communication Subscore
Acute 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	62	1.96	(0.19)	58	2.00	(0.20)	65	2.05	(0.18)	0.721	0.873
Week 8	61	-0.94	(0.20)	54	-0.53	(0.22)	62	-0.57	(0.20)	0.179	0.884
Endpoint	62	-0.94	(0.20)	58	-0.58	(0.21)	65	-0.50	(0.19)	0.102	0.774

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 13.27
Baseline Mean and Mean Change from Baseline at Weekly Intervals--SIP Scale:Recreational Pastimes Subscore
Acute 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	62	3.86	(0.29)	58	3.70	(0.31)	65	4.26	(0.28)	0.303	0.157
Week 8	61	-1.56	(0.36)	54	-1.95	(0.38)	62	-2.02	(0.35)	0.339	0.900
Endpoint	62	-1.61	(0.35)	58	-1.84	(0.37)	65	-1.97	(0.34)	0.443	0.783

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 13.35
Baseline Mean and Mean Change from Baseline at Weekly Intervals--HAMD Depressed Mood Item
Acute 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	90	2.99	(0.08)	94	2.79	(0.08)	87	2.86	(0.08)	0.227		0.514
Week 1	88	-0.91	(0.11)	91	-0.61	(0.11)	84	-0.44	(0.12)	0.003	*	0.269
Week 2	81	-1.39	(0.13)	88	-0.90	(0.13)	80	-0.89	(0.13)	0.005	*	0.955
Week 3	76	-1.44	(0.15)	77	-1.12	(0.15)	75	-1.00	(0.14)	0.027	*	0.552
Week 4	76	-1.76	(0.14)	69	-1.45	(0.15)	73	-1.35	(0.14)	0.031	*	0.630
Week 5	72	-1.70	(0.15)	67	-1.54	(0.16)	70	-1.46	(0.16)	0.235		0.706
Week 6	72	-1.96	(0.15)	62	-1.61	(0.16)	66	-1.53	(0.15)	0.036	*	0.700
Week 7	67	-2.00	(0.16)	54	-1.76	(0.18)	63	-1.58	(0.17)	0.057		0.442
Week 8	67	-2.21	(0.17)	56	-1.76	(0.18)	66	-1.54	(0.17)	0.003	*	0.358
Endpoint	90	-2.00	(0.14)	94	-1.62	(0.14)	87	-1.33	(0.14)	0.001	*	0.135

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

Paroxetine - Protocol 329
Table 13.36
Baseline Mean and Mean Change from Baseline at Weekly Intervals-- K-SADS-L Depressed Mood Item
Acute 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	83	4.57	(0.09)	87	4.29	(0.09)	85	4.63	(0.09)	0.640		0.006	*
Week 2	76	-1.11	(0.16)	81	-0.76	(0.15)	76	-1.17	(0.16)	0.756		0.045	*
Week 4	70	-1.93	(0.17)	59	-1.54	(0.19)	66	-1.53	(0.17)	0.083		0.955	
Week 6	67	-2.22	(0.21)	49	-2.05	(0.24)	54	-1.75	(0.23)	0.094		0.328	
Week 8	66	-2.35	(0.20)	55	-2.05	(0.22)	65	-1.93	(0.20)	0.113		0.661	
Endpoint	83	-2.20	(0.18)	87	-1.77	(0.18)	85	-1.73	(0.18)	0.049	*	0.868	

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

12 Data Source Tables: Safety Results

PAROXETINE - PROTOCOL 329

Table 14.1

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

Total Duration of Exposure (Wks)	PAROXETINE N = 93 Dose (mg) 20 n	%	30 n	%	40 n	%	50 n	%	100 n	%	IMIPRAMINE N = 95 Dose (mg) 150 n	%	200 n	%	250 n	%	300 n	%	PLACEBO N = 87 Dose (mg) 0 n	%
1	7	7.5	24	25.8	7	7.5	91	95.8	92	96.8	79	83.2	24	25.3	23	24.2	8	8.4	2	2.3
2	6	6.5	12	12.9	6	6.5	4	4.2	0	0.0	2	2.1	14	14.7	4	4.2	2	2.1	6	6.9
3	5	5.4	6	6.5	15	16.1	0	0.0	0	0.0	0	0.0	6	6.3	10	10.5	10	10.5	3	3.4
4	30	32.3	8	8.6	0	0.0	0	0.0	0	0.0	0	0.0	9	9.5	1	1.1	0	0.0	2	2.3
5	12	12.9	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0	23	24.2	0	0.0	0	0.0	6	6.9
> 5	33	35.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	68	78.2

PAROXETINE - PROTOCOL 329

Table 14.1

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

	PAROXETINE N = 93						IMIPRAMINE N = 95						PLACEBO N = 87					
	n	mean	sem	median	min	max	n	mean	sem	median	min	max	n	mean	sem	median	min	max
Days of Total Exposure	93	49.2	1.92	56	1	73	95	48.8	1.94	56	8	77	87	54.9	1.88	58	9	79

Table 14.2.1

Summary of Treatment-Emergent Adverse Experiences during Acute 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 :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	86	92.5%	90	94.7%	69	79.3%	245	89.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Body as a Whole	50	53.8	53	55.8	52	59.8	155	56.4
ABDOMINAL PAIN	10	10.8	7	7.4	10	11.5	27	9.8
ABNORMAL LABORATORY VALUE	0	0.0	1	1.1	0	0.0	1	0.4
ALLERGIC REACTION	2	2.2	1	1.1	3	3.4	6	2.2
ASTHENIA	10	10.8	7	7.4	10	11.5	27	9.8
BACK PAIN	4	4.3	2	2.1	10	11.5	16	5.8
CHEST PAIN	2	2.2	5	5.3	2	2.3	9	3.3
CHILLS	1	1.1	3	3.2	0	0.0	4	1.5
FEVER	0	0.0	2	2.1	4	4.6	6	2.2
HEADACHE	32	34.4	38	40.0	34	39.1	104	37.8
INFECTION	10	10.8	5	5.3	9	10.3	24	8.7
PAIN	0	0.0	0	0.0	3	3.4	3	1.1
TRAUMA	2	2.2	3	3.2	6	6.9	11	4.0
Cardiovascular System	7	7.5	41	43.2	11	12.6	59	21.5
ARRHYTHMIA	0	0.0	1	1.1	1	1.1	2	0.7
AV BLOCK	1	1.1	2	2.1	2	2.3	5	1.8
BRADYCARDIA	0	0.0	0	0.0	1	1.1	1	0.4
BUNDLE BRANCH BLOCK	0	0.0	1	1.1	1	1.1	2	0.7
ELECTROCARDIOGRAM ABNORMAL	0	0.0	3	3.2	0	0.0	3	1.1
EXTRASYSTOLES	0	0.0	2	2.1	0	0.0	2	0.7
HEART MALFORMATION	0	0.0	1	1.1	1	1.1	2	0.7
HYPERTENSION	0	0.0	2	2.1	0	0.0	2	0.7
MIGRAINE	1	1.1	1	1.1	0	0.0	2	0.7
NODAL ARRHYTHMIA	0	0.0	0	0.0	1	1.1	1	0.4
PALPITATION	1	1.1	3	3.2	0	0.0	4	1.5
POSTURAL HYPOTENSION	1	1.1	13	13.7	1	1.1	15	5.5
QT INTERVAL PROLONGED	0	0.0	3	3.2	0	0.0	3	1.1
SUPRAVENTRICULAR EXTRASYSTOLES	0	0.0	0	0.0	1	1.1	1	0.4
SYNCOPE	1	1.1	4	4.2	1	1.1	6	2.2
TACHYCARDIA	2	2.2	18	18.9	1	1.1	21	7.6
VASODILATATION	0	0.0	6	6.3	2	2.3	8	2.9
Digestive System	50	53.8	64	67.4	41	47.1	155	56.4
CONSTIPATION	5	5.4	9	9.5	4	4.6	18	6.5
DECREASED APPETITE	7	7.5	2	2.1	4	4.6	13	4.7
DIARRHEA	7	7.5	3	3.2	7	8.0	17	6.2
DRY MOUTH	19	20.4	43	45.3	12	13.8	74	26.9
DYSPEPSIA	6	6.5	9	9.5	4	4.6	19	6.9
DYSPHAGIA	0	0.0	3	3.2	0	0.0	3	1.1

Table 14.2.1

Summary of Treatment-Emergent Adverse Experiences during Acute 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 :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	86	92.5%	90	94.7%	69	79.3%	245	89.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
ESOPHAGITIS	1	1.1	1	1.1	0	0.0	2	0.7
GASTRITIS	0	0.0	1	1.1	0	0.0	1	0.4
GASTROENTERITIS	0	0.0	1	1.1	0	0.0	1	0.4
GASTROINTESTINAL DISORDER	2	2.2	1	1.1	1	1.1	4	1.5
INCREASED APPETITE	3	3.2	1	1.1	1	1.1	5	1.8
NAUSEA	22	23.7	23	24.2	17	19.5	62	22.5
TOOTH DISORDER	5	5.4	2	2.1	2	2.3	9	3.3
ULCERATIVE STOMATITIS	0	0.0	1	1.1	1	1.1	2	0.7
VOMITING	3	3.2	8	8.4	6	6.9	17	6.2
Hemic and Lymphatic System	2	2.2	2	2.1	4	4.6	8	2.9
ANEMIA	1	1.1	0	0.0	0	0.0	1	0.4
EOSINOPHILIA	0	0.0	1	1.1	1	1.1	2	0.7
LEUKOPENIA	0	0.0	1	1.1	0	0.0	1	0.4
LYMPHADENOPATHY	0	0.0	0	0.0	1	1.1	1	0.4
THROMBOCYTHEMIA	1	1.1	0	0.0	1	1.1	2	0.7
WBC ABNORMALITY	0	0.0	0	0.0	1	1.1	1	0.4
Metabolic and Nutritional Disorders	3	3.2	4	4.2	6	6.9	13	4.7
HYPERGLYCEMIA	0	0.0	1	1.1	1	1.1	2	0.7
THIRST	0	0.0	2	2.1	3	3.4	5	1.8
WEIGHT GAIN	1	1.1	0	0.0	0	0.0	1	0.4
WEIGHT LOSS	2	2.2	1	1.1	2	2.3	5	1.8
Musculoskeletal System	3	3.2	1	1.1	6	6.9	10	3.6
ARTHRALGIA	1	1.1	1	1.1	4	4.6	6	2.2
MYALGIA	3	3.2	0	0.0	2	2.3	5	1.8
MYASTHENIA	1	1.1	0	0.0	0	0.0	1	0.4
Nervous System	56	60.2	70	73.7	29	33.3	155	56.4
ABNORMAL DREAMS	2	2.2	4	4.2	2	2.3	8	2.9
AGITATION	2	2.2	2	2.1	0	0.0	4	1.5
AMNESIA	0	0.0	1	1.1	0	0.0	1	0.4
ANXIETY	2	2.2	0	0.0	2	2.3	4	1.5
CONCENTRATION IMPAIRED	1	1.1	1	1.1	0	0.0	2	0.7
DEPERSONALIZATION	0	0.0	1	1.1	1	1.1	2	0.7
DEPRESSION	4	4.3	1	1.1	2	2.3	7	2.5
DIZZINESS	22	23.7	45	47.4	16	18.4	83	30.2
DRUG DEPENDENCE	0	0.0	1	1.1	0	0.0	1	0.4
EMOTIONAL LABILITY	6	6.5	3	3.2	1	1.1	10	3.6

Table 14.2.1

Summary of Treatment-Emergent Adverse Experiences during Acute 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 :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	86	92.5%	90	94.7%	69	79.3%	245	89.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
EUPHORIA	1	1.1	1	1.1	1	1.1	3	1.1
HALLUCINATIONS	1	1.1	1	1.1	0	0.0	2	0.7
HOSTILITY	7	7.5	3	3.2	0	0.0	10	3.6
HYPERKINESIA	1	1.1	2	2.1	1	1.1	4	1.5
HYPERTONIA	1	1.1	1	1.1	1	1.1	3	1.1
HYPESTHESIA	0	0.0	1	1.1	0	0.0	1	0.4
INSOMNIA	14	15.1	13	13.7	4	4.6	31	11.3
MANIC REACTION	2	2.2	0	0.0	1	1.1	3	1.1
MYOCLONUS	2	2.2	1	1.1	0	0.0	3	1.1
NERVOUSNESS	8	8.6	6	6.3	5	5.7	19	6.9
PARANOID REACTION	1	1.1	0	0.0	0	0.0	1	0.4
PARESTHESIA	1	1.1	0	0.0	0	0.0	1	0.4
PERSONALITY DISORDER	1	1.1	0	0.0	0	0.0	1	0.4
SOMNOLENCE	16	17.2	13	13.7	3	3.4	32	11.6
THINKING ABNORMAL	0	0.0	2	2.1	0	0.0	2	0.7
TREMOR	10	10.8	14	14.7	2	2.3	26	9.5
WITHDRAWAL SYNDROME	1	1.1	0	0.0	0	0.0	1	0.4
Respiratory System	29	31.2	26	27.4	29	33.3	84	30.5
ASTHMA	1	1.1	0	0.0	1	1.1	2	0.7
BRONCHITIS	2	2.2	0	0.0	4	4.6	6	2.2
COUGH INCREASED	5	5.4	3	3.2	6	6.9	14	5.1
DYSPNEA	2	2.2	4	4.2	1	1.1	7	2.5
EPISTAXIS	0	0.0	1	1.1	0	0.0	1	0.4
LARYNX DISORDER	1	1.1	0	0.0	0	0.0	1	0.4
PHARYNGITIS	5	5.4	12	12.6	8	9.2	25	9.1
RESPIRATORY DISORDER	10	10.8	7	7.4	11	12.6	28	10.2
RHINITIS	7	7.5	3	3.2	5	5.7	15	5.5
SINUSITIS	6	6.5	2	2.1	7	8.0	15	5.5
Skin and Appendages	12	12.9	14	14.7	8	9.2	34	12.4
ACNE	3	3.2	2	2.1	1	1.1	6	2.2
CONTACT DERMATITIS	0	0.0	1	1.1	1	1.1	2	0.7
FUNGAL DERMATITIS	1	1.1	1	1.1	0	0.0	2	0.7
HERPES ZOSTER	0	0.0	0	0.0	1	1.1	1	0.4
MACULOPAPULAR RASH	0	0.0	2	2.1	1	1.1	3	1.1
PHOTOSENSITIVITY	1	1.1	0	0.0	0	0.0	1	0.4
PRURITUS	0	0.0	1	1.1	0	0.0	1	0.4
RASH	4	4.3	3	3.2	3	3.4	10	3.6
SKIN DISORDER	1	1.1	0	0.0	0	0.0	1	0.4

Table 14.2.1

Summary of Treatment-Emergent Adverse Experiences during Acute 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 :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	86	92.5%	90	94.7%	69	79.3%	245	89.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
SWEATING	1	1.1	6	6.3	1	1.1	8	2.9
URTICARIA	1	1.1	1	1.1	0	0.0	2	0.7
Special Senses	7	7.5	14	14.7	3	3.4	24	8.7
ABNORMAL VISION	1	1.1	7	7.4	2	2.3	10	3.6
CONJUNCTIVITIS	3	3.2	0	0.0	0	0.0	3	1.1
EAR PAIN	1	1.1	2	2.1	0	0.0	3	1.1
EYE DISORDER	0	0.0	0	0.0	1	1.1	1	0.4
KERATOCONJUNCTIVITIS	0	0.0	1	1.1	0	0.0	1	0.4
MYDRIASIS	0	0.0	1	1.1	0	0.0	1	0.4
OTITIS MEDIA	2	2.2	0	0.0	0	0.0	2	0.7
PHOTOPHOBIA	0	0.0	1	1.1	0	0.0	1	0.4
TASTE PERVERSION	0	0.0	3	3.2	0	0.0	3	1.1
TINNITUS	0	0.0	2	2.1	0	0.0	2	0.7
Urogenital System	4	4.3	9	9.5	2	2.3	15	5.5
ALBUMINURIA	0	0.0	0	0.0	2	2.3	2	0.7
CYSTITIS	1	1.1	1	1.1	0	0.0	2	0.7
NOCTURIA	0	0.0	1	1.1	0	0.0	1	0.4
POLYURIA	0	0.0	1	1.1	0	0.0	1	0.4
PYURIA	0	0.0	0	0.0	1	1.1	1	0.4
URINARY FREQUENCY	0	0.0	1	1.1	0	0.0	1	0.4
URINARY RETENTION	0	0.0	3	3.2	0	0.0	3	1.1
URINARY TRACT INFECTION	1	1.1	0	0.0	0	0.0	1	0.4
URINATION IMPAIRED	0	0.0	3	3.2	0	0.0	3	1.1
URINE ABNORMALITY	2	2.2	0	0.0	0	0.0	2	0.7

PAROXETINE - PROTOCOL 329

Table 14.2.3

Summary of Treatment-Emergent Adverse Experiences during Acute 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	:	58	100.0%	56	100.0%	57	100.0%	171	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	4	6.9%	7	12.5%	4	7.0%	15	8.8%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%	N	%
Urogenital System		4	6.9	7	12.5	4	7.0	15	8.8
AMENORRHEA		1	1.7	0	0.0	0	0.0	1	0.6
BREAST ENLARGEMENT		1	1.7	0	0.0	0	0.0	1	0.6
DYSMENORRHEA		2	3.4	5	8.9	4	7.0	11	6.4
FEMALE GENITAL DISORDERS		1	1.7	0	0.0	0	0.0	1	0.6
UNINTENDED PREGNANCY		0	0.0	1	1.8	0	0.0	1	0.6
VAGINAL MONILIASIS		0	0.0	1	1.8	0	0.0	1	0.6

PAROXETINE - PROTOCOL 329

Table 14.3.1

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

TREATMENT GROUP: PAROXETINE PATIENTS RECEIVING STUDY MEDICATION: 93

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	74	79.6%	51	54.8%	27	29.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	26	28.0	25	26.9	11	11.8
ABDOMINAL PAIN	4	4.3	5	5.4	1	1.1
ALLERGIC REACTION	2	2.2	0	0.0	0	0.0
ASTHENIA	4	4.3	4	4.3	2	2.2
BACK PAIN	1	1.1	3	3.2	0	0.0
CHEST PAIN	0	0.0	1	1.1	1	1.1
CHILLS	1	1.1	0	0.0	0	0.0
HEADACHE	11	11.8	18	19.4	3	3.2
INFECTION	3	3.2	3	3.2	4	4.3
TRAUMA	1	1.1	0	0.0	1	1.1
Cardiovascular System	3	3.2	4	4.3	0	0.0
AV BLOCK	0	0.0	1	1.1	0	0.0
MIGRAINE	0	0.0	1	1.1	0	0.0
PALPITATION	0	0.0	1	1.1	0	0.0
POSTURAL HYPOTENSION	1	1.1	0	0.0	0	0.0
SYNCOPE	0	0.0	1	1.1	0	0.0
TACHYCARDIA	2	2.2	0	0.0	0	0.0
Digestive System	36	38.7	17	18.3	4	4.3
CONSTIPATION	2	2.2	3	3.2	0	0.0
DECREASED APPETITE	6	6.5	1	1.1	0	0.0
DIARRHEA	3	3.2	2	2.2	2	2.2
DRY MOUTH	17	18.3	2	2.2	0	0.0
DYSPEPSIA	5	5.4	1	1.1	0	0.0
ESOPHAGITIS	0	0.0	1	1.1	0	0.0
GASTROINTESTINAL DISORDER	1	1.1	1	1.1	0	0.0
INCREASED APPETITE	2	2.2	1	1.1	0	0.0
NAUSEA	15	16.1	5	5.4	2	2.2
TOOTH DISORDER	1	1.1	3	3.2	1	1.1
VOMITING	2	2.2	0	0.0	1	1.1
Hemic and Lymphatic System	2	2.2	0	0.0	0	0.0
ANEMIA	1	1.1	0	0.0	0	0.0
THROMBOCYTHEMIA	1	1.1	0	0.0	0	0.0
Metabolic and Nutritional Disorders	2	2.2	1	1.1	0	0.0
WEIGHT GAIN	0	0.0	1	1.1	0	0.0
WEIGHT LOSS	2	2.2	0	0.0	0	0.0
Musculoskeletal System	0	0.0	3	3.2	0	0.0

Table 14.3.1

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

TREATMENT GROUP: PAROXETINE PATIENTS RECEIVING STUDY MEDICATION: 93

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	74	79.6%	51	54.8%	27	29.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
ARTHRALGIA	0	0.0	1	1.1	0	0.0
MYALGIA	0	0.0	3	3.2	0	0.0
MYASTHENIA	0	0.0	1	1.1	0	0.0
Nervous System	38	40.9	23	24.7	17	18.3
ABNORMAL DREAMS	1	1.1	1	1.1	0	0.0
AGITATION	0	0.0	1	1.1	1	1.1
ANXIETY	1	1.1	0	0.0	1	1.1
CONCENTRATION IMPAIRED	1	1.1	0	0.0	0	0.0
DEPRESSION	0	0.0	1	1.1	3	3.2
DIZZINESS	15	16.1	7	7.5	0	0.0
EMOTIONAL LABILITY	1	1.1	1	1.1	4	4.3
EUPHORIA	0	0.0	0	0.0	1	1.1
HALLUCINATIONS	0	0.0	0	0.0	1	1.1
HOSTILITY	3	3.2	1	1.1	3	3.2
HYPERKINESIA	1	1.1	0	0.0	0	0.0
HYPERTONIA	1	1.1	0	0.0	0	0.0
INSOMNIA	7	7.5	5	5.4	2	2.2
MANIC REACTION	0	0.0	1	1.1	1	1.1
MYOCLONUS	1	1.1	0	0.0	1	1.1
NERVOUSNESS	6	6.5	2	2.2	0	0.0
PARANOID REACTION	0	0.0	1	1.1	0	0.0
PARESTHESIA	1	1.1	0	0.0	0	0.0
PERSONALITY DISORDER	0	0.0	0	0.0	1	1.1
SOMNOLENCE	7	7.5	6	6.5	3	3.2
TREMOR	7	7.5	2	2.2	1	1.1
WITHDRAWAL SYNDROME	0	0.0	0	0.0	1	1.1
Respiratory System	15	16.1	14	15.1	2	2.2
ASTHMA	0	0.0	0	0.0	1	1.1
BRONCHITIS	0	0.0	1	1.1	1	1.1
COUGH INCREASED	2	2.2	3	3.2	0	0.0
DYSPNEA	2	2.2	0	0.0	0	0.0
LARYNX DISORDER	1	1.1	0	0.0	0	0.0
PHARYNGITIS	1	1.1	4	4.3	0	0.0
RESPIRATORY DISORDER	5	5.4	5	5.4	0	0.0
RHINITIS	3	3.2	4	4.3	0	0.0
SINUSITIS	2	2.2	4	4.3	0	0.0
Skin and Appendages	8	8.6	4	4.3	0	0.0
ACNE	2	2.2	1	1.1	0	0.0

Table 14.3.1

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

TREATMENT GROUP: PAROXETINE PATIENTS RECEIVING STUDY MEDICATION: 93

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	74	79.6%	51	54.8%	27	29.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
FUNGAL DERMATITIS	1	1.1	0	0.0	0	0.0
PHOTOSENSITIVITY	1	1.1	0	0.0	0	0.0
RASH	2	2.2	2	2.2	0	0.0
SKIN DISORDER	1	1.1	0	0.0	0	0.0
SWEATING	0	0.0	1	1.1	0	0.0
URTICARIA	1	1.1	0	0.0	0	0.0
Special Senses	3	3.2	3	3.2	1	1.1
ABNORMAL VISION	1	1.1	0	0.0	0	0.0
CONJUNCTIVITIS	2	2.2	1	1.1	0	0.0
EAR PAIN	0	0.0	1	1.1	0	0.0
OTITIS MEDIA	0	0.0	1	1.1	1	1.1
Urogenital System	4	4.3	4	4.3	1	1.1
AMENORRHEA	0	0.0	1	1.1	0	0.0
BREAST ENLARGEMENT	1	1.1	0	0.0	0	0.0
CYSTITIS	1	1.1	0	0.0	0	0.0
DYSMENORRHEA	0	0.0	2	2.2	0	0.0
FEMALE GENITAL DISORDERS	0	0.0	0	0.0	1	1.1
URINARY TRACT INFECTION	1	1.1	0	0.0	0	0.0
URINE ABNORMALITY	1	1.1	1	1.1	0	0.0

Table 14.3.1

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

TREATMENT GROUP: IMIPRAMINE PATIENTS RECEIVING STUDY MEDICATION: 95

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	78	82.1%	66	69.5%	24	25.3%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	20	21.1	28	29.5	13	13.7
ABDOMINAL PAIN	2	2.1	5	5.3	0	0.0
ABNORMAL LABORATORY VALUE	1	1.1	0	0.0	0	0.0
ALLERGIC REACTION	1	1.1	0	0.0	0	0.0
ASTHENIA	3	3.2	3	3.2	1	1.1
BACK PAIN	1	1.1	1	1.1	0	0.0
CHEST PAIN	1	1.1	3	3.2	1	1.1
CHILLS	0	0.0	3	3.2	0	0.0
FEVER	0	0.0	2	2.1	0	0.0
HEADACHE	12	12.6	18	18.9	8	8.4
INFECTION	3	3.2	0	0.0	2	2.1
TRAUMA	1	1.1	1	1.1	1	1.1
Cardiovascular System	22	23.2	21	22.1	2	2.1
ARRHYTHMIA	0	0.0	1	1.1	0	0.0
AV BLOCK	1	1.1	1	1.1	0	0.0
BUNDLE BRANCH BLOCK	1	1.1	0	0.0	0	0.0
ELECTROCARDIOGRAM ABNORMAL	2	2.1	1	1.1	0	0.0
EXTRASYSTOLES	1	1.1	1	1.1	0	0.0
HEART MALFORMATION	1	1.1	0	0.0	0	0.0
HYPERTENSION	1	1.1	1	1.1	0	0.0
MIGRAINE	0	0.0	0	0.0	1	1.1
PALPITATION	1	1.1	2	2.1	0	0.0
POSTURAL HYPOTENSION	7	7.4	6	6.3	0	0.0
QT INTERVAL PROLONGED	1	1.1	2	2.1	0	0.0
SYNCOPE	3	3.2	1	1.1	0	0.0
TACHYCARDIA	8	8.4	9	9.5	1	1.1
VASODILATATION	2	2.1	4	4.2	0	0.0
Digestive System	39	41.1	31	32.6	8	8.4
CONSTIPATION	5	5.3	2	2.1	2	2.1
DECREASED APPETITE	1	1.1	1	1.1	0	0.0
DIARRHEA	1	1.1	1	1.1	1	1.1
DRY MOUTH	25	26.3	17	17.9	1	1.1
DYSPEPSIA	3	3.2	6	6.3	0	0.0
DYSPHAGIA	2	2.1	1	1.1	0	0.0
ESOPHAGITIS	1	1.1	0	0.0	0	0.0
GASTRITIS	0	0.0	1	1.1	0	0.0
GASTROENTERITIS	0	0.0	0	0.0	1	1.1
GASTROINTESTINAL DISORDER	0	0.0	1	1.1	0	0.0
INCREASED APPETITE	0	0.0	1	1.1	0	0.0

Table 14.3.1

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

TREATMENT GROUP: IMIPRAMINE PATIENTS RECEIVING STUDY MEDICATION: 95

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	78	82.1%	66	69.5%	24	25.3%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
NAUSEA	10	10.5	11	11.6	2	2.1
TOOTH DISORDER	0	0.0	2	2.1	0	0.0
ULCERATIVE STOMATITIS	0	0.0	0	0.0	1	1.1
VOMITING	2	2.1	3	3.2	3	3.2
Hemic and Lymphatic System	0	0.0	2	2.1	0	0.0
EOSINOPHILIA	0	0.0	1	1.1	0	0.0
LEUKOPENIA	0	0.0	1	1.1	0	0.0
Metabolic and Nutritional Disorders	2	2.1	1	1.1	1	1.1
HYPERGLYCEMIA	0	0.0	0	0.0	1	1.1
THIRST	1	1.1	1	1.1	0	0.0
WEIGHT LOSS	1	1.1	0	0.0	0	0.0
Musculoskeletal System	1	1.1	0	0.0	0	0.0
ARTHRALGIA	1	1.1	0	0.0	0	0.0
Nervous System	47	49.5	35	36.8	5	5.3
ABNORMAL DREAMS	1	1.1	3	3.2	0	0.0
AGITATION	1	1.1	1	1.1	0	0.0
AMNESIA	1	1.1	0	0.0	0	0.0
CONCENTRATION IMPAIRED	0	0.0	1	1.1	0	0.0
DEPERSONALIZATION	1	1.1	0	0.0	0	0.0
DEPRESSION	0	0.0	1	1.1	0	0.0
DIZZINESS	27	28.4	17	17.9	1	1.1
DRUG DEPENDENCE	1	1.1	0	0.0	0	0.0
EMOTIONAL LABILITY	0	0.0	3	3.2	0	0.0
EUPHORIA	1	1.1	0	0.0	0	0.0
HALLUCINATIONS	0	0.0	0	0.0	1	1.1
HOSTILITY	0	0.0	1	1.1	2	2.1
HYPERKINESIA	2	2.1	0	0.0	0	0.0
HYPERTONIA	1	1.1	0	0.0	0	0.0
HYPESTHESIA	1	1.1	0	0.0	0	0.0
INSOMNIA	9	9.5	4	4.2	0	0.0
MYOCLONUS	1	1.1	0	0.0	0	0.0
NERVOUSNESS	2	2.1	3	3.2	1	1.1
SOMNOLENCE	7	7.4	6	6.3	0	0.0
THINKING ABNORMAL	2	2.1	0	0.0	0	0.0
TREMOR	6	6.3	6	6.3	2	2.1
Respiratory System	20	21.1	7	7.4	1	1.1

Table 14.3.1

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

TREATMENT GROUP: IMIPRAMINE PATIENTS RECEIVING STUDY MEDICATION: 95

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	78	82.1%	66	69.5%	24	25.3%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
COUGH INCREASED	2	2.1	1	1.1	0	0.0
DYSPNEA	3	3.2	0	0.0	1	1.1
EPISTAXIS	1	1.1	0	0.0	0	0.0
PHARYNGITIS	7	7.4	5	5.3	0	0.0
RESPIRATORY DISORDER	5	5.3	2	2.1	0	0.0
RHINITIS	2	2.1	1	1.1	0	0.0
SINUSITIS	2	2.1	0	0.0	0	0.0
Skin and Appendages	7	7.4	7	7.4	1	1.1
ACNE	1	1.1	1	1.1	0	0.0
CONTACT DERMATITIS	0	0.0	1	1.1	0	0.0
FUNGAL DERMATITIS	1	1.1	0	0.0	0	0.0
MACULOPAPULAR RASH	0	0.0	1	1.1	1	1.1
PRURITUS	1	1.1	0	0.0	0	0.0
RASH	1	1.1	2	2.1	0	0.0
SWEATING	4	4.2	2	2.1	0	0.0
URTICARIA	0	0.0	1	1.1	0	0.0
Special Senses	12	12.6	1	1.1	1	1.1
ABNORMAL VISION	6	6.3	0	0.0	1	1.1
EAR PAIN	2	2.1	0	0.0	0	0.0
KERATOCONJUNCTIVITIS	1	1.1	0	0.0	0	0.0
MYDRIASIS	0	0.0	1	1.1	0	0.0
PHOTOPHOBIA	1	1.1	0	0.0	0	0.0
TASTE PERVERSION	3	3.2	0	0.0	0	0.0
TINNITUS	2	2.1	0	0.0	0	0.0
Urogenital System	8	8.4	4	4.2	3	3.2
CYSTITIS	1	1.1	0	0.0	0	0.0
DYSMENORRHEA	2	2.1	2	2.1	1	1.1
NOCTURIA	1	1.1	0	0.0	0	0.0
POLYURIA	1	1.1	0	0.0	0	0.0
UNINTENDED PREGNANCY	0	0.0	0	0.0	1	1.1
URINARY FREQUENCY	1	1.1	0	0.0	0	0.0
URINARY RETENTION	0	0.0	2	2.1	1	1.1
URINATION IMPAIRED	2	2.1	1	1.1	0	0.0

Table 14.3.1

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

TREATMENT GROUP: PLACEBO PATIENTS RECEIVING STUDY MEDICATION: 87

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	62	71.3%	45	51.7%	15	17.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	32	36.8	30	34.5	9	10.3
ABDOMINAL PAIN	6	6.9	4	4.6	0	0.0
ALLERGIC REACTION	0	0.0	2	2.3	1	1.1
ASTHENIA	7	8.0	2	2.3	1	1.1
BACK PAIN	6	6.9	4	4.6	0	0.0
CHEST PAIN	2	2.3	0	0.0	0	0.0
FEVER	2	2.3	2	2.3	0	0.0
HEADACHE	16	18.4	14	16.1	4	4.6
INFECTION	4	4.6	2	2.3	3	3.4
PAIN	3	3.4	0	0.0	0	0.0
TRAUMA	0	0.0	6	6.9	0	0.0
Cardiovascular System	10	11.5	1	1.1	0	0.0
ARRHYTHMIA	1	1.1	0	0.0	0	0.0
AV BLOCK	2	2.3	0	0.0	0	0.0
BRADYCARDIA	1	1.1	0	0.0	0	0.0
BUNDLE BRANCH BLOCK	1	1.1	0	0.0	0	0.0
HEART MALFORMATION	1	1.1	0	0.0	0	0.0
NODAL ARRHYTHMIA	1	1.1	0	0.0	0	0.0
POSTURAL HYPOTENSION	1	1.1	0	0.0	0	0.0
SUPRAVENTRICULAR EXTRASYSTOLES	1	1.1	0	0.0	0	0.0
SYNCOPE	1	1.1	0	0.0	0	0.0
TACHYCARDIA	0	0.0	1	1.1	0	0.0
VASODILATATION	2	2.3	0	0.0	0	0.0
Digestive System	36	41.4	8	9.2	2	2.3
CONSTIPATION	4	4.6	0	0.0	0	0.0
DECREASED APPETITE	4	4.6	0	0.0	0	0.0
DIARRHEA	5	5.7	2	2.3	0	0.0
DRY MOUTH	11	12.6	0	0.0	1	1.1
DYSPEPSIA	3	3.4	1	1.1	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	0	0.0	1	1.1
INCREASED APPETITE	0	0.0	1	1.1	0	0.0
NAUSEA	13	14.9	4	4.6	0	0.0
TOOTH DISORDER	1	1.1	1	1.1	0	0.0
ULCERATIVE STOMATITIS	1	1.1	0	0.0	0	0.0
VOMITING	5	5.7	1	1.1	0	0.0
Hemic and Lymphatic System	4	4.6	0	0.0	0	0.0
EOSINOPHILIA	1	1.1	0	0.0	0	0.0
LYMPHADENOPATHY	1	1.1	0	0.0	0	0.0

Table 14.3.1

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

TREATMENT GROUP: PLACEBO PATIENTS RECEIVING STUDY MEDICATION: 87

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	62	71.3%	45	51.7%	15	17.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
THROMBOCYTHEMIA	1	1.1	0	0.0	0	0.0
WBC ABNORMALITY	1	1.1	0	0.0	0	0.0
Metabolic and Nutritional Disorders	5	5.7	0	0.0	1	1.1
HYPERGLYCEMIA	1	1.1	0	0.0	0	0.0
THIRST	3	3.4	0	0.0	0	0.0
WEIGHT LOSS	1	1.1	0	0.0	1	1.1
Musculoskeletal System	4	4.6	2	2.3	0	0.0
ARTHRALGIA	2	2.3	2	2.3	0	0.0
MYALGIA	2	2.3	0	0.0	0	0.0
Nervous System	21	24.1	11	12.6	4	4.6
ABNORMAL DREAMS	1	1.1	1	1.1	0	0.0
ANXIETY	0	0.0	1	1.1	1	1.1
DEPERSONALIZATION	1	1.1	0	0.0	0	0.0
DEPRESSION	0	0.0	0	0.0	2	2.3
DIZZINESS	12	13.8	4	4.6	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0	1	1.1
EUPHORIA	0	0.0	1	1.1	0	0.0
HYPERKINESIA	1	1.1	0	0.0	0	0.0
HYPERTONIA	0	0.0	1	1.1	0	0.0
INSOMNIA	2	2.3	1	1.1	1	1.1
MANIC REACTION	0	0.0	0	0.0	1	1.1
NERVOUSNESS	4	4.6	1	1.1	0	0.0
SOMNOLENCE	1	1.1	2	2.3	0	0.0
TREMOR	2	2.3	0	0.0	0	0.0
Respiratory System	16	18.4	13	14.9	4	4.6
ASTHMA	0	0.0	1	1.1	0	0.0
BRONCHITIS	1	1.1	3	3.4	0	0.0
COUGH INCREASED	3	3.4	3	3.4	0	0.0
DYSPNEA	1	1.1	0	0.0	0	0.0
PHARYNGITIS	4	4.6	3	3.4	1	1.1
RESPIRATORY DISORDER	8	9.2	2	2.3	1	1.1
RHINITIS	4	4.6	0	0.0	1	1.1
SINUSITIS	1	1.1	3	3.4	3	3.4
Skin and Appendages	5	5.7	3	3.4	0	0.0
ACNE	1	1.1	0	0.0	0	0.0
CONTACT DERMATITIS	1	1.1	0	0.0	0	0.0

Table 14.3.1

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

TREATMENT GROUP: PLACEBO PATIENTS RECEIVING STUDY MEDICATION: 87

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	62	71.3%	45	51.7%	15	17.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
HERPES ZOSTER	0	0.0	1	1.1	0	0.0
MACULOPAPULAR RASH	0	0.0	1	1.1	0	0.0
RASH	2	2.3	1	1.1	0	0.0
SWEATING	1	1.1	0	0.0	0	0.0
Special Senses	1	1.1	2	2.3	0	0.0
ABNORMAL VISION	0	0.0	2	2.3	0	0.0
EYE DISORDER	1	1.1	0	0.0	0	0.0
Urogenital System	2	2.3	3	3.4	1	1.1
ALBUMINURIA	1	1.1	1	1.1	0	0.0
DYSMENORRHEA	1	1.1	2	2.3	1	1.1
PYURIA	0	0.0	1	1.1	0	0.0

PAROXETINE - 108566

Table 14.3.3

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

TREATMENT GROUP: PAROXETINE PATIENTS RECEIVING STUDY MEDICATION: 58

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	1	1.7%	3	5.2%	1	1.7%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Urogenital System	1	1.7	3	5.2	1	1.7
AMENORRHEA	0	0.0	1	1.7	0	0.0
BREAST ENLARGEMENT	1	1.7	0	0.0	0	0.0
DYSMENORRHEA	0	0.0	2	3.4	0	0.0
FEMALE GENITAL DISORDERS	0	0.0	0	0.0	1	1.7

Table 14.3.3

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

TREATMENT GROUP: IMIPRAMINE PATIENTS RECEIVING STUDY MEDICATION: 56

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	2	3.6%	3	5.4%	2	3.6%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Urogenital System	2	3.6	3	5.4	2	3.6
DYSMENORRHEA	2	3.6	2	3.6	1	1.8
UNINTENDED PREGNANCY	0	0.0	0	0.0	1	1.8
VAGINAL MONILIASIS	0	0.0	1	1.8	0	0.0

Table 14.3.3

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

TREATMENT GROUP: PLACEBO PATIENTS RECEIVING STUDY MEDICATION: 57

INTENSITY	MILD		MODERATE		SEVERE	
PATIENTS WITH ADVERSE EXPERIENCES :	1	1.8%	2	3.5%	1	1.8%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Urogenital System	1	1.8	2	3.5	1	1.8
DYSMENORRHEA	1	1.8	2	3.5	1	1.8

PAROXETINE - PROTOCOL 329

Table 14.4.1

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

TREATMENT GROUP: PAROXETINE

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	91	--	86	--	80	--	78	--	76	-
PATIENTS WITH ADVERSE EXPERIENCES :	56	61.5%	26	30.2%	27	33.8%	28	35.9%	13	17.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Body as a Whole	20	22.0	6	7.0	6	7.5	3	3.8	4	5.3
ABDOMINAL PAIN	5	5.5	1	1.2	1	1.3	0	0.0	1	1.3
ALLERGIC REACTION	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
ASTHENIA	5	5.5	0	0.0	1	1.3	0	0.0	0	0.0
BACK PAIN	1	1.1	0	0.0	2	2.5	0	0.0	0	0.0
CHEST PAIN	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
CHILLS	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
HEADACHE	14	15.4	3	3.5	3	3.8	0	0.0	2	2.6
INFECTION	1	1.1	1	1.2	0	0.0	1	1.3	1	1.3
TRAUMA	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0
Cardiovascular System	1	1.1	1	1.2	1	1.3	1	1.3	0	0.0
AV BLOCK	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0
MIGRAINE	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
PALPITATION	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
POSTURAL HYPOTENSION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
SYNCOPE	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
TACHYCARDIA	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
Digestive System	33	36.3	6	7.0	9	11.3	7	9.0	2	2.6
NAUSEA	12	13.2	2	2.3	1	1.3	2	2.6	1	1.3
CONSTIPATION	1	1.1	1	1.2	2	2.5	0	0.0	0	0.0
DECREASED APPETITE	6	6.6	0	0.0	0	0.0	0	0.0	0	0.0
DIARRHEA	4	4.4	1	1.2	1	1.3	1	1.3	0	0.0
DRY MOUTH	12	13.2	4	4.7	0	0.0	1	1.3	0	0.0
DYSPEPSIA	2	2.2	0	0.0	1	1.3	1	1.3	1	1.3
ESOPHAGITIS	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
INCREASED APPETITE	2	2.2	0	0.0	1	1.3	0	0.0	0	0.0
TOOTH DISORDER	1	1.1	0	0.0	1	1.3	2	2.6	0	0.0
VOMITING	2	2.2	0	0.0	0	0.0	1	1.3	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	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
WEIGHT GAIN	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
WEIGHT LOSS	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
Musculoskeletal System	0	0.0	1	1.2	0	0.0	1	1.3	0	0.0

Table 14.4.1

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

TREATMENT GROUP: PAROXETINE

DAYS	DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION :	75	--	72	--	67	-
PATIENTS WITH ADVERSE EXPERIENCES :	19	25.3%	14	19.4%	17	25.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	11	14.7	2	2.8	9	13.4
ABDOMINAL PAIN	1	1.3	0	0.0	1	1.5
ALLERGIC REACTION	0	0.0	1	1.4	0	0.0
ASTHENIA	3	4.0	0	0.0	1	1.5
BACK PAIN	0	0.0	0	0.0	1	1.5
CHEST PAIN	1	1.3	0	0.0	0	0.0
CHILLS	0	0.0	0	0.0	0	0.0
HEADACHE	3	4.0	0	0.0	6	9.0
INFECTION	3	4.0	1	1.4	2	3.0
TRAUMA	0	0.0	0	0.0	1	1.5
Cardiovascular System	2	2.7	1	1.4	0	0.0
AV BLOCK	0	0.0	0	0.0	0	0.0
MIGRAINE	0	0.0	1	1.4	0	0.0
PALPITATION	0	0.0	0	0.0	0	0.0
POSTURAL HYPOTENSION	1	1.3	0	0.0	0	0.0
SYNCOPE	0	0.0	0	0.0	0	0.0
TACHYCARDIA	1	1.3	0	0.0	0	0.0
Digestive System	6	8.0	4	5.6	1	1.5
NAUSEA	3	4.0	1	1.4	0	0.0
CONSTIPATION	0	0.0	0	0.0	1	1.5
DECREASED APPETITE	0	0.0	1	1.4	0	0.0
DIARRHEA	0	0.0	0	0.0	0	0.0
DRY MOUTH	1	1.3	1	1.4	0	0.0
DYSPEPSIA	1	1.3	0	0.0	0	0.0
ESOPHAGITIS	0	0.0	0	0.0	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	1	1.4	0	0.0
INCREASED APPETITE	0	0.0	0	0.0	0	0.0
TOOTH DISORDER	1	1.3	0	0.0	0	0.0
VOMITING	0	0.0	0	0.0	0	0.0
Hemic and Lymphatic System	0	0.0	0	0.0	1	1.5
ANEMIA	0	0.0	0	0.0	1	1.5
Metabolic and Nutritional Disorders	1	1.3	0	0.0	1	1.5
WEIGHT GAIN	0	0.0	0	0.0	1	1.5
WEIGHT LOSS	1	1.3	0	0.0	0	0.0
Musculoskeletal System	0	0.0	1	1.4	1	1.5

Table 14.4.1

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

TREATMENT GROUP: PAROXETINE

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	91	--	86	--	80	--	78	--	76	-
PATIENTS WITH ADVERSE EXPERIENCES :	56	61.5%	26	30.2%	27	33.8%	28	35.9%	13	17.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
ARTHRALGIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
MYALGIA	0	0.0	1	1.2	0	0.0	1	1.3	0	0.0
MYASTHENIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Nervous System	29	31.9	8	9.3	9	11.3	14	17.9	6	7.9
PARESTHESIA	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
ABNORMAL DREAMS	0	0.0	1	1.2	1	1.3	0	0.0	0	0.0
AGITATION	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
ANXIETY	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
CONCENTRATION IMPAIRED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
DEPRESSION	0	0.0	1	1.2	0	0.0	0	0.0	1	1.3
DIZZINESS	12	13.2	1	1.2	2	2.5	2	2.6	0	0.0
EMOTIONAL LABILITY	0	0.0	2	2.3	0	0.0	1	1.3	1	1.3
EUPHORIA	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
HALLUCINATIONS	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0
HOSTILITY	0	0.0	2	2.3	0	0.0	3	3.8	0	0.0
HYPERKINESIA	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
HYPERTONIA	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
INSOMNIA	8	8.8	2	2.3	1	1.3	0	0.0	0	0.0
MANIC REACTION	1	1.1	0	0.0	0	0.0	0	0.0	1	1.3
MYOCLONUS	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
NERVOUSNESS	3	3.3	0	0.0	2	2.5	0	0.0	0	0.0
PARANOID REACTION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
PERSONALITY DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3
SOMNOLENCE	8	8.8	1	1.2	2	2.5	1	1.3	2	2.6
TREMOR	5	5.5	0	0.0	2	2.5	3	3.8	0	0.0
WITHDRAWAL SYNDROME	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Respiratory System	7	7.7	5	5.8	5	6.3	7	9.0	3	3.9
COUGH INCREASED	2	2.2	0	0.0	0	0.0	2	2.6	0	0.0
ASTHMA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
BRONCHITIS	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
DYSPNEA	0	0.0	0	0.0	2	2.5	0	0.0	0	0.0
LARYNX DISORDER	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
PHARYNGITIS	0	0.0	0	0.0	0	0.0	3	3.8	0	0.0
RESPIRATORY DISORDER	1	1.1	4	4.7	1	1.3	0	0.0	2	2.6
RHINITIS	2	2.2	0	0.0	1	1.3	1	1.3	1	1.3
SINUSITIS	3	3.3	1	1.2	0	0.0	1	1.3	0	0.0
Skin and Appendages	1	1.1	0	0.0	4	5.0	5	6.4	0	0.0

Table 14.4.1

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

TREATMENT GROUP: PAROXETINE

DAYS	DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION :	75	--	72	--	67	-
PATIENTS WITH ADVERSE EXPERIENCES :	19	25.3%	14	19.4%	17	25.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
ARTHRALGIA	0	0.0	1	1.4	0	0.0
MYALGIA	0	0.0	0	0.0	1	1.5
MYASTHENIA	0	0.0	0	0.0	1	1.5
Nervous System	5	6.7	5	6.9	6	9.0
PARESTHESIA	0	0.0	0	0.0	0	0.0
ABNORMAL DREAMS	0	0.0	0	0.0	0	0.0
AGITATION	0	0.0	0	0.0	1	1.5
ANXIETY	0	0.0	1	1.4	0	0.0
CONCENTRATION IMPAIRED	0	0.0	0	0.0	1	1.5
DEPRESSION	1	1.3	1	1.4	0	0.0
DIZZINESS	2	2.7	1	1.4	2	3.0
EMOTIONAL LABILITY	0	0.0	0	0.0	1	1.5
EUPHORIA	0	0.0	0	0.0	0	0.0
HALLUCINATIONS	0	0.0	0	0.0	0	0.0
HOSTILITY	0	0.0	0	0.0	1	1.5
HYPERKINESIA	0	0.0	0	0.0	0	0.0
HYPERTONIA	0	0.0	0	0.0	0	0.0
INSOMNIA	0	0.0	2	2.8	1	1.5
MANIC REACTION	0	0.0	0	0.0	0	0.0
MYOCLONUS	1	1.3	0	0.0	0	0.0
NERVOUSNESS	2	2.7	0	0.0	1	1.5
PARANOID REACTION	0	0.0	0	0.0	1	1.5
PERSONALITY DISORDER	0	0.0	0	0.0	0	0.0
SOMNOLENCE	1	1.3	1	1.4	0	0.0
TREMOR	0	0.0	0	0.0	0	0.0
WITHDRAWAL SYNDROME	0	0.0	0	0.0	1	1.5
Respiratory System	3	4.0	2	2.8	1	1.5
COUGH INCREASED	0	0.0	0	0.0	0	0.0
ASTHMA	1	1.3	0	0.0	0	0.0
BRONCHITIS	0	0.0	0	0.0	0	0.0
DYSPNEA	0	0.0	0	0.0	0	0.0
LARYNX DISORDER	0	0.0	0	0.0	0	0.0
PHARYNGITIS	0	0.0	1	1.4	1	1.5
RESPIRATORY DISORDER	1	1.3	1	1.4	0	0.0
RHINITIS	1	1.3	0	0.0	0	0.0
SINUSITIS	1	1.3	0	0.0	0	0.0
Skin and Appendages	0	0.0	0	0.0	2	3.0

Table 14.4.1

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

TREATMENT GROUP: PAROXETINE

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	91	--	86	--	80	--	78	--	76	-
PATIENTS WITH ADVERSE EXPERIENCES :	56	61.5%	26	30.2%	27	33.8%	28	35.9%	13	17.1%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
ACNE	1	1.1	0	0.0	0	0.0	2	2.6	0	0.0
FUNGAL DERMATITIS	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
PHOTOSENSITIVITY	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
RASH	0	0.0	0	0.0	1	1.3	1	1.3	0	0.0
SKIN DISORDER	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
SWEATING	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
URTICARIA	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
Special Senses	3	3.3	0	0.0	0	0.0	3	3.8	0	0.0
ABNORMAL VISION	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
CONJUNCTIVITIS	1	1.1	0	0.0	0	0.0	1	1.3	0	0.0
EAR PAIN	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
OTITIS MEDIA	1	1.1	0	0.0	0	0.0	1	1.3	0	0.0
Urogenital System	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
CYSTITIS	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
URINARY TRACT INFECTION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
URINE ABNORMALITY	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: PAROXETINE

DAYS		DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION	:	75	--	72	--	67	-
PATIENTS WITH ADVERSE EXPERIENCES	:	19	25.3%	14	19.4%	17	25.4%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%
ACNE		0	0.0	0	0.0	0	0.0
FUNGAL DERMATITIS		0	0.0	0	0.0	0	0.0
PHOTOSENSITIVITY		0	0.0	0	0.0	0	0.0
RASH		0	0.0	0	0.0	2	3.0
SKIN DISORDER		0	0.0	0	0.0	0	0.0
SWEATING		0	0.0	0	0.0	0	0.0
URTICARIA		0	0.0	0	0.0	0	0.0
Special Senses		0	0.0	1	1.4	0	0.0
ABNORMAL VISION		0	0.0	0	0.0	0	0.0
CONJUNCTIVITIS		0	0.0	1	1.4	0	0.0
EAR PAIN		0	0.0	0	0.0	0	0.0
OTITIS MEDIA		0	0.0	0	0.0	0	0.0
Urogenital System		0	0.0	0	0.0	2	3.0
CYSTITIS		0	0.0	0	0.0	0	0.0
URINARY TRACT INFECTION		0	0.0	0	0.0	1	1.5
URINE ABNORMALITY		0	0.0	0	0.0	1	1.5

Table 14.4.1

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

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	95	--	91	--	83	--	78	--	75	-
PATIENTS WITH ADVERSE EXPERIENCES :	71	74.7%	32	35.2%	38	45.8%	23	29.5%	20	26.7%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Body as a Whole	29	30.5	4	4.4	12	14.5	5	6.4	3	4.0
ABDOMINAL PAIN	4	4.2	2	2.2	1	1.2	0	0.0	0	0.0
ALLERGIC REACTION	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
ASTHENIA	5	5.3	0	0.0	0	0.0	0	0.0	1	1.3
BACK PAIN	0	0.0	1	1.1	1	1.2	0	0.0	0	0.0
CHEST PAIN	2	2.1	0	0.0	2	2.4	0	0.0	0	0.0
CHILLS	1	1.1	0	0.0	1	1.2	0	0.0	0	0.0
FEVER	2	2.1	0	0.0	0	0.0	0	0.0	0	0.0
HEADACHE	19	20.0	1	1.1	6	7.2	3	3.8	3	4.0
INFECTION	0	0.0	0	0.0	3	3.6	1	1.3	0	0.0
TRAUMA	2	2.1	0	0.0	0	0.0	0	0.0	0	0.0
Cardiovascular System	18	18.9	8	8.8	8	9.6	3	3.8	5	6.7
ARRHYTHMIA	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3
AV BLOCK	0	0.0	0	0.0	2	2.4	0	0.0	0	0.0
BUNDLE BRANCH BLOCK	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ELECTROCARDIOGRAM ABNORMAL	1	1.1	0	0.0	0	0.0	0	0.0	1	1.3
EXTRASYSTOLES	1	1.1	0	0.0	1	1.2	0	0.0	0	0.0
HEART MALFORMATION	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
HYPERTENSION	1	1.1	0	0.0	0	0.0	1	1.3	0	0.0
MIGRAINE	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
PALPITATION	1	1.1	0	0.0	2	2.4	0	0.0	0	0.0
POSTURAL HYPOTENSION	4	4.2	4	4.4	2	2.4	0	0.0	1	1.3
QT INTERVAL PROLONGED	0	0.0	0	0.0	1	1.2	0	0.0	1	1.3
SYNCOPE	1	1.1	2	2.2	0	0.0	0	0.0	1	1.3
TACHYCARDIA	8	8.4	3	3.3	2	2.4	1	1.3	2	2.7
VASODILATATION	4	4.2	0	0.0	2	2.4	0	0.0	0	0.0
Digestive System	33	34.7	11	12.1	12	14.5	10	12.8	6	8.0
GASTROENTERITIS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
NAUSEA	11	11.6	2	2.2	1	1.2	1	1.3	3	4.0
CONSTIPATION	2	2.1	2	2.2	1	1.2	1	1.3	1	1.3
DECREASED APPETITE	2	2.1	0	0.0	0	0.0	0	0.0	0	0.0
DIARRHEA	2	2.1	0	0.0	0	0.0	0	0.0	0	0.0
DRY MOUTH	20	21.1	7	7.7	8	9.6	3	3.8	2	2.7
DYSPEPSIA	3	3.2	1	1.1	1	1.2	1	1.3	0	0.0
DYSPHAGIA	1	1.1	0	0.0	0	0.0	2	2.6	0	0.0
ESOPHAGITIS	0	0.0	0	0.0	1	1.2	0	0.0	0	0.0
GASTRITIS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3

Table 14.4.1

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

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION :	68	--	61	--	57	-
PATIENTS WITH ADVERSE EXPERIENCES :	19	27.9%	15	24.6%	10	17.5%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	4	5.9	2	3.3	1	1.8
ABDOMINAL PAIN	0	0.0	0	0.0	0	0.0
ALLERGIC REACTION	0	0.0	0	0.0	0	0.0
ASTHENIA	0	0.0	0	0.0	0	0.0
BACK PAIN	0	0.0	0	0.0	0	0.0
CHEST PAIN	1	1.5	0	0.0	0	0.0
CHILLS	1	1.5	0	0.0	0	0.0
FEVER	0	0.0	0	0.0	0	0.0
HEADACHE	2	2.9	1	1.6	1	1.8
INFECTION	1	1.5	0	0.0	0	0.0
TRAUMA	0	0.0	1	1.6	0	0.0
Cardiovascular System	0	0.0	2	3.3	3	5.3
ARRHYTHMIA	0	0.0	0	0.0	0	0.0
AV BLOCK	0	0.0	0	0.0	0	0.0
BUNDLE BRANCH BLOCK	0	0.0	0	0.0	1	1.8
ELECTROCARDIOGRAM ABNORMAL	0	0.0	1	1.6	0	0.0
EXTRASYSTOLES	0	0.0	0	0.0	0	0.0
HEART MALFORMATION	0	0.0	0	0.0	0	0.0
HYPERTENSION	0	0.0	0	0.0	0	0.0
MIGRAINE	0	0.0	0	0.0	0	0.0
PALPITATION	0	0.0	0	0.0	0	0.0
POSTURAL HYPOTENSION	0	0.0	1	1.6	1	1.8
QT INTERVAL PROLONGED	0	0.0	0	0.0	1	1.8
SYNCOPE	0	0.0	0	0.0	0	0.0
TACHYCARDIA	0	0.0	0	0.0	0	0.0
VASODILATATION	0	0.0	0	0.0	0	0.0
Digestive System	8	11.8	4	6.6	2	3.5
GASTROENTERITIS	0	0.0	1	1.6	0	0.0
NAUSEA	2	2.9	1	1.6	1	1.8
CONSTIPATION	1	1.5	0	0.0	1	1.8
DECREASED APPETITE	0	0.0	0	0.0	0	0.0
DIARRHEA	1	1.5	0	0.0	0	0.0
DRY MOUTH	1	1.5	0	0.0	0	0.0
DYSPEPSIA	2	2.9	0	0.0	0	0.0
DYSPHAGIA	0	0.0	0	0.0	0	0.0
ESOPHAGITIS	0	0.0	0	0.0	0	0.0
GASTRITIS	1	1.5	0	0.0	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	95	--	91	--	83	--	78	--	75	-
PATIENTS WITH ADVERSE EXPERIENCES :	71	74.7%	32	35.2%	38	45.8%	23	29.5%	20	26.7%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
INCREASED APPETITE	0	0.0	0	0.0	1	1.2	0	0.0	0	0.0
TOOTH DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ULCERATIVE STOMATITIS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
VOMITING	0	0.0	0	0.0	1	1.2	3	3.8	1	1.3
Hemic and Lymphatic System	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
LEUKOPENIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
EOSINOPHILIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Metabolic and Nutritional Disorders	1	1.1	1	1.1	1	1.2	0	0.0	0	0.0
HYPERGLYCEMIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
THIRST	1	1.1	0	0.0	1	1.2	0	0.0	0	0.0
WEIGHT LOSS	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0
Nervous System	32	33.7	14	15.4	16	19.3	10	12.8	10	13.3
ABNORMAL DREAMS	1	1.1	0	0.0	0	0.0	0	0.0	3	4.0
AGITATION	2	2.1	0	0.0	0	0.0	0	0.0	0	0.0
AMNESIA	0	0.0	0	0.0	1	1.2	0	0.0	0	0.0
CONCENTRATION IMPAIRED	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
DEPERSONALIZATION	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
DEPRESSION	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
DIZZINESS	21	22.1	7	7.7	8	9.6	1	1.3	5	6.7
DRUG DEPENDENCE	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0	1	1.2	2	2.6	0	0.0
EUPHORIA	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
HALLUCINATIONS	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3
HOSTILITY	1	1.1	0	0.0	0	0.0	0	0.0	1	1.3
HYPERKINESIA	0	0.0	0	0.0	1	1.2	1	1.3	0	0.0
HYPERTONIA	0	0.0	0	0.0	1	1.2	0	0.0	0	0.0
HYPESTHESIA	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
INSOMNIA	5	5.3	2	2.2	1	1.2	0	0.0	0	0.0
MYOCLONUS	0	0.0	0	0.0	1	1.2	0	0.0	0	0.0
NERVOUSNESS	2	2.1	1	1.1	0	0.0	1	1.3	1	1.3
SOMNOLENCE	6	6.3	3	3.3	4	4.8	0	0.0	0	0.0
THINKING ABNORMAL	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3
TREMOR	6	6.3	2	2.2	2	2.4	2	2.6	0	0.0
Respiratory System	8	8.4	3	3.3	3	3.6	5	6.4	1	1.3
COUGH INCREASED	1	1.1	0	0.0	0	0.0	1	1.3	0	0.0
RHINITIS	1	1.1	0	0.0	1	1.2	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION :	68	--	61	--	57	-
PATIENTS WITH ADVERSE EXPERIENCES :	19	27.9%	15	24.6%	10	17.5%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
INCREASED APPETITE	0	0.0	0	0.0	0	0.0
TOOTH DISORDER	0	0.0	2	3.3	0	0.0
ULCERATIVE STOMATITIS	0	0.0	1	1.6	0	0.0
VOMITING	1	1.5	1	1.6	0	0.0
Hemic and Lymphatic System	0	0.0	0	0.0	2	3.5
LEUKOPENIA	0	0.0	0	0.0	1	1.8
EOSINOPHILIA	0	0.0	0	0.0	1	1.8
Metabolic and Nutritional Disorders	0	0.0	0	0.0	1	1.8
HYPERGLYCEMIA	0	0.0	0	0.0	1	1.8
THIRST	0	0.0	0	0.0	0	0.0
WEIGHT LOSS	0	0.0	0	0.0	0	0.0
Nervous System	8	11.8	5	8.2	0	0.0
ABNORMAL DREAMS	0	0.0	0	0.0	0	0.0
AGITATION	0	0.0	0	0.0	0	0.0
AMNESIA	0	0.0	0	0.0	0	0.0
CONCENTRATION IMPAIRED	0	0.0	0	0.0	0	0.0
DEPERSONALIZATION	0	0.0	0	0.0	0	0.0
DEPRESSION	0	0.0	0	0.0	0	0.0
DIZZINESS	2	2.9	1	1.6	0	0.0
DRUG DEPENDENCE	0	0.0	0	0.0	0	0.0
EMOTIONAL LABILITY	0	0.0	0	0.0	0	0.0
EUPHORIA	0	0.0	0	0.0	0	0.0
HALLUCINATIONS	0	0.0	0	0.0	0	0.0
HOSTILITY	0	0.0	1	1.6	0	0.0
HYPERKINESIA	0	0.0	0	0.0	0	0.0
HYPERTONIA	0	0.0	0	0.0	0	0.0
HYPESTHESIA	0	0.0	0	0.0	0	0.0
INSOMNIA	2	2.9	3	4.9	0	0.0
MYOCLONUS	0	0.0	0	0.0	0	0.0
NERVOUSNESS	1	1.5	0	0.0	0	0.0
SOMNOLENCE	0	0.0	0	0.0	0	0.0
THINKING ABNORMAL	1	1.5	0	0.0	0	0.0
TREMOR	2	2.9	0	0.0	0	0.0
Respiratory System	4	5.9	3	4.9	0	0.0
COUGH INCREASED	1	1.5	0	0.0	0	0.0
RHINITIS	1	1.5	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	95	--	91	--	83	--	78	--	75	-
PATIENTS WITH ADVERSE EXPERIENCES :	71	74.7%	32	35.2%	38	45.8%	23	29.5%	20	26.7%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
DYSPNEA	2	2.1	0	0.0	0	0.0	0	0.0	0	0.0
EPISTAXIS	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
PHARYNGITIS	6	6.3	2	2.2	2	2.4	1	1.3	0	0.0
RESPIRATORY DISORDER	1	1.1	0	0.0	0	0.0	2	2.6	1	1.3
SINUSITIS	1	1.1	1	1.1	0	0.0	0	0.0	0	0.0
Skin and Appendages	10	10.5	1	1.1	4	4.8	1	1.3	0	0.0
FUNGAL DERMATITIS	0	0.0	0	0.0	1	1.2	0	0.0	0	0.0
CONTACT DERMATITIS	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
ACNE	2	2.1	0	0.0	0	0.0	0	0.0	0	0.0
MACULOPAPULAR RASH	1	1.1	0	0.0	0	0.0	1	1.3	0	0.0
PRURITUS	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
RASH	2	2.1	0	0.0	1	1.2	0	0.0	0	0.0
SWEATING	3	3.2	1	1.1	2	2.4	0	0.0	0	0.0
URTICARIA	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
Special Senses	7	7.4	4	4.4	2	2.4	0	0.0	0	0.0
ABNORMAL VISION	3	3.2	1	1.1	0	0.0	0	0.0	0	0.0
EAR PAIN	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0
KERATOCONJUNCTIVITIS	0	0.0	1	1.1	0	0.0	0	0.0	0	0.0
MYDRIASIS	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
PHOTOPHOBIA	0	0.0	0	0.0	1	1.2	0	0.0	0	0.0
TASTE PERVERSION	3	3.2	0	0.0	0	0.0	0	0.0	0	0.0
TINNITUS	0	0.0	1	1.1	1	1.2	0	0.0	0	0.0
Urogenital System	5	5.3	1	1.1	0	0.0	0	0.0	0	0.0
CYSTITIS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
URINARY FREQUENCY	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
NOCTURIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
POLYURIA	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
URINARY RETENTION	1	1.1	1	1.1	0	0.0	0	0.0	0	0.0
URINATION IMPAIRED	2	2.1	0	0.0	0	0.0	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION :	68	--	61	--	57	-
PATIENTS WITH ADVERSE EXPERIENCES :	19	27.9%	15	24.6%	10	17.5%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
DYSPNEA	2	2.9	0	0.0	0	0.0
EPISTAXIS	0	0.0	0	0.0	0	0.0
PHARYNGITIS	1	1.5	0	0.0	0	0.0
RESPIRATORY DISORDER	0	0.0	3	4.9	0	0.0
SINUSITIS	0	0.0	0	0.0	0	0.0
Skin and Appendages	0	0.0	0	0.0	0	0.0
FUNGAL DERMATITIS	0	0.0	0	0.0	0	0.0
CONTACT DERMATITIS	0	0.0	0	0.0	0	0.0
ACNE	0	0.0	0	0.0	0	0.0
MACULOPAPULAR RASH	0	0.0	0	0.0	0	0.0
PRURITUS	0	0.0	0	0.0	0	0.0
RASH	0	0.0	0	0.0	0	0.0
SWEATING	0	0.0	0	0.0	0	0.0
URTICARIA	0	0.0	0	0.0	0	0.0
Special Senses	1	1.5	1	1.6	1	1.8
ABNORMAL VISION	1	1.5	1	1.6	0	0.0
EAR PAIN	0	0.0	0	0.0	1	1.8
KERATOCONJUNCTIVITIS	0	0.0	0	0.0	0	0.0
MYDRIASIS	0	0.0	0	0.0	0	0.0
PHOTOPHOBIA	0	0.0	0	0.0	0	0.0
TASTE PERVERSION	0	0.0	0	0.0	0	0.0
TINNITUS	0	0.0	0	0.0	0	0.0
Urogenital System	0	0.0	1	1.6	1	1.8
CYSTITIS	0	0.0	0	0.0	1	1.8
URINARY FREQUENCY	0	0.0	0	0.0	0	0.0
NOCTURIA	0	0.0	1	1.6	0	0.0
POLYURIA	0	0.0	0	0.0	0	0.0
URINARY RETENTION	0	0.0	0	0.0	0	0.0
URINATION IMPAIRED	0	0.0	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: PLACEBO

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	87	--	85	--	80	--	76	--	75	-
PATIENTS WITH ADVERSE EXPERIENCES :	37	42.5%	30	35.3%	28	35.0%	25	32.9%	19	25.3%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Body as a Whole	17	19.5	15	17.6	12	15.0	11	14.5	12	16.0
ABDOMINAL PAIN	5	5.7	3	3.5	0	0.0	1	1.3	1	1.3
ALLERGIC REACTION	1	1.1	1	1.2	0	0.0	0	0.0	0	0.0
ASTHENIA	3	3.4	1	1.2	1	1.3	2	2.6	1	1.3
BACK PAIN	1	1.1	2	2.4	3	3.8	2	2.6	1	1.3
CHEST PAIN	1	1.1	1	1.2	0	0.0	0	0.0	0	0.0
FEVER	0	0.0	0	0.0	0	0.0	0	0.0	2	2.7
HEADACHE	8	9.2	7	8.2	7	8.8	3	3.9	5	6.7
INFECTION	1	1.1	3	3.5	1	1.3	1	1.3	2	2.7
PAIN	0	0.0	0	0.0	1	1.3	0	0.0	1	1.3
TRAUMA	0	0.0	0	0.0	0	0.0	3	3.9	0	0.0
Cardiovascular System	4	4.6	2	2.4	2	2.5	3	3.9	0	0.0
ARRHYTHMIA	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
AV BLOCK	0	0.0	2	2.4	0	0.0	0	0.0	0	0.0
BRADYCARDIA	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
BUNDLE BRANCH BLOCK	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
HEART MALFORMATION	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
NODAL ARRHYTHMIA	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
POSTURAL HYPOTENSION	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
SUPRAVENTRICULAR EXTRASYSTOLES	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
SYNCOPE	0	0.0	0	0.0	0	0.0	1	1.3	0	0.0
TACHYCARDIA	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
VASODILATATION	0	0.0	0	0.0	2	2.5	0	0.0	0	0.0
Digestive System	17	19.5	8	9.4	8	10.0	7	9.2	3	4.0
CONSTIPATION	1	1.1	0	0.0	2	2.5	0	0.0	0	0.0
DECREASED APPETITE	1	1.1	0	0.0	1	1.3	1	1.3	0	0.0
DIARRHEA	3	3.4	2	2.4	1	1.3	0	0.0	0	0.0
DRY MOUTH	5	5.7	1	1.2	0	0.0	1	1.3	1	1.3
DYSPEPSIA	1	1.1	0	0.0	1	1.3	1	1.3	1	1.3
GASTROINTESTINAL DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
INCREASED APPETITE	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
NAUSEA	7	8.0	2	2.4	4	5.0	2	2.6	1	1.3
TOOTH DISORDER	0	0.0	2	2.4	0	0.0	0	0.0	0	0.0
ULCERATIVE STOMATITIS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
VOMITING	0	0.0	2	2.4	1	1.3	3	3.9	0	0.0
Hemic and Lymphatic System	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
EOSINOPHILIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: PLACEBO

DAYS	DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION :	70	--	70	--	67	-
PATIENTS WITH ADVERSE EXPERIENCES :	10	14.3%	13	18.6%	12	17.9%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Body as a Whole	0	0.0	8	11.4	2	3.0
ABDOMINAL PAIN	0	0.0	0	0.0	0	0.0
ALLERGIC REACTION	0	0.0	1	1.4	0	0.0
ASTHENIA	0	0.0	2	2.9	0	0.0
BACK PAIN	0	0.0	0	0.0	1	1.5
CHEST PAIN	0	0.0	0	0.0	0	0.0
FEVER	0	0.0	2	2.9	0	0.0
HEADACHE	0	0.0	3	4.3	1	1.5
INFECTION	0	0.0	0	0.0	1	1.5
PAIN	0	0.0	1	1.4	0	0.0
TRAUMA	0	0.0	1	1.4	0	0.0
Cardiovascular System	0	0.0	0	0.0	0	0.0
ARRHYTHMIA	0	0.0	0	0.0	0	0.0
AV BLOCK	0	0.0	0	0.0	0	0.0
BRADYCARDIA	0	0.0	0	0.0	0	0.0
BUNDLE BRANCH BLOCK	0	0.0	0	0.0	0	0.0
HEART MALFORMATION	0	0.0	0	0.0	0	0.0
NODAL ARRHYTHMIA	0	0.0	0	0.0	0	0.0
POSTURAL HYPOTENSION	0	0.0	0	0.0	0	0.0
SUPRAVENTRICULAR EXTRASYSTOLES	0	0.0	0	0.0	0	0.0
SYNCOPE	0	0.0	0	0.0	0	0.0
TACHYCARDIA	0	0.0	0	0.0	0	0.0
VASODILATATION	0	0.0	0	0.0	0	0.0
Digestive System	3	4.3	3	4.3	4	6.0
CONSTIPATION	0	0.0	1	1.4	0	0.0
DECREASED APPETITE	0	0.0	0	0.0	1	1.5
DIARRHEA	0	0.0	0	0.0	1	1.5
DRY MOUTH	2	2.9	1	1.4	1	1.5
DYSPEPSIA	0	0.0	0	0.0	0	0.0
GASTROINTESTINAL DISORDER	0	0.0	1	1.4	0	0.0
INCREASED APPETITE	0	0.0	0	0.0	0	0.0
NAUSEA	1	1.4	0	0.0	0	0.0
TOOTH DISORDER	0	0.0	0	0.0	0	0.0
ULCERATIVE STOMATITIS	0	0.0	0	0.0	1	1.5
VOMITING	0	0.0	0	0.0	0	0.0
Hemic and Lymphatic System	0	0.0	0	0.0	2	3.0
EOSINOPHILIA	0	0.0	0	0.0	1	1.5

Table 14.4.1

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

TREATMENT GROUP: PLACEBO

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	87	--	85	--	80	--	76	--	75	-
PATIENTS WITH ADVERSE EXPERIENCES :	37	42.5%	30	35.3%	28	35.0%	25	32.9%	19	25.3%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
LYMPHADENOPATHY	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
THROMBOCYTHEMIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Metabolic and Nutritional Disorders	1	1.1	1	1.2	1	1.3	0	0.0	0	0.0
WEIGHT LOSS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
HYPERGLYCEMIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
THIRST	1	1.1	1	1.2	1	1.3	0	0.0	0	0.0
Musculoskeletal System	0	0.0	1	1.2	0	0.0	2	2.6	2	2.7
ARTHRALGIA	0	0.0	1	1.2	0	0.0	0	0.0	2	2.7
MYALGIA	0	0.0	0	0.0	0	0.0	2	2.6	0	0.0
Nervous System	11	12.6	5	5.9	6	7.5	4	5.3	6	8.0
ABNORMAL DREAMS	1	1.1	1	1.2	0	0.0	0	0.0	0	0.0
ANXIETY	0	0.0	1	1.2	0	0.0	1	1.3	0	0.0
DEPERSONALIZATION	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0
DEPRESSION	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
DIZZINESS	5	5.7	1	1.2	4	5.0	0	0.0	4	5.3
EMOTIONAL LABILITY	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
EUPHORIA	0	0.0	0	0.0	1	1.3	0	0.0	0	0.0
HYPERKINESIA	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
HYPERTONIA	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3
INSOMNIA	2	2.3	0	0.0	0	0.0	0	0.0	0	0.0
NERVOUSNESS	1	1.1	1	1.2	1	1.3	1	1.3	1	1.3
SOMNOLENCE	2	2.3	0	0.0	1	1.3	0	0.0	0	0.0
TREMOR	0	0.0	0	0.0	0	0.0	2	2.6	0	0.0
Respiratory System	8	9.2	5	5.9	4	5.0	5	6.6	2	2.7
COUGH INCREASED	1	1.1	1	1.2	0	0.0	0	0.0	1	1.3
RHINITIS	0	0.0	1	1.2	0	0.0	0	0.0	2	2.7
BRONCHITIS	2	2.3	0	0.0	1	1.3	1	1.3	0	0.0
DYSPNEA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
PHARYNGITIS	1	1.1	0	0.0	2	2.5	1	1.3	1	1.3
RESPIRATORY DISORDER	5	5.7	2	2.4	2	2.5	1	1.3	0	0.0
SINUSITIS	0	0.0	2	2.4	2	2.5	2	2.6	1	1.3
Skin and Appendages	3	3.4	2	2.4	1	1.3	0	0.0	0	0.0
ACNE	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0
CONTACT DERMATITIS	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
HERPES ZOSTER	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: PLACEBO

DAYS	DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION :	70	--	70	--	67	-
PATIENTS WITH ADVERSE EXPERIENCES :	10	14.3%	13	18.6%	12	17.9%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
LYMPHADENOPATHY	0	0.0	0	0.0	0	0.0
THROMBOCYTHEMIA	0	0.0	0	0.0	1	1.5
Metabolic and Nutritional Disorders	0	0.0	1	1.4	2	3.0
WEIGHT LOSS	0	0.0	1	1.4	1	1.5
HYPERGLYCEMIA	0	0.0	0	0.0	1	1.5
THIRST	0	0.0	0	0.0	0	0.0
Musculoskeletal System	0	0.0	1	1.4	0	0.0
ARTHRALGIA	0	0.0	1	1.4	0	0.0
MYALGIA	0	0.0	0	0.0	0	0.0
Nervous System	2	2.9	3	4.3	0	0.0
ABNORMAL DREAMS	0	0.0	0	0.0	0	0.0
ANXIETY	0	0.0	0	0.0	0	0.0
DEPERSONALIZATION	0	0.0	0	0.0	0	0.0
DEPRESSION	1	1.4	0	0.0	0	0.0
DIZZINESS	0	0.0	2	2.9	0	0.0
EMOTIONAL LABILITY	1	1.4	0	0.0	0	0.0
EUPHORIA	0	0.0	0	0.0	0	0.0
HYPERKINESIA	0	0.0	0	0.0	0	0.0
HYPERTONIA	0	0.0	0	0.0	0	0.0
INSOMNIA	1	1.4	1	1.4	0	0.0
NERVOUSNESS	0	0.0	0	0.0	0	0.0
SOMNOLENCE	0	0.0	0	0.0	0	0.0
TREMOR	0	0.0	0	0.0	0	0.0
Respiratory System	5	7.1	1	1.4	0	0.0
COUGH INCREASED	2	2.9	0	0.0	0	0.0
RHINITIS	2	2.9	0	0.0	0	0.0
BRONCHITIS	0	0.0	0	0.0	0	0.0
DYSPNEA	1	1.4	0	0.0	0	0.0
PHARYNGITIS	2	2.9	1	1.4	0	0.0
RESPIRATORY DISORDER	1	1.4	0	0.0	0	0.0
SINUSITIS	0	0.0	0	0.0	0	0.0
Skin and Appendages	0	0.0	0	0.0	2	3.0
ACNE	0	0.0	0	0.0	0	0.0
CONTACT DERMATITIS	0	0.0	0	0.0	0	0.0
HERPES ZOSTER	0	0.0	0	0.0	1	1.5

Table 14.4.1

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

TREATMENT GROUP: PLACEBO

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	87	--	85	--	80	--	76	--	75	-
PATIENTS WITH ADVERSE EXPERIENCES :	37	42.5%	30	35.3%	28	35.0%	25	32.9%	19	25.3%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
MACULOPAPULAR RASH	1	1.1	0	0.0	0	0.0	0	0.0	0	0.0
RASH	1	1.1	0	0.0	1	1.3	0	0.0	0	0.0
SWEATING	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0
Special Senses	0	0.0	1	1.2	0	0.0	0	0.0	1	1.3
EYE DISORDER	0	0.0	0	0.0	0	0.0	0	0.0	1	1.3
ABNORMAL VISION	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0
Urogenital System	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ALBUMINURIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
PYURIA	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 14.4.1

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

TREATMENT GROUP: PLACEBO

DAYS		DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION	:	70	--	70	--	67	-
PATIENTS WITH ADVERSE EXPERIENCES	:	10	14.3%	13	18.6%	12	17.9%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%
MACULOPAPULAR RASH		0	0.0	0	0.0	0	0.0
RASH		0	0.0	0	0.0	1	1.5
SWEATING		0	0.0	0	0.0	0	0.0
Special Senses		0	0.0	1	1.4	0	0.0
EYE DISORDER		0	0.0	0	0.0	0	0.0
ABNORMAL VISION		0	0.0	1	1.4	0	0.0
Urogenital System		0	0.0	0	0.0	2	3.0
ALBUMINURIA		0	0.0	0	0.0	2	3.0
PYURIA		0	0.0	0	0.0	1	1.5

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Table 14.4.3

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

TREATMENT GROUP: PAROXETINE

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	58	--	54	--	51	--	50	--	50	-
PATIENTS WITH ADVERSE EXPERIENCES :	1	1.7%	0	0.0%	0	0.0%	1	2.0%	1	2.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Urogenital System	1	1.7	0	0.0	0	0.0	1	2.0	1	2.0
AMENORRHEA	1	1.7	0	0.0	0	0.0	0	0.0	0	0.0
BREAST ENLARGEMENT	0	0.0	0	0.0	0	0.0	1	2.0	0	0.0
DYSMENORRHEA	0	0.0	0	0.0	0	0.0	0	0.0	1	2.0
FEMALE GENITAL DISORDERS	1	1.7	0	0.0	0	0.0	0	0.0	0	0.0

Table 14.4.3

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

TREATMENT GROUP: PAROXETINE

DAYS	DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION :	49	--	47	--	44	-
PATIENTS WITH ADVERSE EXPERIENCES :	0	0.0%	1	2.1%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%
Urogenital System	0	0.0	1	2.1	0	0.0
AMENORRHEA	0	0.0	0	0.0	0	0.0
BREAST ENLARGEMENT	0	0.0	0	0.0	0	0.0
DYSMENORRHEA	0	0.0	1	2.1	0	0.0
FEMALE GENITAL DISORDERS	0	0.0	0	0.0	0	0.0

Table 14.4.3

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

TREATMENT GROUP: IMIPRAMINE

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	56	--	54	--	50	--	47	--	45	-
PATIENTS WITH ADVERSE EXPERIENCES :	1	1.8%	1	1.9%	0	0.0%	0	0.0%	1	2.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Urogenital System	1	1.8	1	1.9	0	0.0	0	0.0	1	2.2
DYSMENORRHEA	1	1.8	1	1.9	0	0.0	0	0.0	1	2.2
VAGINAL MONILIASIS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 14.4.3

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

TREATMENT GROUP: IMIPRAMINE

DAYS		DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION	:	40	--	35	--	32	-
PATIENTS WITH ADVERSE EXPERIENCES	:	1	2.5%	1	2.9%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%
Urogenital System		1	2.5	1	2.9	0	0.0
DYSMENORRHEA		1	2.5	0	0.0	0	0.0
VAGINAL MONILIASIS		0	0.0	1	2.9	0	0.0

Table 14.4.3

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

TREATMENT GROUP: PLACEBO

DAYS	DAY 1-11		DAY 12-18		DAY 19-25		DAY 26-32		DAY 33-39	
PATIENTS WHO RECEIVED STUDY MEDICATION :	57	--	56	--	54	--	52	--	51	-
PATIENTS WITH ADVERSE EXPERIENCES :	0	0.0%	0	0.0%	2	3.7%	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%	N	%
Urogenital System	0	0.0	0	0.0	2	3.7	0	0.0	0	0.0
DYSMENORRHEA	0	0.0	0	0.0	2	3.7	0	0.0	0	0.0

Table 14.4.3

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

TREATMENT GROUP: PLACEBO

DAYS		DAY 40-46		DAY 47-53		> DAY 53	
PATIENTS WHO RECEIVED STUDY MEDICATION	:	50	--	50	--	47	-
PATIENTS WITH ADVERSE EXPERIENCES	:	1	2.0%	0	0.0%	1	2.1%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%
Urogenital System		1	2.0	0	0.0	1	2.1
DYSMENORRHEA		1	2.0	0	0.0	1	2.1

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Table 14.5.1

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	8	8.6%	9	9.5%	2	2.3%	19	6.9%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Body as a Whole	2	2.2	2	2.1	1	1.1	5	1.8
ASTHENIA	1	1.1	0	0.0	0	0.0	1	0.4
HEADACHE	1	1.1	2	2.1	1	1.1	4	1.5
Cardiovascular System	0	0.0	1	1.1	0	0.0	1	0.4
ELECTROCARDIOGRAM ABNORMAL	0	0.0	1	1.1	0	0.0	1	0.4
Digestive System	3	3.2	3	3.2	0	0.0	6	2.2
CONSTIPATION	0	0.0	2	2.1	0	0.0	2	0.7
DECREASED APPETITE	1	1.1	0	0.0	0	0.0	1	0.4
DRY MOUTH	0	0.0	2	2.1	0	0.0	2	0.7
DYSPEPSIA	1	1.1	2	2.1	0	0.0	3	1.1
NAUSEA	2	2.2	0	0.0	0	0.0	2	0.7
Nervous System	6	6.5	7	7.4	2	2.3	15	5.5
ANXIETY	1	1.1	0	0.0	0	0.0	1	0.4
DEPERSONALIZATION	0	0.0	0	0.0	1	1.1	1	0.4
DIZZINESS	2	2.2	1	1.1	0	0.0	3	1.1
EUPHORIA	0	0.0	1	1.1	0	0.0	1	0.4
INSOMNIA	1	1.1	0	0.0	0	0.0	1	0.4
NERVOUSNESS	1	1.1	1	1.1	1	1.1	3	1.1
SOMNOLENCE	2	2.2	1	1.1	0	0.0	3	1.1
TREMOR	1	1.1	4	4.2	0	0.0	5	1.8
Respiratory System	0	0.0	0	0.0	1	1.1	1	0.4
DYSPNEA	0	0.0	0	0.0	1	1.1	1	0.4
Skin and Appendages	1	1.1	0	0.0	0	0.0	1	0.4
SKIN DISORDER	1	1.1	0	0.0	0	0.0	1	0.4
Special Senses	0	0.0	2	2.1	0	0.0	2	0.7
ABNORMAL VISION	0	0.0	1	1.1	0	0.0	1	0.4
TASTE PERVERSION	0	0.0	1	1.1	0	0.0	1	0.4

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Table 14.5.3

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

TREATMENT GROUP		PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS	:	58	100.0%	56	100.0%	57	100.0%	171	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	1	1.7%	0	0.0%	0	0.0%	1	0.6%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%	N	%
Urogenital System		1	1.7	0	0.0	0	0.0	1	0.6
FEMALE GENITAL DISORDERS		1	1.7	0	0.0	0	0.0	1	0.6

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Table 14.6.1

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	46	49.5%	42	44.2%	46	52.9%	134	48.7%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Body as a Whole	27	29.0	25	26.3	36	41.4	88	32.0
ABDOMINAL PAIN	3	3.2	2	2.1	3	3.4	8	2.9
ALLERGIC REACTION	1	1.1	1	1.1	2	2.3	4	1.5
BACK PAIN	4	4.3	1	1.1	5	5.7	10	3.6
CHILLS	0	0.0	1	1.1	0	0.0	1	0.4
FEVER	0	0.0	1	1.1	4	4.6	5	1.8
HEADACHE	20	21.5	20	21.1	23	26.4	63	22.9
INFECTION	4	4.3	2	2.1	7	8.0	13	4.7
PAIN	0	0.0	0	0.0	1	1.1	1	0.4
TRAUMA	1	1.1	2	2.1	3	3.4	6	2.2
Digestive System	10	10.8	10	10.5	4	4.6	24	8.7
CONSTIPATION	1	1.1	1	1.1	0	0.0	2	0.7
DIARRHEA	2	2.2	0	0.0	0	0.0	2	0.7
DYSPEPSIA	2	2.2	4	4.2	2	2.3	8	2.9
GASTRITIS	0	0.0	1	1.1	0	0.0	1	0.4
GASTROENTERITIS	0	0.0	1	1.1	0	0.0	1	0.4
GASTROINTESTINAL DISORDER	1	1.1	0	0.0	0	0.0	1	0.4
NAUSEA	2	2.2	4	4.2	1	1.1	7	2.5
TOOTH DISORDER	4	4.3	2	2.1	2	2.3	8	2.9
ULCERATIVE STOMATITIS	0	0.0	1	1.1	0	0.0	1	0.4
VOMITING	0	0.0	3	3.2	0	0.0	3	1.1
Musculoskeletal System	1	1.1	1	1.1	1	1.1	3	1.1
ARTHRALGIA	1	1.1	1	1.1	1	1.1	3	1.1
MYALGIA	1	1.1	0	0.0	0	0.0	1	0.4
Nervous System	6	6.5	2	2.1	4	4.6	12	4.4
ANXIETY	0	0.0	0	0.0	2	2.3	2	0.7
DEPRESSION	1	1.1	0	0.0	1	1.1	2	0.7
DIZZINESS	1	1.1	0	0.0	0	0.0	1	0.4
HOSTILITY	1	1.1	0	0.0	0	0.0	1	0.4
HYPERTONIA	0	0.0	0	0.0	1	1.1	1	0.4
INSOMNIA	1	1.1	2	2.1	0	0.0	3	1.1
SOMNOLENCE	1	1.1	0	0.0	0	0.0	1	0.4
TREMOR	1	1.1	0	0.0	0	0.0	1	0.4
WITHDRAWAL SYNDROME	1	1.1	0	0.0	0	0.0	1	0.4
Respiratory System	21	22.6	17	17.9	21	24.1	59	21.5
ASTHMA	1	1.1	0	0.0	1	1.1	2	0.7

Table 14.6.1

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

TREATMENT GROUP	PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	46	49.5%	42	44.2%	46	52.9%	134	48.7%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
BRONCHITIS	2	2.2	0	0.0	3	3.4	5	1.8
COUGH INCREASED	4	4.3	3	3.2	3	3.4	10	3.6
DYSPNEA	1	1.1	0	0.0	0	0.0	1	0.4
PHARYNGITIS	4	4.3	9	9.5	5	5.7	18	6.5
RESPIRATORY DISORDER	8	8.6	5	5.3	7	8.0	20	7.3
RHINITIS	6	6.5	3	3.2	3	3.4	12	4.4
SINUSITIS	4	4.3	1	1.1	6	6.9	11	4.0
Skin and Appendages	1	1.1	4	4.2	0	0.0	5	1.8
ACNE	1	1.1	0	0.0	0	0.0	1	0.4
CONTACT DERMATITIS	0	0.0	1	1.1	0	0.0	1	0.4
FUNGAL DERMATITIS	0	0.0	1	1.1	0	0.0	1	0.4
MACULOPAPULAR RASH	0	0.0	1	1.1	0	0.0	1	0.4
RASH	0	0.0	2	2.1	0	0.0	2	0.7
URTICARIA	0	0.0	1	1.1	0	0.0	1	0.4
Special Senses	4	4.3	1	1.1	0	0.0	5	1.8
CONJUNCTIVITIS	1	1.1	0	0.0	0	0.0	1	0.4
EAR PAIN	1	1.1	1	1.1	0	0.0	2	0.7
OTITIS MEDIA	2	2.2	0	0.0	0	0.0	2	0.7
Urogenital System	1	1.1	1	1.1	0	0.0	2	0.7
CYSTITIS	1	1.1	1	1.1	0	0.0	2	0.7

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Table 14.6.3

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

TREATMENT GROUP		PAROXETINE		IMIPRAMINE		PLACEBO		TOTAL	
TOTAL NUMBER OF PATIENTS	:	58	100.0%	56	100.0%	57	100.0%	171	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	2	3.4%	4	7.1%	4	7.0%	10	5.8%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%	N	%	N	%
Urogenital System		2	3.4	4	7.1	4	7.0	10	5.8
DYSMENORRHEA		2	3.4	3	5.4	4	7.0	9	5.3
VAGINAL MONILIASIS		0	0.0	1	1.8	0	0.0	1	0.6

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Table 14.8

Listing of Serious Adverse Experiences by Treatment Group and Patient
Acute 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
329.001.00065	Depression	WORSENING OF DEPRESSION HOSPITALIZED	30NOV94	14, .	Not Stated	20	CON	SEV	STP	PSR	No	Yes
	Hostility	NEEDED 6 STITCHES TO HAND AFTER BREAKING PICTURES (DUE TO ANGER) RESULTED IN HOSPITALIZATION TO PREVENT AGGRESSION AGAINST SELF	30NOV94	14, .	1 Days	20	CON	MOD	STP	PBU	No	Yes
329.002.00106	Hostility	OPPOSITIONAL DEFIANT DISORDER	15SEP95	51, .	16 Days	40	CON	SEV	NO	PBU	No	Yes
329.002.00245	Emotional Lability	TYLENOL OVERDOSE {INTENTIONAL}	10APR96	14, .	1 Days	20	1	SEV	STP	UNR	No	Yes
329.003.00089	Euphoria	ELATION AND EXPANSIVE MOOD	04APR95	29, .	Not Stated	20	CON	SEV	STP	PSR	No	Yes
329.003.00248	Withdrawal Syndrome	MIGRAINE HEADACHE {WITHDRAWAL SYMPTOM}	29APR96	60, .	6 Days	30	CON	SEV	NO	REL	Yes	Yes
329.003.00250	Emotional Lability	OVERDOSE {INTENTIONAL}	19APR96	37, -21	21 Days	40	CON	MOD	NO	UNR	No	Yes
329.003.00313	Emotional Lability	SUPERFICIAL CUTS RISK TO SELF	28MAY96	12, .	6 Days	20	CON	SEV	STP	PBU	No	Yes
	Hallucinations	AUDITORY HALLUCINATIONS	28MAY96	12, .	6 Days	20	CON	SEV	STP	PBU	No	Yes
329.005.00333	Emotional Lability	SUICIDAL IDEATION	28FEB97	37, .	103 Days	20	CON	SEV	NO	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 14.8

Listing of Serious Adverse Experiences by Treatment Group and Patient
Acute 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
329.006.00038	Emotional Lability	ATTEMPTED SUICIDE {INTENTIONAL}	12APR95	57, .	1 Days	20	1	SEV	STP	UNR	No	Yes
329.009.00201	Agitation	AGITATION	03APR96	58, .	Not Stated	20	CON	SEV	STP	PSR	No	Yes
	Hostility	AGGRESSIVE ASSAULTIVE BEHAVIOR	03APR96	58, .	Not Stated	20	CON	SEV	STP	PSR	Yes	Yes
	Paranoid Reaction	PARANOIA	03APR96	58, .	Not Stated	20	CON	MOD	STP	PSR	No	Yes
329.009.00240	Depression	WORSENING OF DEPRESSION	02MAR97	48, .	Not Stated	30	CON	SEV	STP	UNR	Yes	Yes
	Insomnia	WORSENING OF SLEEP DISTURBANCE	05MAR97	51, .	Not Stated	30	CON	SEV	NO	PSR	Yes	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 14.8

Listing of Serious Adverse Experiences by Treatment Group and Patient
Acute 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
329.002.00321	Hostility	PSYCHIATRIC HOSPITALIZATION FOLLOWING ASSAULTIVE BEHAVIOR	02JUN96	11, .	Not Stated	50	1	SEV	STP	UNR	No	Yes
329.004.00215	Abnormal Dreams	NIGHTMARES	25APR97	37, .	7 Days	200	CON	MOD	STP	REL	No	Yes
	Dizziness	DIZZINESS	25APR97	37, .	Not Stated	200	CON	MOD	STP	REL	No	Yes
	Hallucinations	VISUAL HALLUCINATIONS	25APR97	37, .	7 Days	200	CON	SEV	STP	REL	No	Yes
	Nervousness	IRRITABILITY	25APR97	37, .	7 Days	200	CON	SEV	STP	REL	No	Yes
329.007.00270	Chest Pain	CHEST PAIN, CHEST TIGHTNESS	19JUN96	42, .	03:00 Hrs	200	1	SEV	STP	PSR	No	Yes
	Dyspnea	SHORTNESS OF BREATH	19JUN96	42, .	03:00 Hrs	200	1	SEV	STP	PSR	No	Yes
329.007.00307	Maculopapular Rash	MORBILLIFORM "MEASLES LIKE" ERUPTION, GENERALIZED SIMILAR TO TRICYCLIC RASH, ON TRUNK, BACK, EXTREMITIES, CHEST, BUTTOCKS, TORSO/FRONT AND BACK, AND LOWER NECK	16JUN96	32, .	10 Days	200	CON	MOD	STP	REL	Yes	Yes
329.012.00223	Depression	MAJOR DEPRESSION	29SEP96	31, .	Not Stated	200	CON	MOD	NO	UNR	No	Yes
	Emotional Lability	SELF MUTILATION	29SEP96	31, .	Not Stated	200	CON	MOD	NO	UNR	No	Yes
	Hypertension	HYPERTENSION	30SEP96	32, .	Not Stated	200	CON	MOD	NO	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 14.8

Listing of Serious Adverse Experiences by Treatment Group and Patient
Acute 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
329.001.00123	Depression	WORSENING OF DEPRESSION	18FEB96	46, .	Not Stated	0	CON	SEV	STP	REL	No	Yes
	Emotional Lability	SUICIDAL THOUGHTS	18FEB96	46, .	Not Stated	0	CON	SEV	STP	REL	No	Yes
329.012.00217	Depression	DEPRESSION (WORSENING)	19JUN96	30, .	8 Days	0	CON	SEV	NO	UNR	Yes	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]

Confidential

SmithKline Beecham

Paroxetine

BRL-029060

Serious Adverse Experiences Patient Narratives

329

Table 14.8a

SB Document Number: BRL-029060/RSD-100TX0/1

PID 329.001.00065 (94011450-1)

Primary Adverse Experience: **WORSENING DEPRESSION, HOSTILITY**

Demography: Age: 14 YEARS Date of Birth: 08-FEB-80 Sex: Male
Height: 65.0 in Weight: 125.6 lbs Race: Caucasian

Country: **United States**

Medical History: **Dizziness (when changing position), hand tremors, headaches, nausea, Osgood-Schlatter Disease**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 17-Nov-94 **End: 30-Nov-94**

AE Remarks:
This 14 year old Caucasian male patient was a participant in study 29060/329 for depression/affective disorders. On 17-Nov-94, the patient received his first dose of study medication.

On 30-Nov-94, the patient became very angry. He punched pictures, broke glass, and sustained lacerations that required six sutures. His anger subsided, but he expressed hopelessness and possible suicide thoughts. The patient was hospitalized due to his severe anger outburst and a worsening of his depression. The investigator broke the study blind and determined that the patient was on paroxetine. Study medication was discontinued on this day.

In the opinion of the investigator, the worsening of depression was possibly related to the study medication and the anger outburst was probably unrelated to study medication.

Concomitant Drugs:	**Start**	**End**
TYLENOL (ACETAMINOPHEN)	01-FEB-89	Unknown

PID 329.001.00065 (94011450-1)

Medical History Remarks:
History of major depressive disorder since 1992.

Reporter Attribution for Primary AE:	POSSIBLY RELATED/ SUSPECTED
Reason for Seriousness:	HOSPITALIZATION REQUIRED

PID 329.001.00123 (96002477-1)

Primary Adverse Experience: **WORSENING DEPRESSION, EMOTIONAL LABILITY**

Demography: Age: 16 YEARS Date of Birth: 14-FEB-79 Sex: Female
Height: 69.3 in Weight182.6 lbs Race: Black

Country: **United States**

Medical History: Asthma, bacterial vaginal rash, broken ankle, broken wrist, epiphysis (joint disorder), hip-left femoral epiphysis, hip-right femoral epiphysis, menstrual cramps, replacement of cannulated lag screw in right hip, suicidal ideation, surgery-pinning left hip, surgery-removal of pins in right and left hip

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Placebo**

Start: 04-Jan-96 **End: 21-Feb-96**

AE Remarks:
Patient 329.001.00123 was a 17 year old Black female who was enrolled in study 29060/329, a double-blind, placebo-controlled study of Paroxetine and Imipramine in adolescents, for unipolar major depression. She commenced study medication on 04-Jan-96.

Approximately 6 weeks after commencing study 329, the patient experienced severe worsening of depression with severe suicidal thoughts. The investigator broke the code (patient was on placebo) and set up an appointment for the patient to be seen at a children's hospital. Study drug was stopped on 21-Feb-96.

The investigator reported that the worsening of depression and suicidal thought were life threatening and definitely related to study medication in that there was a lack of effect and they could be associated with the patient's history of depression.

PID 329.001.00123 (96002477-1)

Concomitant Drugs:	**Start**	**End**
ORTH-CEPT (DESOGESTREL/ ETHINYL ESTRADIOL)	21-JAN-96	Unknown
ASPIRIN	15-JAN-96	Unknown
TYLENOL (ACETAMINOPHEN)	21-FEB-96	Unknown

Medical History Remarks:
During the study, the patient took aspirin 650 mg for headache and Tylenol 650 mg for menstrual cramps, concomitantly since 21-Feb-96. Patient has a history of suicidal ideation without a definite plan. She has never had a suicide attempt.

Reporter Attribution for Primary AE: DEFINITELY RELATED

Reason for Seriousness: LIFE THREATENING

PID 329.002.00106 (95010303-1)

Primary Adverse Experience: HOSTILITY

Demography:	Age: 15 YEARS	Date of Birth: 25-APR-80	Sex: Female
	Height: 68 in	Weight: 147.6 lbs	Race: Caucasian

Country: United States

Study Diagnosis: Depression/Affective Disorders

Study Drug: Paroxetine

Start: 27-Jun-95 End: 12-Sep-95

AE Remarks:
This 15 year old Caucasian female patient, weight 147.6 lbs, height 68.0 in, was a participant in study 29060/329, for depression/affective disorders. On 27-Jun-95, the patient received her first dose of study medication.

On 15-Sep-95, the patient had to be hospitalized after an argument. She had become combative with her mother and had threatened suicide. She was prescribed Zoloft. Several days before her hospitalization, she had not taken her study medication. At the time of discharge, the patient was experiencing some depressive symptoms.

In the opinion of the investigator, the event was probably not related to the study medication but to the parent's primary condition and family problems.

Treatment Drugs:	**Start**	**End**
ZOLOFT	Unknown	Unknown

Lab Remarks:
Labs were all normal at week 4 visit.

Medical History Remarks:
Concomitant medications: none. Relevant medical history: none.

PID 329.002.00106 (95010303-1)

Reporter Attribution for Primary AE:	PROBABLY UNRELATED/ UNLIKELY
Reason for Seriousness:	HOSPITALIZATION REQUIRED

PID 329.002.00245 (96005505-1)

Primary Adverse Experience: **EMOTIONAL LABILITY (TYLENOL OVERDOSE INTENTIONAL/ ASYMPTOMATIC)**

Demography: Age: 14 YEARS Date of Birth: 01-JUN-81 Sex: Female
Height: 66.0 in Weight: 126.7 lbs Race: Caucasian

Country: **United States**

Medical History: **Conduct disorder, migraine headaches**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 28-Mar-96 **End: 14-Apr-96**

AE Remarks:
This 15 year old Caucasian female patient, weight 126.7 lbs, height 66.0 in, was a participant in study 29060/329, for depression/affective disorders. On 28-Mar-96, the patient received her first dose of study medication.

On 10-Apr-96, the patient had overdosed on Tylenol. She had ingested 27 or 28 capsules in response to being grounded and was taken into an emergency room for her stomach to be pumped. She was released and scheduled for follow-up liver function test. On 14-Apr-96, the patient was withdrawn from the study.

In the opinion of the investigator, the event is associated with the patient's primary condition and also with her conduct disorder. He considers the event to be unrelated to study medication.

Medical History Remarks:
No concomitant medication. Major depressive disorder since March, 1995 and conduct disorder since September 1995. No history of previous attempts of overdose.

Reporter Attribution for Primary AE: UNRELATED/NOT RELATED

Reason for Seriousness: OVERDOSE

PID 329.002.00321 (96007756-1)

Primary Adverse Experience: **HOSTILITY**

Demography: Age: 14 YEARS Date of Birth: 03-JUL-81 Sex: Male
Height: 65.0 in Weight: 113.7 lbs Race - Caucasian

Country: **United States**

Medical History: **Conduct Disorder**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Imipramine**

Start: 23-May-96 **End: 03-Jun-96**

AE Remarks:
This 14 year old Caucasian male patient, weight 113.7 lbs., height 65 in., was a participant in study 29060/329 for depression/affective disorders. On 23-May-96, the patient received his first dose of study medication.

On 02-Jun-96, the patient was hospitalized for a conduct disorder. He had a violent outburst and punched his mother's boyfriend. The patient has a history of a conduct disorder for several years and the investigator felt that this contributed to the violent outburst. The patient was withdrawn from the study at this time so that more intensive family treatment could be obtained.

In the opinion of the investigator, this event was unrelated to the study medication.

Medical History Remarks:
The patient was previously hospitalized for depression and instances of aggression.

Reporter Attribution for Primary AE: UNRELATED/NOT RELATED

Reason for Seriousness: HOSPITALIZATION REQUIRED

PID 329.003.00089 (95004404-1)

Primary Adverse Experience: EUPHORIA

Demography: Age: 14 YEARS Date of Birth: 01-JUN-80 Sex: Female
Height: 67.5 in Weight: 114.8 lbs Race - Caucasian

Country: United States

Study Diagnosis: Depression/Affective Disorders

Study Drug: Paroxetine

Start: 07-Mar-95 End: 05-May-95

AE Remarks:
This 14 year old Caucasian female patient, weight 114.8 lbs, height 67.5 in, was a participant in study 29060/329 for depression/affective disorders. On 07-Mar-95, the patient received her first dose of study medication.

As reported by the site, the patient began exhibiting symptoms of disinhibition, grandiosity, and expansive mood at around week four of the study. A clinical judgement was made by site medical staff to observe the patients behavior for the next one to two weeks for diagnostic and intervention planning. Her behavioral symptoms reportedly worsened over that time period through completion of week 8 of the study.

On 04-Apr-95, the patient reported increased feelings of elation and expansive mood. There was also a decreased need for sleep, increased energy and an inflated self esteem. Other symptoms included accelerated speech, flight of ideas, motor hyperactivity. The school reported impulsive and sexually provocative behavior. Her behavior was closely monitored.

On 02-May 95, the patient became agitated and said she would kill herself following threats of punishment from her mother to control her behavior. The patient was deemed a risk to herself and was brought to the crisis service. She was hospitalized on 02-May-95 and the decision was made that she would not enter the continuation phase.

In the opinion of the investigator, the event was possibly related to the study drug, and also related to the primary condition and to undiagnosed mania possibly caused by family discord.

PID 329.003.00089 (95004404-1)

Reporter Attribution for Primary AE:	POSSIBLY RELATED/ SUSPECTED
Reason for Seriousness:	HOSPITALIZATION REQUIRED

PID 329.003.00248 (97013994-1)

Primary Adverse Experience: **WITHDRAWAL SYNDROME (MIGRAINE HEADACHE)**

Demography: Age: 14 YEARS Date of Birth: 07-JAN-82 Sex: Female
Height: 65.5 in Weight: 120.8 lbs Race: Caucasian

Country: **United States**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 01-Mar-96 **End: 02-May-96**

AE Remarks:
This 14 year old Caucasian female patient, weight 120.8 lbs, height 65.5 in, was a participant in study 29060/329 for depression/affective disorders. On 01-Mar-96, the patient received her first dose of study medication. She completed the visit on 23-Apr-96. Due to lack of efficacy, it was decided that the patient would not enter the continuation phase of the study.

Per the protocol the patient began down-titration dosing on 23-Apr-1996. Four days after beginning down-titration, the patient noticed her mood declining (non-serious). Two days later on 29-Apr-1996 she developed a migraine headache. The patient took acetaminophen for the pain, and missed two days of school.

The investigator reported that the headache was serious and related to the lowering of her medication (i.e. withdrawal syndrome). Study medication was discontinued on 02-May-96.

Treatment Drugs:	**Start**	**End**
TYLENOL (ACETAMINOPHEN)	29-APR-96	Unknown

Reporter Attribution for Primary AE: DEFINITELY RELATED

Reason for Seriousness: PER CRF

PID 329.003.00250 (96007553-1)

Primary Adverse Experience: **EMOTIONAL LABILITY (OVERDOSE INTENTIONAL/ ASYMPTOMATIC)**

Demography: Age: 15 YEARS Date of Birth: 07-DEC-80 Sex: Female
Height: 64.0 in Weight: 181.5 lbs Race: Black

Country: **United States**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 14-Mar-96 **End: 09-May-96**

AE Remarks:
This 15 year old Black female patient, weight 181.5 lbs, height 64.0 in, was a participant in study 29060/329, for depression/affective disorders. On 14-Mar-96, the patient received her first dose of study medication.

The patient exceeded compliance from 19-Apr-96 through 09-May-96. The overdose was rated by the investigator as serious, moderate in intensity and unrelated to the patient's use of study drug. The patient continued in the study and completed the acute phase week 8 visit on 09-May-96.

Medical History Remarks:
The patient was diagnosed with a major depressive disorder 01-Sep-95.

Reporter Attribution for Primary AE: UNRELATED/NOT RELATED

Reason for Seriousness: OVERDOSE

PID 329.003.00313 (96007544-1)

Primary Adverse Experience: **HALLUCINATIONS (AUDITORY)**

Other Adverse Experience: **EMOTIONAL LABILITY (RISK TO SELF, SUPERFICIAL CUTS)**

Demography: Age: 18 YEARS Date of Birth: 10-FEB-78 Sex: Male
Height: 63.0 in Weight: 174.7 lbs Race - Hispanic

Country: **United States**

Medical History: **Major Depressive Disorder, Overweight, Tuberculosis**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 17-May-96 **End: 28-May-96**

AE Remarks:
This 18 year old Hispanic male patient, weight 174.7 lbs, height 63.0 in, was a participant in study 29060/329 for depression/affective disorders. On 17-May-96, the patient received his first dose of study medication.

On 28-May-96, the patient was hospitalized for psychosis with auditory hallucinations and superficial cuts. A voice commanded him to hurt himself. All the cuts closed without medical attention. The voice also commanded the patient to jump from the roof. Although the patient went to the roof he did not jump. It was determined that the patient was a risk to himself. Study medication was discontinued on admission.

As of 30-May-96, the patient was no longer hearing voices but his depression continues.

In the opinion of the investigator, these events were probably unrelated to the study medication.

Medical History Remarks:
No concomitant medications. No previous history of psychosis.

PID 329.003.00313 (96007544-1)

Reporter Attribution for Primary AE:	PROBABLY UNRELATED/ UNLIKELY
Reason for Seriousness:	HOSPITALIZATION REQUIRED

PID 329.004.00215 (97010925-1)

Primary Adverse Experience: **HALLUCINATIONS (VISUAL), DIZZINESS, NERVOUSNESS, ABNORMAL DREAMS**

Demography:	Age: 14 YEARS	Date of Birth: 24-APR-82	Sex: Female
	Height: 58.3 in	Weight: 97.5 lbs	Race - Oriental

Country: **Canada**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Imipramine**

Start: 20-Mar-97 **End: 28-Apr-97**

AE Remarks:
This 15 year old Oriental female patient, weight 97.5 lbs, height 58.3 in, was a participant in study 29060/329 for depression/affective disorders. On 20-Mar-97, the patient received her first dose of study medication.

On 25-Apr-97, the patient began complaining of visual hallucinations, irritability, dizziness and nightmares. The investigator was notified of these symptoms on 28-Apr-97. Study medication was discontinued on 29-Apr-97. The symptoms cleared on 01-May-97. The patient had also experienced nausea, vomiting, arthralgia, asthenia, and headache which were non-serious, however, led to the patient's withdrawl from study.

In the opinion of the investigator, these symptoms were related to study medication and were also consistent with a central anticholinergic syndrome. The investigator broke the study blind and it was revealed that the patient was taking imipramine.

Concomitant Drugs:	**Start**	**End**
UNKNOWN CHINESE HERBAL TEA	01-NOV-96	11-MAR-97

Reporter Attribution for Primary AE: DEFINITELY RELATED

Reason for Seriousness: DISABLING

PID 329.005.00333 (97005671-1)

Primary Adverse Experience: **EMOTIONAL LABILITY (SUICIDE IDEATION)**

Demography: Age: 16 YEARS Date of Birth: 26-JUN-80 Sex: Female
Height: 64.2 in Weight: 123.6 lbs Race - Caucasian

Country: **United States**

Medical History: **Adenoidectomy, Environmental Allergies, Tonsillectomy**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 23-Jan-97 **End: 24-Feb-97**

AE Remarks:
This 16 year old Caucasian female patient, weight 123.6 lbs, height 64.2 in, was a participant in study 29060/329, for depression/affective disorders.

On 23-Jan-97, the patient received her first dose of study medication.

On 24-Feb-97, the patient became more isolative, sleeping more and not attending to school. The study medication was discontinued on 24-Feb-97 by the patient's mother without the knowledge of the study investigator or coordinator. The patient started Prozac the following day. Four days later, on 28-Feb-97, the patient did not sleep well all night, cried and experienced suicidal intentions. She was subsequently hospitalized for severe suicidal ideation.

In the opinion of the investigator, the suicidal ideations were unrelated to the study medication and could be associated with the patient's primary condition.

Concomitant Drugs:	**Start**	**End**
PROZAC (FLUOXETINE)	25-FEB-97	Unknown
TYLENOL	24-JAN-97	24-JAN-97
ADVIL	14-FEB-97	16-FEB-97
ADVIL	24-FEB-97	24-FEB-97

PID 329.005.00333 (97005671-1)

IMODIUM AD	21-FEB-97	21-FEB-97
ALLERGA	01-JUN-96	Unknown

Reporter Attribution for Primary AE: UNRELATED/NOT RELATED

Reason for Seriousness: HOSPITALIZATION REQUIRED

PID 329.006.00038 (95003398-1)

Primary Adverse Experience: **EMOTIONAL LABILITY (ATTEMPTED SUICIDE, INTENTIONAL OVERDOSE)**

Other Adverse Experience: **HEADACHE, CONSTIPATION, MYALGIA, MYASTHENIA, DIZZINESS**

Demography: Age: 15 YEARS Date of Birth:28-MAR-79 Sex: Female
Height: 67.0 in Weight: 170.7 lbs Race: Caucasian

Country: **United States**

Medical History: **Asthma**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 15-Feb-95 **End: 12-Apr-95**

AE Remarks:
This 16 year old Caucasian female patient, weight 170.7 lbs, height 67.0 in, was a participant in study 29060/329, for depression/affective disorders. On 15-Feb-95, the patient received her first dose of study medication. She completed the week 7 visit of the acute phase on 05-Apr-97.

Following a disagreement with her mother, on 12-Apr-95, the patient intentionally overdosed. She consumed 12 tablets of study drug (level 4), 23 Advil, 12 Ibuprofen 400's, 23 Ibuprofen 600's, 29 "long skinny white pills", 4 Tylenol's and 10 fiorinal tablets. The patient reported headache, constipation, myalgia, myasthenia, and dizziness. The patient was withdrawn from the study on 12-Apr-95, prior to completion of the final study visit.

In the opinion of the investigator, the event was considered unrelated to the study medication.

Concomitant Drugs:	**Start**	**End**
ADVIL (IBUPROFEN)	12-APR-95	12-APR-95
IBUPROFEN 400	12-APR-95	12-APR-95
TYLENOL (ACETAMINOPHEN)	12-APR-95	12-APR-95

PID 329.006.00038 (95003398-1)

FIORINAL (ASPIRIN, CAFFEINE, BUTALBITAL)	12-APR-95	12-APR-95
IBUPROFEN 600	12-APR-95	12-APR-95

Medical History Remarks:
The patient's parents are divorced and there is a history of sexual abuse at the hands of a stepfather. There is also a history of significant disagreements with the mother over the patient's activity.

Reporter Attribution for Primary AE: UNRELATED/NOT RELATED

Reason for Seriousness: OVERDOSE

PID 329.007.00270 (96008934-1)

Primary Adverse Experience: CHEST PAIN, DYSPNEA

Demography: Age: 15 YEARS Date of Birth: 01-DEC-80 Sex: Male
Height: 68.0 in Weight: 134.6 lbs Race: Caucasian

Country: United States

Medical History: Broken left femur, food allergies (dairy), occasional headaches, ringworm, strep throat

Study Diagnosis: Depression/Affective Disorders

Study Drug: Imipramine

Start-09-May-96 End-20-Jun-96

AE Remarks:
This 15 year old Caucasian male patient, weight 134.6 lbs, height 68.0 in, was a participant in study 29060/329, for depression/affective disorders. On 09-May-96, the patient received his first dose of study medication.

On 19-Jun-96, the patient reported severe chest pain, chest tightness and shortness of breath. Study medication was stopped on 20-Jun-96. On 21-Jun-96, the patient reported mild chest tightness and pain.

PID 329.007.00270 (96008934-1)

Concomitant Drugs:	**Start**	**End**
LOTRIMIN CREAM (CLOTRIMAZOLE)	29-APR-96	19-MAY-96
CALAMINE LOTION	17-MAY-97	19-MAY-97
BENEDRYL (DIPHENYDRAMINE HYDROCHLORIDE)	17-MAY-96	19-MAY-96
ANTIFUNGAL CREAM	05-JUL-96	05-JUL-96
ACTIFED SINUS	20-JUL-96	24-JUL-96

Lab Remarks:
Study medication started 09-May-96 at one tablet 2x/day, then 23-May-96 two tablets in the morning and one at night, then beginning 30-May-96 two tablets 2x/day. The patient's blood pressure and pulse were normal. 20-Jun-96 no EKG changes were noted from prior weeks.

Medical History Remarks:
No prior episodes of similar symptoms were reported.

Reporter Attribution for Primary AE: POSSIBLY RELATED/ SUSPECTED

Reason for Seriousness: SIGNIFICANT HAZARD, SIDE EFFECT OR PRECAUTION

PID 329.007.00307 (96010032-1)

Primary Adverse Experience: MACULOPAPULAR RASH

Demography: Age: 15 YEARS Date of Birth: 23-Oct-80 Sex: Female
Height: 61.0 in Weight: 145.6 lbs Race - Caucasian

Country: United States

Medical History: Insomnia, Occasional Headaches, Seasonal Allergies, Sinusitis

Study Diagnosis: Depression/Affective Disorders

Study Drug: Imipramine

Start: 16-MAY-96 End: 20-JUN-96

AE Remarks:
This 15 year old Caucasian female patient, weight 145.6 lb, height 61.0 in, was a participant in study 29060/329 for depression/affective disorders. On 16-May-96, the patient received her first dose of study medication.

On 16-Jun-96, the patient developed a generalized morbilliform rash on her trunk, back, extremities, chest, buttocks, torso and lower neck. Study medication was discontinued on 20-Jun-96 and the patient was treated with diphenhydramine and prednisone. The rash was examined by the investigator and the patient's primary care physician who both reported that the rash was typical to a tricyclic antidepressant allergic reaction.

In the opinion of the investigator, the rash was related to the study medication.

PID 329.007.00307 (96010032-1)

Concomitant Drugs:	**Start**	**End**
ADVIL (IBUPROFEN)	17-MAY-96	17-MAY-96
ADVIL (IBUPROFEN)	29-MAY-96	29-MAY-96
ADVIL (IBUPROFEN)	03-JUN-96	04-JUN-96
AMOXICILLIN	02-JUN-96	07-JUN-96
ACTIFED (PSEUDOEPHEDRINE & TRIPROLIDINE)	15-JUN-96	16-JUN-96
CLARITIN (LORATADINE)	13-JUL-96	20-JUL-96
INHALER	13-JUL-96	20-JUL-96
AUGMENTIN (AMOXICILLIN/ CLAVULANATE)	23-JUL-96	Unknown

Treatment Drugs:	**Start**	**End**
BENADRYL (DIPHENHYDRAMINE)	16-JUN-96	21-JUN-96
PREDNISONE	24-JUN-96	29-JUN-96

Medical History Remarks:
Phase I study medication: two tablets/day 16-May-96 to 30-May-96, two tablets in am and one tablet at bedtime 30-May to 06-Jun-96, two tablets 2x/day 06-Jun-96 to 20-Jun-96. Concomitant medications: Advil 200 mg as needed 17-May-96 to 04-Jun-96 for headaches; Amoxicillin 500 mg 02-Jun-96 to 07-Jun-96 for sinusitis; Actifed 2 tablets 15-Jun-96 to 16-Jun-96 for airborn allergies; Benedryl 150 mg po and Prednisone 5-30 mg po for rash; Claritin 2 tabs po and inhaler nasal for sinuses; Augmentin 875 mg po for sinus infection.

Reporter Attribution for Primary AE: DEFINITELY RELATED

Reason for Seriousness: SIGNIFICANT HAZARD

PID 329.009.00201 (96004543-1)

Primary Adverse Experience: **AGITATION, HOSTILITY, PARANOID REACTION**

Demography:	Age: 14 YEARS	Date of Birth: 11-NOV-81	Sex: Male
	Height: 67.0 in	Weight: 151.6 lbs	Race: Caucasian

Country: **United States**

Medical History: **Fever, headache, strep throat, tonsillitis**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 06-Feb-96 **End: 04-Apr-96**

AE Remarks:
This 14 year old Caucasian male patient, weight 151.6 lb, height 67.0 in, was a participant in study 29060/329, for depression/affective disorders. On 06-Feb-96, the patient received his first dose of study medication.

On 31-Mar-96, the patient had an episode of extreme anger and agitation that lasted two to three hours. On 03-Apr-96, the patient again became very angry and agitated. He got into a physical fight with his brother. He was later admitted to a psychiatric unit. The patient also had a weight gain at week 8 of 13 lbs from baseline. On 04-Apr-96, his medication was discontinued.

In the opinion of the investigator, the events could be associated with the patient's primary condition and is possibly related to the study medication.

PID 329.009.00201 (96004543-1)

Concomitant Drugs:	**Start**	**End**
AUGMENTIN (AMOXICILLIN/ CLAVULANATE POTASSIUM)	01-APR-96	Unknown
AUGMENTIN (AMOXICILLIN/ CLAVULANATE POTASSIUM)	28-JAN-96	Unknown
CODIMAL DH	01-APR-96	Unknown
PROZAC (FLUOXETINE)	12-APR-96	Unknown
TRAZADONE	12-APR-96	Unknown
ENTEX LA (PHENYLPROPAN-OLAMINE HYDROCHLORIDE)	07-APR-96	Unknown
TYLENOL (ACETAMINOPHEN)	28-JAN-96	Unknown

Treatment Drugs:	**Start**	**End**
DROPERIDOL	08-APR-96	08-APR-96
LOXITANE (LOXAPINE SUCCINATE)	08-APR-96	08-APR-96

Medical History Remarks:
Concomitant medication: Augmentin 250 mg tid for tonsilitis and Codimal DH one teaspoon four to five times daily. Tylenol 650 mg prn for fever.

Reporter Attribution for Primary AE: POSSIBLY RELATED/ SUSPECTED

Reason for Seriousness: HOSPITALIZATION REQUIRED

PID 329.009.00240 (97005670-1)

Primary Adverse Experience: DEPRESSION, INSOMNIA

Demography:	Age: 14 YEARS	Date of Birth: 25-JAN-82	Sex: Male
	Height: 67.7 in	Weight: 167.6 lbs	Race: Caucasian

Country: **United States**

Medical History: **Headaches, Meningitis, Sleep Disturbance**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Paroxetine**

Start: 14-Jan-97 **End: 05-Mar-97**

AE Remarks:
This 15 year old male patient, weight 167.6 lb, height 67.7 in, was a participant in study 29060/329 for depression/affective disorders.

On 14-Jan-97, the patient received his first dose of study medication.

On 02-Mar-97, the patient experienced severe worsening of depression with worsening sleep disturbance and an inability to function with normal activities of daily living resulting in hospitalization. He was treated with Effexor, Trazodone, and Ritalin. The study medication was discontinued on 05-Mar-97 due to worsening of depression. A phone call to the site revealed that the patient was receiving Paxil at level 5. Patient was released from "day treatment" on 30-Apr-97 but the worsening depression is ongoing per investigator.

The investigator reported that the worsening of depression is unrelated to the study medication but could be associated with the patient's primary condition. Insomnia was reported as possibly related.

Concomitant Drugs:	**Start**	**End**
ADVIL (IBUPROFEN)	01-JAN-97	Unknown

PID 329.009.00240 (97005670-1)

Treatment Drugs:	Start	End
EFFEXOR (VENLAFAXINE HYDROCHLORIDE)	14-MAR-97	24-MAR-97
EFFEXOR (VENLAFAXINE HYDROCHLORIDE)	24-MAR-97	Unknown
TRAZODONE	25-MAR-97	Unknown
RITALIN (METHYLPHENIDATE HYDROCHLORIDE)	Unknown	Unknown

Medical History Remarks:
Patient has a prior history of hospitalization for school refusal and sleep disturbance which began on 01-Oct-96, prior to study medication administration.

Reporter Attribution for Primary AE: UNRELATED/NOT RELATED

Reason for Seriousness: HOSPITALIZATION REQUIRED

PID 329.012.00217 (96008957-1)

Primary Adverse Experience: DEPRESSION (WORSENING)

Demography:	Age: 14 YEARS	Date of Birth: 24-OCT-81	Sex: Female
	Height: 61.4 in	Weight: 109.8 lbs	Race: Caucasian

Country: **Canada**

Medical History: **Asthma, Cold, Headache, Ligament Tears (Left Foot And Ankle), Mononucleosis (Episode One), Mononucleosis (Episode Two)**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Placebo**

Start: 21-May-96 **End: 14-Jun-96**

AE Remarks:
This 14 year old Caucasian female patient, weight 109.8 lbs, height 61.4 in, was a participant in study 29060/329 for depression/affective disorders. On 21-May-96, the patient received her first dose of study medication.

On 15-Jun-96, the patient was diagnosed with the flu (non-serious, unrelated to the study medication). However, study medication was discontinued on 14-Jun-96, 1 day before flu was diagnosed reportedly due to the patient's ambivalence about medication, viral illness, and desire to know which medication she was on. On 19-Jun-96, the patient was hospitalized with worsening depression. She exhibited extreme hopelessness (without suicidality), misery and family conflict. The patient was started on sertraline.

In the opinion of the investigator, worsening depression was unrelated to the study medication.

PID 329.012.00217 (96008957-1)

Concomitant Drugs:	**Start**	**End**
ROBITUSSIN (GUAIFENESIN & GLYCERYL GUIAIACOLATE)	10-JUN-96	12-JUN-96
SINUTAB	05-JUN-96	05-JUN-96
PEPTO BISMOL	18-JUN-96	19-JUN-96
PULMICORT	18-JUN-96	19-JUN-96
TYLENOL (ACETAMINOPHEN)	01-MAR-96	Unknown

Treatment Drugs:	**Start**	**End**
ZOLOFT (SERTRALINE HYDROCHLORIDE)	19-JUN-96	Unknown

Reporter Attribution for Primary AE: UNRELATED/NOT RELATED

Reason for Seriousness: HOSPITALIZATION REQUIRED

PID 329.012.00223 (96014423-1)

Primary Adverse Experience: **WORSENING DEPRESSION, EMOTIONAL LABILITY (SELF MUTILATION), HYPERTENSION**

Demography:	Age: 13 YEARS	Date of Birth: 06-JUL-83	Sex: Female
	Height: 61.8 in	Weight: 194.7 lbs	Race - Caucasian

Country: **Canada**

Medical History: **Allergies, Brochospasm, Fatty Infiltration (Clinically Normal), Headaches (Frequent), History Of High Average/Borderline High Blood Pressure, Lump In Left Foot (Benign), Pyelonephritis, Radial Fracture, Urinary Tract Infection (Frequent)**

Study Diagnosis: **Depression/Affective Disorders**

Study Drug: **Imipramine**

Start: 30-Aug-96 **End: 12-Oct-96**

AE Remarks:
This 13 year old Caucasian female patient, weight 194.7 lbs, height 61.8 in, was a participant in study 29060/329 for adolescent depression.

The patient received her first dose and last dose of study 29060/329 medication on the 30-Aug-96 and 12-Oct-96, respectively.

On the 29-Sep-96, the patient experienced depression and self mutilation for which she was hospitalized. On the 30-Sep-96, as part of a routine assessment, it was noted that the patient had high blood pressure (142/114 to 150/112) but at the time of reporting it had returned to a normal of 120/90.

In the evening of the 01-Oct-96, the patient started down level titration at level 3. Then on the 12-Oct-96, she decided to stop taking study medication and she eventually withdrew from the study on the 16-Oct-96.

PID 329.012.00223 (96014423-1)

In the investigator's opinion, the events were considered to be unrelated to the study medication.

Concomitant Drugs:	**Start**	**End**
FLONASE (FLUTICASONE)	15-MAY-96	Unknown
SODIUM CROMOGLYCATE	15-MAY-96	Unknown
TYLENOL (ACETAMINOPHEN)	1994	Unknown

Lab Test Code/Name	**Date**	**Lab Value**	**Units**	**Normal Range**
ALAT	23-Aug-96	67	U/L	0-48 U/L
ASAT	23-Aug-96	44	U/L	0-41 U/L
CREATININE	23-Aug-96	.7	MG/DL	0.8-1.5 MG/DL

Medical History Remarks:
Medical history: major depression disorder and pyelonephritis since 1995 and is ongoing. Concomitant medication: Flonase one puff inhalation as required for bronchospasm, sodium cromoglycate 2 drops in eye prn for allergic reaction, Tylenol 500 mg prn for headache.

Reporter Attribution for Primary AE: UNRELATED/NOT RELATED

Reason for Seriousness: HOSPITALIZATION REQUIRED

Table 14.9.1

Summary of Adverse Experiences Leading to Withdrawal during Acute 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 :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	10	10.8%	32	33.7%	6	6.9%	48	17.5%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Body as a Whole	2	2.2	7	7.4	1	1.1	10	3.6
ABNORMAL LABORATORY VALUE	0	0.0	1	1.1	0	0.0	1	0.4
ASTHENIA	0	0.0	2	2.1	0	0.0	2	0.7
CHEST PAIN	0	0.0	2	2.1	0	0.0	2	0.7
HEADACHE	2	2.2	1	1.1	0	0.0	3	1.1
INFECTION	0	0.0	0	0.0	1	1.1	1	0.4
TRAUMA	0	0.0	2	2.1	0	0.0	2	0.7
Cardiovascular System	1	1.1	13	13.7	2	2.3	16	5.8
ARRHYTHMIA	0	0.0	1	1.1	0	0.0	1	0.4
AV BLOCK	1	1.1	1	1.1	0	0.0	2	0.7
BUNDLE BRANCH BLOCK	0	0.0	0	0.0	1	1.1	1	0.4
ELECTROCARDIOGRAM ABNORMAL	0	0.0	1	1.1	0	0.0	1	0.4
EXTRASYSTOLES	0	0.0	1	1.1	0	0.0	1	0.4
HYPERTENSION	0	0.0	1	1.1	0	0.0	1	0.4
POSTURAL HYPOTENSION	0	0.0	2	2.1	0	0.0	2	0.7
QT INTERVAL PROLONGED	0	0.0	2	2.1	0	0.0	2	0.7
TACHYCARDIA	0	0.0	8	8.4	1	1.1	9	3.3
Digestive System	2	2.2	8	8.4	1	1.1	11	4.0
CONSTIPATION	1	1.1	1	1.1	0	0.0	2	0.7
DIARRHEA	1	1.1	0	0.0	0	0.0	1	0.4
DRY MOUTH	0	0.0	1	1.1	0	0.0	1	0.4
DYSPEPSIA	0	0.0	1	1.1	0	0.0	1	0.4
GASTROENTERITIS	0	0.0	1	1.1	0	0.0	1	0.4
NAUSEA	1	1.1	5	5.3	1	1.1	7	2.5
ULCERATIVE STOMATITIS	0	0.0	1	1.1	0	0.0	1	0.4
VOMITING	1	1.1	3	3.2	1	1.1	5	1.8
Musculoskeletal System	1	1.1	1	1.1	0	0.0	2	0.7
ARTHRALGIA	0	0.0	1	1.1	0	0.0	1	0.4
MYALGIA	1	1.1	0	0.0	0	0.0	1	0.4
MYASTHENIA	1	1.1	0	0.0	0	0.0	1	0.4
Nervous System	8	8.6	7	7.4	2	2.3	17	6.2
ABNORMAL DREAMS	0	0.0	1	1.1	0	0.0	1	0.4
AGITATION	1	1.1	0	0.0	0	0.0	1	0.4
DEPRESSION	2	2.2	0	0.0	0	0.0	2	0.7
DIZZINESS	1	1.1	5	5.3	1	1.1	7	2.5
EMOTIONAL LABILITY	3	3.2	1	1.1	0	0.0	4	1.5

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TOTAL NUMBER OF PATIENTS :	93	100.0%	95	100.0%	87	100.0%	275	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	10	10.8%	32	33.7%	6	6.9%	48	17.5%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
HALLUCINATIONS	1	1.1	1	1.1	0	0.0	2	0.7
HOSTILITY	2	2.2	1	1.1	0	0.0	3	1.1
MANIC REACTION	2	2.2	0	0.0	1	1.1	3	1.1
NERVOUSNESS	0	0.0	2	2.1	0	0.0	2	0.7
PARANOID REACTION	1	1.1	0	0.0	0	0.0	1	0.4
SOMNOLENCE	0	0.0	1	1.1	0	0.0	1	0.4
Respiratory System	0	0.0	2	2.1	0	0.0	2	0.7
DYSPNEA	0	0.0	2	2.1	0	0.0	2	0.7
Skin and Appendages	0	0.0	4	4.2	1	1.1	5	1.8
ACNE	0	0.0	1	1.1	0	0.0	1	0.4
MACULOPAPULAR RASH	0	0.0	2	2.1	1	1.1	3	1.1
RASH	0	0.0	1	1.1	0	0.0	1	0.4
Special Senses	0	0.0	1	1.1	0	0.0	1	0.4
MYDRIASIS	0	0.0	1	1.1	0	0.0	1	0.4
Urogenital System	0	0.0	3	3.2	0	0.0	3	1.1
URINARY RETENTION	0	0.0	2	2.1	0	0.0	2	0.7
URINATION IMPAIRED	0	0.0	1	1.1	0	0.0	1	0.4

Confidential

SmithKline Beecham

Paroxetine

BRL-029060

Adverse Experiences Leading to Withdrawal Patient Narratives

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Table 14.9.1a

SB Document Number: BRL-029060/RSD-100TWZ/1

PID 329.001.00061

Primary Adverse Experience:	**QT INTERVAL PROLONGED (widened corrected QT interval)**
Other Adverse Experience:	**DRY MOUTH** **DYSPHAGIA (difficulty swallowing 1 hour duration after awakening)** **CONCENTRATION IMPAIRED** **DIZZINESS (dizziness upon getting up suddenly)** **INSOMNIA (middle insomnia)** **TREMOR (hand tremors)** **PHARYNGITIS (sore throat 1 hour duration after awakening)**

Demography:	Age: 16 yrs	Date of Birth: 27-Aug-77	Sex: Female
	Height: 61 in	Weight: 145 lbs	Race: Caucasian

Country: United States

Medical History: Headaches, insomnia, repeated sinus infections (approximately monthly), foot turned at birth and casted (1977), respiratory difficulties at birth (1977), repeated strep throat infections (1978), tonsillectomy (1989)

Study Diagnosis: MAJOR DEPRESSIVE DISORDER

Study Drug: **Imipramine**

Start: 29-Jul-94

End: 14-Sep-94

PID 329.001.00061

AE Remarks: This 16 year old female was randomized to imipramine 50mg/day on 29-Jul-94. Patient was then up-titrated to 100mg/day the following week, to 150mg/day the third week, and to 200mg/day beginning the fourth week in study.

During the seventh week in study (day 35) the patient was seen to have widened QTc (0.48) and QRS (0.12). In the investigator's opinion the event was mild and related to study medication. No corrective therapy was required.

The patient was withdrawn from the study due to this event. Other adverse experiences in the investigator's opinion related to study medication consisted of fatigue/tiredness of mild intensity starting 30-Jul-94, decreased concentration of moderate intensity from 30-Jul-94 to 11-Aug-94, dry mouth of mild intensity starting 11-Aug-94, dizziness upon getting up suddenly of mild intensity from 06-Aug-94, seven episodes of insomnia (middle) of mild intensity starting 18-Aug-94, and four episodes of hand tremors of mild intensity starting 25-Aug-94. In addition, decreased concentration of mild intensity starting 01-Sep-94, in the investigator's opinion probably unrelated to study medication, and difficulty swallowing with sore throat of mild intensity for 1 hour after awakening was, in the investigator's opinion, possibly related to study medication.

Patient also experienced a vital sign of potential clinical concern at week 2 consisting of a high standing pulse rate of 124 bpm. Pulse returned to normal for remainder of trial.

Concomitant Drugs:
None

PID 329.001.00063

Primary Adverse Experience:	**MANIC REACTION**
Other Adverse Experience:	**ABDOMINAL PAIN (stomache ache)** **DECREASED APPETITE** **DIARRHEA** **DIZZINESS** **EAR PAIN** **NAUSEA** **PARESTHESIA (tingling legs and feet)** **PHARYNGITIS** **TENDINOUS DISORDER (pain in left wrist)** **TRAUMA (left wrist)** **TREMOR (tremors and trembling jaw)**

Demography:	Age: 14 yrs	Date of Birth: 12-Aug-80	Sex: Female
	Height: 70 in	Weight: 177.5 lbs	Race: Caucasian

Country:	**United States**
Medical History:	**Acne, allergy to pollen, headaches, pain in left wrist (possible sprain), slight obesity**
Study Diagnosis:	**MAJOR DEPRESSIVE DISORDER**
Study Drug:	**Paroxetine**
Start:	**08-Nov-94**
End:	**25-Dec-94**

AE Remarks: This 14 year old female was randomized to paroxetine 20mg on 08-Nov-94.

After 5 weeks on study medication the patient was withdrawn because of mania symptoms of moderate intensity which, in the investigator's opinion, were possibly related to study medication. No corrective therapy was required.

PID 329.001.00063

Other adverse experiences of mild intensity which, in the investigator's opinion, were possibly related to study medication were: three episodes of diarrhea over 14 days, five episodes of stomach ache over 7 days, two episodes of tingling in the leg and feet over 7 days, three episodes of trembling jaw over 7 days, one episode of dizziness lasting 5 minutes, anorexia of unstated duration, stomach ache/nausea of unstated duration, and three episodes of tremors of unstated duration. Adverse experiences which, in the investigator's opinion, were unrelated to study medication were mild pain in the left wrist lasting 12 days, sore throat of moderate intensity lasting 9 days, and right earache of moderate intensity lasting 9 days.

Concomitant Drugs:	**Start**	**Stop**
Benadryl (diphenhydramine HCl)	01-Sep-83	continuing
Actifed (pseudoephedrine HCl + triprolidine HCl)	01-Sep-83	continuing
Tylenol (acetaminophen)	01-Sep-90	continuing
Amoxicillin	06-Dec-94	16-Dec-94

PID 329.001.00066

Primary Adverse Experience:	**TACHYCARDIA**
Other Adverse Experience:	**ABNORMAL VISION (blurred vision when reading for long time)** **DECREASED APPETITE** **DIZZINESS** **HEADACHE** **NAUSEA**

Demography:	Age: 17 yrs	Date of Birth: 16-Feb-77	Sex: Female
	Height: 68 in	Weight: 142 lbs	Race: Caucasian

Country: **United States**

Medical History: **Headaches, acne (mild), raised mole (benign) on left knee, stomach aches, mole excised below umbilicus (1984), sutures in chin (1980)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **22-Nov-94**

End: **13-Dec-94**

AE Remarks: This 17 year old female was randomized to imipramine 50mg/day on 22-Nov-94. Patient was uptitrated to 100mg/day the following week. Beginning the third week the patient developed tachycardia (standing pulse 124bpm).

This patient was withdrawn and took her last dose of study medication on 13-Dec-94 because of increased heart rate of moderate intensity which, in the investigator's opinion, was related to study medication. No corrective therapy was required.

PID 329.001.00066

Other adverse experinces of mild intensity considered by the investigator to be possibly related to study medication were: two episodes of headache from 23-Nov-94 to 27-Nov-94, nausea from 23-Nov-94 to 05-Dec-94, decrease in appetite starting 23-Nov-94, three episodes of blurred vision when reading a long time starting 02-Dec-94, and one episode of dizziness lasting 5 minutes on 02-Dec-94.

Concomitant Drugs:	**Start**	**Stop**
Alka-Selzer (acetylsalycylic acid))	21-Nov-92	continuing
Tylenol (acetaminophen)	21-Nov-92	continuing

PID 329.001.00067

Primary Adverse Experience: **POSTURAL HYPOTENSION, DIZZINESS**
Other Adverse Experience: **SOMNOLENCE**

Demography: Age: 14 yrs | Date of Birth: 25-May-80 | Sex: Male
Height: 64.5 in | Weight: 105.5 lbs | Race: Caucasian

Country: **United States**

Medical History: **None**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **22-Nov-94**

End: **13-Dec-94**

AE Remarks: This 14 year old male was randomized to imipramine 50mg/day on 22-Nov-94. The patient was up-titrated to 100mg/day the following week. On day 9 of the trial the patient developed faintness, hypersomnia, and postural hypotension. After being on study medication for 22 days the patient was withdrawn for faintness/postural hypotention of moderate intensity which, in the investigator's opinion, was possibly related to study medication. No corrective therapy was required.

Other adverse experiences were five episodes of mild hypersomnia beginning on 30-Nov-94 which were, in the investigator's opinion, possibly related to study medication.

Concomitant Drugs:
None

PID 329.001.00070

Primary Adverse Experience:	**TACHYCARDIA**
Other Adverse Experience:	**SYNCOPE (faintness upon standing)** **VASODILATATION (hot flashes)** **DRY MOUTH** **NAUSEA** **AGITATION (increased agitation)** **INSOMNIA (middle, terminal insomnia)** **TREMOR (hand tremors)**

Demography:	Age: 12 yrs	Date of Birth: 02-Sep-82	Sex: Male
	Height: 58 in	Weight: 76 lbs	Race: Caucasian

Country: **United States**

Medical History: **Allergies to caffeine, chocolate and mold, enlarged lymph nodes, headaches, bruised foot (1990), bruised hand (1993), ear infections (1983), sinus infections (1991), sprained ankle (1992), sprained foot (1990)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **22-Feb-95**

End: **24-Mar-95**

AE Remarks: This 12 year old male was randomized to imipramine 50mg/day on 22-Feb-95. The patient was up-titrated to 100mg/day the following week and to 150mg/day beginning day 15.

This patient was withdrawn after 31 days because of an increased pulse rate (≥110 bpm) for 2 consecutive weeks which, in the investigator's opinion, was severe and related to study medication. No corrective therapy was required.

PID 329.001.00070

Other adverse experiences of mild intensity which, in the investigator's opinion, were possibly related to study medication were nausea from 23-Feb-95 to end of study, hand tremors from 23-Feb-95 to end of study, three episodes of faintness upon standing from 10-Mar-95 to end of study. Adverse experiences of mild intensity which, in the investigator's opinion, were probably unrelated to study medication were insomnia (middle) from 22-Feb-95 to 09-Mar-95, increased agitation from 28-Feb-95 to end of study, and two episodes of hot flashes on 01-Mar-95. Mild dry mouth from 08-Mar-95 to end of study was, in the investigator's opinion, related to study medication.

Concomitant Drugs:
None

PID 329.001.00205

Primary Adverse Experience: **MANIC REACTION (mania and hypomania symptoms)**

Other Adverse Experience: **DECREASED APPETITE**

Demography: Age: 12 yrs | Date of Birth: 03-Nov-83 | Sex: Male
Height: 60.3 in | Weight: 132.3 lbs | Race: Caucasian

Country: **United States**

Medical History: **Sinus congestion, facial lacerations due to dog bite (1986), plastic surgery for facial scars (1994)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Paroxetine**

Start: **07-Feb-96**

End: **14-Feb-96**

AE Remarks: This 12 year old male was randomized to paroxetine 20mg/day on 07-Feb-96. After being in the study 8 days he was withdrawn because of severe symptoms of mania and hypomania starting on 10-Feb-96, which were, in the investigator's opinion, possibly related to study medication. No corrective therapy was required. Slight decrease in appetite of mild intensity starting on 09-Feb-96 to end of study was also reported and was, in the investigator's opinion, possibly related to study medication.

Concomitant Drugs:
None

PID 329.002.00050

Primary Adverse Experience:	**POSTURAL HYPOTENSION (dizziness with orthostatic hypotension)** **TACHYCARDIA** **URINATION IMPAIRED (urinary hesitancy)**
Other Adverse Experience:	**FEVER** **HEADACHE** **COUGH INCREASED (coughing)** **PHARYNGITIS (sore throat)**

Demography:	Age: 16 yrs	Date of Birth: 03-Jul-78	Sex: Male
	Height: 67.5 in	Weight: 152.15 lbs	Race: Caucasian

Country: **United States**

Medical History: **Acne, intermittently decreased glucose, congenital anomalies (hypospadias [male] and left ureteral duplication, 1978), right vesicoureteral reflux (1978)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **23-Mar-95**

End: **26-Apr-95**

AE Remarks: This 16 year old male was randomized to imipramine 50mg/day on 23-Mar-95. Patient was up-titrated to 100mg/day the following week and to 150mg/day beginning the third week. Within the first two weeks of treatment the patient developed mild dizziness with orthostatic hypotension, heart rate increase of moderate intensity, and mild urinary hesitancy. In the investigator's opinion, these adverse experiences were possibly related to study medication. Patient was withdrawn from the study after 4 weeks due to these events. No corrective therapy was required.

PID 329.002.00050

Other adverse experiences which were, in the investigator's opinion, probably unrelated to study medication were: moderate fever from 23-Mar-95 to 28-Mar-95, moderate sore throat from 23-Mar-95 to 28-Mar-95, mild headache from 23-Mar-95 to 27-March-95, and continuous mild coughing from 23-Mar-95 to 03-Apr-95.

Concomitant Drugs:	**Start**	**Stop**
Cleocin (clindamycin phosphate) lotion	01-Jan-92	continuing
Minocycline	01-Jan-92	continuing
Aspirin	26-Mar-95	26-Mar-95
Aleve (naproxen sodium)	27-Mar-95	28-Mar-95
Amoxicillin	27-Mar-95	08-Apr-95

PID 329.002.00056

Primary Adverse Experience: TACHYCARDIA

Demography:	Age: 17 yrs	Date of Birth: 09-Jul-76	Sex: Female
	Height: 59.4 in	Weight: 111 lbs	Race: Caucasian

Country: **United States**

Medical History: **Pregnancy and miscarriage (1994)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **19-Jul-94**

End: **23-Aug-94**

AE Remarks: This 17 year old female patient was randomized to imipramine 50mg/day on 19-Jul-94. The patient was up-titrated to 200mg/day in 50 mg/week increments by week 4. Patient developed tachycardia during the third week and investigator reduced dose to 150mg/day beginning week 5. Tachycardia persisted and patient was withdrawn due to increased heart rate of mild intensity and, in the investigator's opinion, possibly related to study medication. No corrective therapy was required.

There were vital signs of clinical concern consisting of a high sitting pulse rate at week 3 of 132 bpm and a high standing pulse rate at week 4 of 140 bpm.

Concomitant Drugs:
None

PID 329.002.00243

Primary Adverse Experience:	**TRAUMA (dizziness, hit head during fall)**
Other Adverse Experience:	**ABDOMINAL PAIN (stomach aches)** **ASTHENIA (tiredness and drowsiness)** **POSTURAL HYPOTENSION** **CONSTIPATION** **NAUSEA** **TREMOR ([worsening] entire body shakes and shaky hands)** **RASH**

Demography:	Age: 15 yrs	Date of Birth: 07-Jan-81	Sex: Female
	Height: 62 in	Weight: 112.5 lbs	Race: Caucasian

Country: **United States**

Medical History: **Headaches, shakiness, sore throat due to tonsillitis**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **14-Mar-96**

End: **05-Apr-96**

AE Remarks: This 15 year old female was randomized to imipramine 50mg/day on 14-Mar-96. Patient was up-titrated to 100mg/day the second week and to 150 mg/day beginning the third week. This patient was withdrawn approximately 3 weeks after the start of study medication because of dizziness of moderate intensity starting 17-Mar-96 and resulting in a fall on 1-Apr-96. In the investigator's opinion, the dizziness was possibly related to study medication. No corrective therapy was required.

PID 329.002.00243

Other adverse experiences consisted of mild nausea and stomach ache starting 21-Mar-96 to end of study and considered by the investigator to be related to study medication, and moderate tiredness and drowsiness starting 14-Mar-96 to end of study and severe constipation reported 04-Apr-96 considered by the investigator possibly related to study medication.

Concomitant Drugs:	**Start**	**Stop**
Pen-Vee-K (penicillin V potassium)	14-Mar-96	21-Mar-96
Benadryl (diphenhydramine HCl)	17-Mar-96	24-Mar-96
Caladryl (calamine) lotion	17-Mar-96	24-Mar-96
Tylenol (acetaminophen)	04-Apr-96	04-Apr-96

PID 329.002.00322

Primary Adverse Experience: **Orthostatic changes (Arrythmia, Dizziness)**
Other Adverse Experiences: **Abdominal pain**

Demography: Age: 14 yrs Date of Birth: 27-Aug-82 Sex: Male
Height: 68.5 in Weight: 136.0 lbs Race: Caucasian

Country: **United States**

Medical History: **None**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **09-Jan-97**

End: **23-Feb-97**

AE Remarks: This 16 year old female was randomized to imipramine 50mg/day on 9-Jan-97. By week 4 the dose was up-titrated to 200mg/day in 50mg/week increments. This patient was withdrawn for orthostatic changes which began in week 5, were moderate in intensity, and in the investigator's opinion, were possibly related to study medication. No corrective therapy was required.

Other adverse experiences consisted of dizziness, which began 3 days after the start of study medication, was moderate in intensity and and stomach ache, which began on 21-Jan-97, lasted 2 hours,and was moderate in intensity.

PID 329.002.00322

No corrective therapy was required. In the investigator's opinion, both the dizziness and stomach ache were probably unrelated to study medication. A mild stomach ache recurred on 06-Feb-97 and lasted until 25-Feb-97, when the patient was withdrawn. In the investigator's opinion, the recurring stomach ache was possibly related to study medication. No corrective therapy was required. Vital signs of potential clinical concern occurred at week 1 consisting of a high standing pulse rate of 130 bpm, at week 8 consisting of low standing systolic blood pressure 0f 88 mmHg, and at week 5 consisting of a high standing pulse rate of 132 bpm.

Concomitant Drugs:
None

PID 329.003.00073

Primary Adverse Experience:	**VOMITING**
Other Adverse Experience:	**GASTROINTESTINAL DISORDER (nausea, vomiting, headaches, diarrhea [gastrointestinal illness])** **POSTURAL HYPOTENSION**

Demography:	Age: 16 yrs	Date of Birth: 26-Jun-78	Sex: Female
	Height: 63.8 in	Weight: 138.92 lbs	Race: Caucasian

Country: **United States**

Medical History: **Sprained ankle**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **19-Jan-95**

End: **04-Mar-95**

AE Remarks: This 16 year old female was randomized to imipramine 50mg/day on 19-Jan-95. The patient was up-titrated to 250mg/day by week 6 in 50mg/week increments. This patient was withdrawn approximately 7 weeks after the start of study medication for severe vomiting which, in the opinion of the investigator, was possibly related to study medication. Corrective therapy consisted of Bentyl taken for 2 days.

Other adverse experiences were moderate orthostatic symptoms starting 03-Feb-95 and continuing to the end of the study and, in the investigator's opinion, possibly related to study medication; nausea and vomiting of moderate intensity in the investigator's opinion, unrelated to study medication; headaches and diarrhea of moderate intensity, unrelated to study medication.

PID 329.003.00073

There were vital signs of clinical concern consisting of high standing pulse rates at week 3 of 132 bpm, week 5 of 130 bpm, week 6 of 128 bpm, and week 7 of 140 bpm. At week 7, the patients weight was 127.82 lbs, representing a decrease of 10.78 lbs from baseline weight of 138.60 lbs.

Concomitant Drugs:	**Start**	**Stop**
Pain medication (nos)	08-Jan-95	continuing
Dexatrim (phenylprooanolamine HCl)	31-Jan-95	03-Feb-95
Bentyl (dicyclomine HCl)	04-Mar-95	06-Mar-95

PID 329.003.00088

Primary Adverse Experience: **URINARY RETENTION**

Other Adverse Experiences: **POSTURAL HYPOTENSION, CONSTIPATION, DRY MOUTH, DIZZINESS, ABNORMAL VISION, TASTE PERVERSION**

Demography:	Age: 15 yrs	Date of Birth: 17-SEP-79	Sex: Female
	Height: 132.7 cm	Weight: 50.1 kg	Race: Caucasian

Country: **United States**

Study Diagnosis: **DEPRESSION/AFFECTIVE DISORDERS**

Study Drug: **Imipramine**

Start: **28-FEB-95**

End: **09-APR-95**

AE Remarks: This 15 year old female was randomized to imipramine 50mg/day on 28-Feb-95. Dose was up-titrated to 200mg/day by week 4 in 50mg/week increments. Patient experienced severe urinary retention starting 2 weeks after the start of study medication until her withdrawal. In the investigator's opinion, the adverse event was related to the study medication.

Other adverse events considered possibly related to study medication included mild orthostatic hypotension, constipation, dry mouth, blurred vision, and bad taste. A longstanding symptom of dizziness was present during the study and rated as probably unrelated to study medication.

Concomitant Drugs:
None

PID 329.003.00290

Primary Adverse Experience: **HYPERTENSION**
TACHYCARDIA
Other Adverse Experiences: **DRY MOUTH**

Demography:	Age: 17 yrs	Date of Birth: 19-Jul-78	Sex: Male
	Height: 66.1 in	Weight: 176.18 lbs	Race: Hispanic

Country: **United States**

Medical History: **Nearsightedness, frequent sore throats (1994), tonsillectomy and adenoidectomy (1994)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **11-Mar-96**

End: **22-Mar-96**

AE Remarks: This 17 year old male was randomized to imipramine 50mg/day on 11-Mar-96. The dose was up-titrated to 100mg/day on day 10. The same day it was discovered that the patient had developed hypertention. The patient was withdrawn on day 12 because of mild hypertension which, in the investigator's opinion, was possibly related to study medication. At baseline, his blood pressure was 122/70 sitting and 128/72 standing. On day 10 his standing blood pressure was 160/86. On day 12 his blood pressure was 135/70 sitting and 160/88 standing. No corrective therapy was required.

PID 329.003.00290

Other adverse experiences were mild dry mouth starting 12-Mar-96 and continuing to the end of study and in the investigator's opinion, probably unrelated to study medication and mild tachycardia starting 20-Mar-96 and continuing to end of study which was, in the investigator's opinion, possibly related to study medication.

Concomitant Drugs:
None

PID 329.004.00014

Primary Adverse Experience:	**NAUSEA (retching)**
Other Adverse Experience:	**CONSTIPATION** **DYSPHAGIA (lump in the throat)** **POLYURIA** **RESPIRATORY DISORDER (common cold)**

Demography:	Age: 14 yrs	Date of Birth: 15-Sep-80	Sex: Male
	Height: 72.8 in	Weight: 145.31 lbs	Race: Caucasian

Country: **Canada**

Medical History: **None**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **29-Nov-94**

End: **13-Dec-94**

AE Remarks: This 14 year-old male patient on imipramine 100mg/day was withdrawn because of retching of moderate intensity that occurred 1 week after the start of study medication and was, in the investigator's opinion, possibly related to study medication. No corrective therapy was required.

Other adverse experiences consisted of constipation and dysphagia, both in the investigator's opinion, related to study medication. Two reports of nausea, one lasting 3 days of moderate intensity, the other of unknown duration of severe intensity, and mild polyuria lasting 1 day, all, in the investigator's opinion, were possibly related to study medication. A mild cold lasting 6 days was treated with Vitamin C and, unrelated to study medication in the investigator's opinion.

PID 329.004.00014

Concomitant Drugs:	**Start**	**Stop**
Vitamin C (ascorbic acid)	24-Nov-94	continuing

PID 329.004.00211

Primary Adverse Experience:	**TRAUMA (mouth cuts)** **ULCERATIVE STOMATITIS (mouth sores)** **DRY MOUTH** **GASTROENTERITIS**
Other Adverse Experience:	**POSTURAL HYPOTENSION** **DIZZINESS** **HYPERTONIA (stiff neck)** **TREMOR** **HEADACHE**

Demography:	Age: 18 yrs	Date of Birth: 30-Aug-77	Sex: Female
	Height: 63 in	Weight: 102.53 lbs	Race: Caucasian

Country: **Canada**

Medical History: **None**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **02-Feb-96**

End: **21-Mar-96**

AE Remarks: This 18 year old female was randomized to imipramine 50mg/day on 02-Feb-96. Dose was up-titrated to 200mg/day by week 4 in 50mg/week increments. The patient was withdrawn approximately 7 weeks after the start of study medication because of severe mouth sores and cuts, dry mouth, nausea/vomiting, diarrhea, dehydration, dizziness, and sweating and moderate tremors. In the investigator's opinion, the mouth sores and cuts and dry mouth were related to study medication, the dizziness and tremors were possible related, and the sweating, nausea/vomiting, diarrhea, and dehydration were unrelated to study medication. Corrective therapy consisted of an analgesic for the mouth sores, intravenous fluids for dehydration, Immodium for diarrhea, an antiemetic for nausea/vomiting, and an antibiotic for diarrhea.

PID 329.004.00211

Other adverse experiences consisted of three reports of dry mouth (one mild, one moderate, one severe), with the first occurrence considered by the investigator as possibly related to study medication and the second and third occurrences related to study medication; three reports of orthostatic hypotension (two mild, one moderate), with the first occurrence considered possibly related to study medication and the second and third occurrences related; two reports of tremors (one mild, one moderate), both considered to be possibly related to study medication; two reports of dizziness (one mild, one severe), the first considered related to study medication and the second possibly related; headache over a 15-day period of moderate severity and considered by the investigator as probably unrelated to study medication; and mild stiff neck for 16 days, considered probably unrelated to study medication. No corrective therapy was instituted, except for Tylenol for the headache.

Concomitant Drugs:	**Start**	**Stop**
Vitamin C	unknown	continuing
Vitamin B complex	unknown	continuing
Antiemetic, nos	21-Mar-96	22-Mar-96
Imodium (loperamide HCl)	21-Mar-96	22-Mar-96
Intravenous fluids	21-Mar-96	22-Mar-96
Analgesic, nos	21-Mar-96	22-Mar-96
Antibiotic, nos	22-Mar-96	23-Mar-96

PID 329.005.00003

Primary Adverse Experience:	**TACHYCARDIA ("racing heart")**
Other Adverse Experience:	**DIZZINESS**
	HEADACHE
	SWEATING
	TREMOR (shakiness)
	SWEATING

Demography:	Age: 13 yrs	Date of Birth: l6-Aug-81	Sex: Female
	Height: 60 in	Weight: 116.5 lbs	Race: Caucasian

Country: **United States**

Medical History: **Environmental allergies, history of heart murmur**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **20-Sep-94**

End: **04-Oct-94**

AE Remarks: This 13 year old female was randomized to imipramine 50mg/day on 20-Sep-94. Dose was up-titrated to 100mg/day the following week. The patient developed tachycardia three days later and was withdrawn 15 days after starting study. The investigator considered the racing heart beat moderate in intensity and related to study medication. No corrective therapy was required.

Other adverse experiences consisted of moderate dizziness and shakiness for 10 days and, in the investigator's opinion, possibly related to study medication. No corrective therapy was required.

Concomitant Drugs:	**Start**	**Stop**
Naldecon (chlorpheniramine maleate + phenylephrine HCl + phenylpropanolamine HCl)	unknown	continuing
Tussi-Organidin (guiafenesin + codeine phosphate)	unknown	continuing

PID 329.005.00005

Primary Adverse Experience: **TACHYCARDIA**
Other Adverse Experience: **ASTHENIA (slightly tired)**
DIZZINESS (slightly dizzy)

Demography: Age: 13 yrs | Date of Birth: 28-May-81 | Sex: Female
Height: 60.5 in | Weight: 111.57 lbs | Race: Caucasian

Country: **United States**

Medical History: **None**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Placebo**

Start: **01-Nov-94**

End: **09-Nov-94**

AE Remarks: This 13 year old female was randomized to placebo on 01-Nov-94. Patient was withdrawn 9 days after the start of study medication due to elevated heart rate (136bpm-standing) of moderate intensity.

Other adverse experiences consisted of feeling slightly dizzy and slightly tired from 03-Nov-94 to 16-Nov-94; both were mild in intensity. In the investigator's opinion, these adverse experiences were possibly related to the study drug.

Concomitant Drugs:
None

PID 329.005.00110

Primary Adverse Experience: **UNINTENDED PREGNANCY**
Other Adverse Experience: **DIZZINESS**

Demography:	Age: 17 yrs	Date of Birth: 17-Nov-77	Sex: Female
	Height: 67 in	Weight: 123.5 lbs	Race: Black

Country: **United States**

Medical History: **Asthma (1984)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **11-Jan-95**

End: **19-Jan-95**

AE Remarks: This 17 year old female was randomized to imipramine 50mg/day on 11-Jan-95. This patient was withdrawn as a result of a positive pregnancy test. Study medication was tapered and stopped with the last dose on 19-Jan-95 and the last visit on 25-Jan-95 (week 2).

An adverse experience of mild dizziness lasting 5 minutes was reported on 15-Jan-95 which, in the investigator's opinion, was possibly related to study medication.

Concomitant Drugs:
None

PID 329.005.00113

Primary Adverse Experience:	**EMOTIONAL LABILITY (suicidal ideation)**
Other Adverse Experience:	**HEADACHE, TACHYCARDIA (questionable), DRY MOUTH, DIZZINESS, TREMORS (hand tremors), ABNORMAL VISION (blurred vision), PALPITATION**

Demography:	Age: 15 yrs	Date of Birth: 12-Mar-79	Sex: Female
	Height: 67 in	Weight: 145 lbs	Race: Black

Country: **United States**

Medical History: **Asthma, abortion (1994)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **30-Jan-95**

End: **02-Mar-95**

AE Remarks: This 15 year old female was randomized to imipramine 50mg/day on 30-Jan-95. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4. Study medication was stopped on day 32 because of suicidal ideation with gesture considered to be of moderate severity. In the investigator's opinion, the event was unrelated to study medication.

Other adverse experiences consisted of severe headache starting 31-Jan-95 and lasting 3.45 hours and considered by the investigator to be unrelated to study medication; mild blurred vision, dizziness, and tremor starting 06-Feb-95 of unknown duration, moderate dry mouth starting 05-Feb-95 of unknown duration, and moderate palpitation and tachycardia starting 19-Feb-95 and lasting 30 minutes, all considered related to study medication.

PID 329.005.00113

Concomitant Drugs:	**Start**	**Stop**
Ventolin (albuterol sulfate)	01-Apr-85	Continuing
Tylenol (acetaminophen)	31-Jan-95	31-Jan-95

PID 329.005.00152

Primary Adverse Experience: **HEADACHE**
DIARRHEA
NAUSEA
VOMITING

Demography: Age: 15 yrs | Date of Birth:17-Sep-80 | Sex: Female
Height: 66 in | Weight: 128 lbs | Race: Caucasian

Country: **United States**

Medical History: **Broken arm (1985)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Paroxetine**

Start: **26-Oct-95**

End: **30-Oct-95**

AE Remarks: This patient was randomized to paroxetine 20mg/day on 26-Oct-95 but was withdrawn five days later due to severe nausea, vomiting, diarrhea, and headache. No corrective therapy was required. In the investigator's opinion, these adverse experiences were related to study medication.

Concomitant Drugs:
None

PID 329.006.00040

Primary Adverse Experience: **ASTHENIA (fatigue)**
CONSTIPATION
DYSPEPSIA (indigestion)
DIZZINESS
NERVOUSNESS (irritable mood)
MYDRIASIS
URINARY RETENTION
TACHYCARDIA

Demography: Age: 18 yrs Date of Birth: 05-Dec-76 Sex: Female
Height: 63.4 in Weight: 102.75 lbs Race: Caucasian

Country: **United States**

Medical History: **Allergies, ovarian cyst**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **16-Feb-95**

End: **01-Mar-95**

AE Remarks: This 18 year old female was randomized to imipramine 50mg/day on 16-Feb-95. Dose was up-titrated the second week to 100mg/day. This patient was withdrawn 2 weeks after the start of study medication because of moderate eye dilation, dizziness, severe fatigue, elevated heart rate, indigestion, irritable mood, urinary retention and constipation, and severe fatigue. In the investigator's opinion, all of these adverse experiences were related to study medication, except for indigestion, which was possibly related. No corrective therapy was required.

There were vital signs of clinical concern at week 2 consisting of a high sitting pulse rate of 132 bpm and standing pulse rate of 140 bpm.

PID 329.006.00040

Concomitant Drugs:	**Start**	**Stop**
Loestrin (ethinyl estradiol + norethindrone acetate)	15-Dec-94	continuing
Baclofen	01-Jan-85	continuing
Vancenase (beclomethasone dipropionate)	01-Jan-85	continuing
Ventolin (albuterol +sulfate)	01-Jan-85	continuing

PID 329.007.00139

Primary Adverse Experience: **DYSPNEA (shortness of breath)**
CHEST PAIN

Demography: Age: 12 yrs Date of Birth: 11-Nov-82 Sex: Female
Height: 56.5 in Weight: 78 lb Race: Caucasian

Country: **United States**

Medical History: **Fractured right arm (1995)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **08-May-95**

End: **25-May-95**

AE Remarks: This 12 year old female was randomized to imipramine 50mg/day on 08-May-95. Dose was up-titrated to 100mg/day the following week. On day 10 patient developed moderate chest pain and mild shortness of breath considered to be possibly related to study medication by the investigator. This patient was withdrawn on day 18 due to these events. No corrective therapy was required.

Concomitant Drugs:
None

PID 329.007.00141

Primary Adverse Experience: **ANGINA PECTORIS (angina on exertion)**

Demography: Age: 13 yrs Date of Birth: 13-Sep-82 Sex: Male
Height: 66 in Weight: 181 lbs Race: Caucasian

Country: **United States**

Medical History: **Angina (1995), insomnia (1994), Eustachian tube placement (1982), hypertension (1994)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Placebo**

Start: **21-Sep-95**

End: **12-Oct-95**

AE Remarks: This 13 year old male was randomized to placebo on 21-Sep-95. This patient was withdrawn on day 22 due to angina on exertion of moderate intensity which, in the investigator's opinion, was probably unrelated to study medication. Angina was present prior to study start and continued during study. No corrective therapy was required.

Concomitant Drugs:
None

PID 329.007.00143

Primary Adverse Experience: ACNE

Demography:	Age: 13 yrs	Date of Birth: 14-May-82	Sex: Female
	Height: 63 in	Weight: 212 lbs	Race: Caucasian

Country: **United States**

Medical History: **Cold symptoms, mild obesity, hospitalization for depression (1994), urinary tract infection (1994)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **09-Nov-95**

End: **01-Dec-95**

AE Remarks: This 13 year old female was randomized to imipramine 50mg/day on 09-Nov-95. Dose was up-titrated to 100mg/day the following week. This patient was withdrawn on day 23 because of acne of moderate intensity which began on day 7, and was, in the investigator's opinion, possibly related to study medication. No corrective therapy was required.

Concomitant Drugs:	**Start**	**Stop**
Tylenol (acetaminophen)	08-Nov-95	09-Nov-95

PID 329.007.00269

Primary Adverse Experience:	**TACHYCARDIA** **ELECTROCARDIOGRAM ABNORMALITY (low or negative T-waves)**
Other Adverse Experience:	**TRAUMA (foot pain [injury])** **NAUSEA**

Demography:	Age: 15 yrs	Date of Birth: 20-May-80	Sex: Male
	Height: 68 in	Weight: 239 lbs	Race: Caucasian

Country: **United States**

Medical History: **Headaches (occasional), recurrent sinusitis due to seasonal allergies, upset stomach, Achilles tendon casted for 6 weeks (1994), bilateral hernia repair (1980), Sever's disease (1994)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **11-Apr-96**

End: **25-Apr-96**

AE Remarks: This patient was randomized to imipramine 50mg/day on 11-Apr-96. Dose was up-titrated to 100mg/day the following week. This patient was withdrawn on day 15 because of mild tachycardia and low or negative T waves which, in the investigator's opinion, were related to study medication. No corrective therapy was required.

Other adverse experiences consisted of mild foot pain related to an injury and lasting 2 days which was, in the investigator's opinion, unrelated to study medication; and mild nausea lasting 1 day which was, in the investigator's opinion, possibly related to study medication

PID 329.007.00269

Concomitant Drugs:	**Start**	**Stop**
Pepcid AC (famotidine)	01-Jan-96	continuing
Pseudoephedrine	01-Jan-96	continuing
Tylenol (acetaminophen), prn	unknown	continuing
Tylenol (acetaminophen)	21-Apr-96	21-Apr-96

PID 329.009.00127

Primary Adverse Experience:	**NAUSEA**
Other Adverse Experience:	**CHEST PAIN (chest pain when taking meds)** **DIZZINESS** **HEADACHE (occasional)** **INSOMNIA (initial insomnia)** **SOMNOLENCE (daytime drowsiness)**

Demography:	Age: 12 yrs	Date of Birth: 13-Aug-82	Sex: Female
	Height: 58 in	Weight: 79.9 lbs	Race: Hispanic

Country: **United States**

Medical History: **Initial insomnia, separation anxiety**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **10-Apr-95**

End: **26-May-95**

AE Remarks: This 12 year old female patient was randomized to imipramine 50mg/day on 10-Apr-95. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4. Approximately 7 weeks after the start of study medication the patient was withdrawn for noncompliance secondary to mild nausea. In the investigator's opinion, the nausea was related to study medication. No corrective therapy was required.

PID 329.009.00127

Other adverse experiences consisted of initial insomnia lasting 45 days of moderate intensity and, in the investigator's opinion, possibly related to study medication; and dizziness lasting 38 days of moderate intensity and, in the investiator's opinion, related to study medication. These adverse experiences did not require corrective therapy.

Concomitant Drugs:
None

PID 329.009.00128

Primary Adverse Experience: **BUNDLE BRANCH BLOCK (right bundle branch block)**

Demography: Age: 13 yrs Date of Birth: 08-Jul-81 Sex: Male
Height: 62.2 in Weight: 114.88 lbs Race: Caucasian

Country: **United States**

Medical History: **Generalized anxiety, seasonal allergies, attention deficit disorder (1994)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Placebo**

Start: **11-Apr-95**

End: **02-May-95**

AE Remarks: This 13 year old male was randomized to placebo on 11-Apr-95. Patient was withdrawn on day 22 because of mild right bundle branch which, in the opinion of the investigator, was possibly related to study medication. No corrective therapy was required.

Concomitant Drugs:	**Start**	**Stop**
Dimetapp (brompheniramine maleate + phenylpropanolamine HCl), prn	01-Jan-93	continuing

PID 329.009.00171

Primary Adverse Experience:	**MACULOPAPULAR RASH (rash [fine macular, on face, inside elbows, back])**
Other Adverse Experience:	**PHARYNGITIS (sore throat)** **SINUSITIS (sinus congestion)**

Demography:	Age: 16 yrs	Date of Birth: 23-Sep-79	Sex: Female
	Height: 62 in	Weight: 200.6 lbs	Race: Caucasian

Country: **United States**

Medical History: **Allergic to iodine, sexual assault (1992), pregnancy and childbirth (1994), previous suicide attempt (1994), weight loss (planned, approximately 52 lbs, 1995)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **07-Nov-95**

End: **14-Nov-95**

AE Remarks: This 16 year old female was randomized to imipramine 50mg/day on 07-Nov-95. This patient was withdrawn 8 days later due to a severe macular rash on the face, inside of the elbows, and back which, in the investigator's opinion, was probably unrelated to study medication. No corrective therapy was required.

Other adverse experiences were mild sore throat and sinus congestion lasting 1 day and, in the investigator's opinion, probably unrelated to study medication. No corrective therapy was required.

Concomitant Drugs:	**Start**	**Stop**
Triphasil (ethinyl estradiol + levonorgestrel))	07-Nov-95	continuing

PID 329.009.00195

Primary Adverse Experience:	**EXTRASYSTOLES (cardiac arrhythmia [premature ventricular contractions])**
Other Adverse Experience:	**CHEST PAIN** **HEADACHE (head pain)** **VASODILATATION (facial flushing)** **WEIGHT LOSS** **DIZZINESS** **SWEATING**

Demography:	Age: 14 yrs	Date of Birth: 22-Jun-81	Sex: Female
	Height: 64 in	Weight: 112.4 lbs	Race: Caucasian

Country: **United States**

Medical History: **Allergies to aspirin and sulfa drugs, asthma, anemia, headaches (occasional), menstrual cramps (occasional), mild obesity**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **15-Dec-95**

End: **19-Jan-96**

AE Remarks: This 14 year old female was randomized to imipramine 50mg/day on 15-Dec-95. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4, however, reduced back to 150mg the following week. Patient was withdrawn approximately 5 weeks after the start of study medication due to cardiac arrhythmia (premature ventricular contractions) of 14 days' duration, which were moderate in intensity and, in the investigator's opinion, related to study medication. No corrective therapy was indicated.

PID 329.009.00195

Other adverse experiences consisted of facial flushing lasting 29 days, dizziness lasting 19 days, sweating lasting 29 days, head pain lasting 20 days, chest pain lasting 18 days ; all of moderate untensity and, in the investigator's opinion, possibly related to study medication; and mild weight loss over 13 days, possibly related to study medication. None of these adverse experiences required corrective therapy.

There was a vital sign of clinical concern consisting of a high standing pulse rate of 129 bpm at week 3.

Concomitant Drugs:	**Start**	**Stop**
Tylenol (acetaminophen), prn	01-Jan-91	continuing
Advil (ibuprofen), prn	01-Jan-91	continuing
Anaprox (naproxen sodium), prn	01-Jan-94	continuing
Proventil (albuterol sulfate) inhaler, prn	01-Jan-95	continuing

PID 329.009.00203

Primary Adverse Experience:	**QT INTERVAL PROLONGED** **ATRIOVENTRICULAR BLOCK (1st degree)**
Other Adverse Experience:	**PALPITATION** **VASODILATATION (hot flashes [facial flushing])** **NAUSEA (nausea when taking PM meds)** **THIRST (increased thirst)**

Demography:	Age: 12 yrs	Date of Birth: 13-Feb-84	Sex: Female
	Height: 57.5 in	Weight: 85.8 lbs	Race: Caucasian

Country: **United States**

Medical History: **Asthma, left axis deviation on EKG, seasonal allergies**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **04-Mar-96**

End: **05-Apr-96**

AE Remarks: This 12 year old female was randomized to imipramine 50mg/day on 04-Mar-96. Dose was uptitrated to 100mg/day the second week and to 150mg/day at the start of the third week. At the same the patient developed first degree AV block with borderline prolonged QT-QTC of moderate intensity and, in the investigator's opinion, related to study medication. Patient was withdrawn from the study due to these events. No corrective therapy was required.

Other adverse experiences were mild thirst, mild nausea when taking pm medications, palpitations of moderate intensity, and hot flashes (facial flushing of moderate intensity. All were, in the investigator's opinion, possibly related to study medication and none required corrective therapy.

PID 329.009.00203

Concomitant Drugs:	**Start**	**Stop**
Allergy shots	01-Jan-94	continuing
Codimal DH (hydrocodone bitartrate + phenyephrine HCl + pyrilamine maleate)	01-Jan-96	continuing
Advil (ibuprofen)	01-Jan-96)	continuing

PID 329.009.00236

Primary Adverse Experience: **DIZZINESS**
SOMNOLENCE (daytime sedation)
Other Adverse Experience: **MIDDLE INSOMNIA**

Demography: Age: 13 yrs Date of Birth: 25-Sep-83 Sex: Female
Height: 63.1 in Weight: 146.9 lbs Race: Caucasian

Country: **United States**

Medical History: **Headaches, menstrual cramps, stomach aches (1996)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **30-Dec-96**

End: **08-Feb-97**

AE Remarks: This 13 year old female was randomized to imipramine 50mg/day on 30-Dec-96. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4. The patient was withdrawn on day 41 for dizziness and daytime sedation, both moderate in intensity, lasting 1 day and, in the investigator's opinion, related to study medication. No corrective therapy was required.

This patient also had middle insomnia of mild intensity lasting 5 days and, in the investigator's opinion, possibly related to study medication. No corrective therapy was required.

There was a clinically significant vital sign abnormality of a high standing pulse of 121 bpm at week 1.

PID 329.009.00236

Concomitant Drugs:	**Start**	**Stop**
Tylenol (acetaminophen)	15-Nov-96	continuing
Midol (ibuprofen)	15-Jul-96	continuing

PID 329.009.00302

Primary Adverse Experience: **MACULOPAPULAR RASH (on wrist, elbows, ankle)**
NODAL ARRHYTHMIA (junctional escape pattern)

Demography: Age: 17 yrs | Date of Birth: 16-Dec-78 | Sex: Male
Height: 68 in | Weight: 157.1 lbs | Race: Caucasian

Country: **United States**

Medical History: **Surgery for abdominal cyst (1990), tendonitis (1996)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Placebo**

Start: **27-Mar-96**

End: **10-Apr-96**

AE Remarks: This 17 year old male patient was randomized to placebo on 27-Mar-96. Patient was withdrawn 2 weeks later for maculopapular rash on wrist, elbows, and ankle of moderate intensity and for mild bradycardia with arrhythmia and junctional escape pattern on EKG, which, in the investigator's opinion, were possibly related to study medication. No corrective therapy was required.

Concomitant Drugs:
None

PID 329.009.00330

Primary Adverse Experience:	**NAUSEA** **DIZZINESS** **VOMITING**
Other Adverse Experience:	**BRADYCARDIA, HEART MALFORMATION,** **SUPRAVENTRICULAR EXTRASYSTOLS**

Demography:	Age: 12yrs	Date of Birth: 25-Feb-84	Sex: Male
	Height: 59.0 in	Weight: 93.5 lbs	Race: Caucasian

Country:	**United States**
Medical History:	**ADHD, broken ear drum, sinus bradycardia with sinus arrhythymia and possible ventricular hypertrophy (1996)**
Study Diagnosis:	**MAJOR DEPRESSIVE DISORDER**
Study Drug:	**Placebo**
Start:	**21-Oct-96**
End:	**04-Nov-96**

AE Remarks: This 12 year old male patient was randomized to placebo on 21-Oct-96. After 2 weeks the patient was withdrawn for nausea and dizziness lasting 15 days of moderate intensity, and two episodes of mild vomiting in 24 hours. The nausea and dizziness, in the investigator's opinion, were related to study medication and vomiting was possibly related. No corrective therapy was required.

Another adverse experience consisted of mild sinus bradycardia with occasional premature atrial complexes and possible left ventricular hypertrophy, which in the investigator's opinion, possibly related to study medication No corrective therapy was required.

PID 329.009.00330

Concomitant Drugs:	**Start**	**Stop**
Augmentin (amoxicillin + clavulanic acid)	01-Oct-96	continuing
Cylert (pemoline)	08-Oct-96	08-Oct-96

PID 329.011.00163

Primary Adverse Experience:	**NAUSEA**
	VOMITING
Other Adverse Experience:	**HEADACHE**
	DIZZINESS
	PHARYNGITIS (sore throat)
	RASH

Demography:	Age: 15 yrs	Date of Birth: 15-Jan-80	Sex: Female
	Height: 58 in	Weight: 136 lbs	Race: Caucasian

Country: **United States**

Medical History: **Migraine headaches, stress-induced asthma, temporomandibular joint syndrome, eye surgery to correct strabismus (1985)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Imipramine**

Start: **25-Nov-95**

End: **22-Dec-95**

AE Remarks: This 15 year old female patient was randomized to imipramine 50mg/day on 25-Nov-95. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4. After 4 weeks the patient was withdrawn for nausea and vomiting lasting 3 days, both of moderate intensity, and possibly related to study medication in the investigator's opinion. No corrective therapy was required.

Other adverse experiences consisted of mild rash of unknown duration, not related to study medication in the investigator's opinion, and treated with oral Benadryl and Benadryl ointment; two occurrences of headache, one of mild intensity, lasting 4 hours, unrelated to study medication, the other occurrence of moderate intensity, lasting 18 hours, probably unrelated to study medication; both occurrences were treated with Tylenol.

PID 329.011.00163

Concomitant Drugs:	**Start**	**Stop**
Ventolin (albuterol sulfate) inhaler	01-Apr-94	continuing
Tylenol (acetaminophen)	23-Nov-95	continuing
Robitussin (guaifenesin)	30-Nov-95	01-Dec-95
Benadryl ointment (diphenhydramine hydrochloride)	21-Nov-95	continuing
Benadryl oral	21-Nov-95	continuing

PID 329.012.00226

Primary Adverse Experience: **AV BLOCK**

Other Adverse Experience: **NAUSEA**
RESPIRATORY DISORDER (cold symptoms [sore throat, cough])

Demography:	Age: 16 yrs	Date of Birth: 27-Nov-80	Sex: Male
	Height: 73.2 in	Weight: 176.4 lbs	Race: Caucasian

Country: **United States**

Medical History: **Recurrent headaches (mild), fractured right leg (1988), eye surgery to correct strabismus (1983)**

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: **Paroxetine**

Start: **03-Dec-96**

End: **20-Dec-96**

AE Remarks: This 16 year old male patient was randomized to paroxetine 20mg/day on 03-Dec-96. On day 18 the patient was withdrawn for PR-prolongation and cardiac conduction delay which was moderate in intensity, and, in the investigator's opinion, possibly related to study medication. No corrective therapy was required.

Other adverse experience consisted of mild cold symptoms (sore throat, cough), lasting 24 days, and, in the investigator's opinion, unrelated to study medication and mild nausea lasting 20 days, probably related to study medication. No treatment was required.

PID 329.012.00226

Concomitant Drugs:
None

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Table 14.9.3

Summary of Adverse Experiences Leading to Withdrawal during Acute 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 :	58	100.0%	56	100.0%	57	100.0%	171	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	0	0.0%	1	1.8%	0	0.0%	1	0.6%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%	N	%	N	%
Urogenital System	0	0.0	1	1.8	0	0.0	1	0.6
UNINTENDED PREGNANCY	0	0.0	1	1.8	0	0.0	1	0.6

Table 14.10.1

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

TREATMENT GROUP: PAROXETINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	39	100.0%	54	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	35	89.7%	51	94.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	18	46.2	32	59.3
ABDOMINAL PAIN	6	15.4	4	7.4
ALLERGIC REACTION	0	0.0	2	3.7
ASTHENIA	6	15.4	4	7.4
BACK PAIN	3	7.7	1	1.9
CHEST PAIN	1	2.6	1	1.9
CHILLS	0	0.0	1	1.9
HEADACHE	10	25.6	22	40.7
INFECTION	5	12.8	5	9.3
TRAUMA	1	2.6	1	1.9
Cardiovascular System	3	7.7	4	7.4
AV BLOCK	0	0.0	1	1.9
MIGRAINE	0	0.0	1	1.9
PALPITATION	1	2.6	0	0.0
POSTURAL HYPOTENSION	0	0.0	1	1.9
SYNCOPE	1	2.6	0	0.0
TACHYCARDIA	1	2.6	1	1.9
Digestive System	20	51.3	30	55.6
CONSTIPATION	1	2.6	4	7.4
DECREASED APPETITE	5	12.8	2	3.7
DIARRHEA	3	7.7	4	7.4
DRY MOUTH	9	23.1	10	18.5
DYSPEPSIA	0	0.0	6	11.1
ESOPHAGITIS	0	0.0	1	1.9
GASTROINTESTINAL DISORDER	0	0.0	2	3.7
INCREASED APPETITE	2	5.1	1	1.9
NAUSEA	9	23.1	13	24.1
TOOTH DISORDER	2	5.1	3	5.6
VOMITING	2	5.1	1	1.9
Hemic and Lymphatic System	1	2.6	1	1.9
ANEMIA	1	2.6	0	0.0
THROMBOCYTHEMIA	0	0.0	1	1.9
Metabolic and Nutritional Disorders	2	5.1	1	1.9
WEIGHT GAIN	1	2.6	0	0.0
WEIGHT LOSS	1	2.6	1	1.9

Table 14.10.1

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

TREATMENT GROUP: PAROXETINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	39	100.0%	54	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	35	89.7%	51	94.4%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Musculoskeletal System	0	0.0	3	5.6
ARTHRALGIA	0	0.0	1	1.9
MYALGIA	0	0.0	3	5.6
MYASTHENIA	0	0.0	1	1.9
Nervous System	27	69.2	29	53.7
ABNORMAL DREAMS	1	2.6	1	1.9
AGITATION	1	2.6	1	1.9
ANXIETY	0	0.0	2	3.7
CONCENTRATION IMPAIRED	1	2.6	0	0.0
DEPRESSION	3	7.7	1	1.9
DIZZINESS	11	28.2	11	20.4
EMOTIONAL LABILITY	1	2.6	5	9.3
EUPHORIA	1	2.6	0	0.0
HALLUCINATIONS	0	0.0	1	1.9
HOSTILITY	5	12.8	2	3.7
HYPERKINESIA	0	0.0	1	1.9
HYPERTONIA	1	2.6	0	0.0
INSOMNIA	9	23.1	5	9.3
MANIC REACTION	2	5.1	0	0.0
MYOCLONUS	1	2.6	1	1.9
NERVOUSNESS	4	10.3	4	7.4
PARANOID REACTION	1	2.6	0	0.0
PARESTHESIA	1	2.6	0	0.0
PERSONALITY DISORDER	1	2.6	0	0.0
SOMNOLENCE	9	23.1	7	13.0
TREMOR	4	10.3	6	11.1
WITHDRAWAL SYNDROME	1	2.6	0	0.0
Respiratory System	12	30.8	17	31.5
ASTHMA	0	0.0	1	1.9
BRONCHITIS	0	0.0	2	3.7
COUGH INCREASED	2	5.1	3	5.6
DYSPNEA	1	2.6	1	1.9
LARYNX DISORDER	0	0.0	1	1.9
PHARYNGITIS	4	10.3	1	1.9
RESPIRATORY DISORDER	5	12.8	5	9.3
RHINITIS	2	5.1	5	9.3
SINUSITIS	2	5.1	4	7.4

Table 14.10.1

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

TREATMENT GROUP: PAROXETINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	39	100.0%	54	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	35	89.7%	51	94.4%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Skin and Appendages		7	17.9	5	9.3
ACNE		1	2.6	2	3.7
FUNGAL DERMATITIS		1	2.6	0	0.0
PHOTOSENSITIVITY		1	2.6	0	0.0
RASH		2	5.1	2	3.7
SKIN DISORDER		1	2.6	0	0.0
SWEATING		0	0.0	1	1.9
URTICARIA		1	2.6	0	0.0
Special Senses		3	7.7	4	7.4
ABNORMAL VISION		0	0.0	1	1.9
CONJUNCTIVITIS		1	2.6	2	3.7
EAR PAIN		1	2.6	0	0.0
OTITIS MEDIA		1	2.6	1	1.9
Urogenital System		3	7.7	1	1.9
CYSTITIS		0	0.0	1	1.9
URINARY TRACT INFECTION		1	2.6	0	0.0
URINE ABNORMALITY		2	5.1	0	0.0

Table 14.10.1

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

TREATMENT GROUP: IMIPRAMINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	38	100.0%	57	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	34	89.5%	56	98.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	18	47.4	35	61.4
ABDOMINAL PAIN	5	13.2	2	3.5
ABNORMAL LABORATORY VALUE	1	2.6	0	0.0
ALLERGIC REACTION	0	0.0	1	1.8
ASTHENIA	3	7.9	4	7.0
BACK PAIN	0	0.0	2	3.5
CHEST PAIN	4	10.5	1	1.8
CHILLS	1	2.6	2	3.5
FEVER	0	0.0	2	3.5
HEADACHE	11	28.9	27	47.4
INFECTION	1	2.6	4	7.0
TRAUMA	0	0.0	3	5.3
Cardiovascular System	13	34.2	28	49.1
ARRHYTHMIA	1	2.6	0	0.0
AV BLOCK	2	5.3	0	0.0
BUNDLE BRANCH BLOCK	1	2.6	0	0.0
ELECTROCARDIOGRAM ABNORMAL	1	2.6	2	3.5
EXTRASYSTOLES	1	2.6	1	1.8
HEART MALFORMATION	1	2.6	0	0.0
HYPERTENSION	1	2.6	1	1.8
MIGRAINE	0	0.0	1	1.8
PALPITATION	1	2.6	2	3.5
POSTURAL HYPOTENSION	3	7.9	10	17.5
QT INTERVAL PROLONGED	1	2.6	2	3.5
SYNCOPE	1	2.6	3	5.3
TACHYCARDIA	5	13.2	13	22.8
VASODILATATION	3	7.9	3	5.3
Digestive System	19	50.0	45	78.9
CONSTIPATION	3	7.9	6	10.5
DECREASED APPETITE	0	0.0	2	3.5
DIARRHEA	0	0.0	3	5.3
DRY MOUTH	12	31.6	31	54.4
DYSPEPSIA	2	5.3	7	12.3
DYSPHAGIA	1	2.6	2	3.5
ESOPHAGITIS	1	2.6	0	0.0
GASTRITIS	0	0.0	1	1.8
GASTROENTERITIS	0	0.0	1	1.8
GASTROINTESTINAL DISORDER	0	0.0	1	1.8

Table 14.10.1

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

TREATMENT GROUP: IMIPRAMINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	38	100.0%	57	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	34	89.5%	56	98.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
INCREASED APPETITE	0	0.0	1	1.8
NAUSEA	12	31.6	11	19.3
TOOTH DISORDER	0	0.0	2	3.5
ULCERATIVE STOMATITIS	0	0.0	1	1.8
VOMITING	3	7.9	5	8.8
Hemic and Lymphatic System	0	0.0	2	3.5
EOSINOPHILIA	0	0.0	1	1.8
LEUKOPENIA	0	0.0	1	1.8
Metabolic and Nutritional Disorders	2	5.3	2	3.5
HYPERGLYCEMIA	0	0.0	1	1.8
THIRST	1	2.6	1	1.8
WEIGHT LOSS	1	2.6	0	0.0
Musculoskeletal System	1	2.6	0	0.0
ARTHRALGIA	1	2.6	0	0.0
Nervous System	25	65.8	45	78.9
ABNORMAL DREAMS	3	7.9	1	1.8
AGITATION	2	5.3	0	0.0
AMNESIA	0	0.0	1	1.8
CONCENTRATION IMPAIRED	0	0.0	1	1.8
DEPERSONALIZATION	0	0.0	1	1.8
DEPRESSION	1	2.6	0	0.0
DIZZINESS	16	42.1	29	50.9
DRUG DEPENDENCE	0	0.0	1	1.8
EMOTIONAL LABILITY	2	5.3	1	1.8
EUPHORIA	0	0.0	1	1.8
HALLUCINATIONS	1	2.6	0	0.0
HOSTILITY	2	5.3	1	1.8
HYPERKINESIA	1	2.6	1	1.8
HYPERTONIA	0	0.0	1	1.8
HYPESTHESIA	0	0.0	1	1.8
INSOMNIA	4	10.5	9	15.8
MYOCLONUS	0	0.0	1	1.8
NERVOUSNESS	1	2.6	5	8.8
SOMNOLENCE	9	23.7	4	7.0
THINKING ABNORMAL	2	5.3	0	0.0
TREMOR	2	5.3	12	21.1

Table 14.10.1

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

TREATMENT GROUP: IMIPRAMINE

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	38	100.0%	57	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	34	89.5%	56	98.2%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Respiratory System	6	15.8	20	35.1
COUGH INCREASED	1	2.6	2	3.5
DYSPNEA	1	2.6	3	5.3
EPISTAXIS	0	0.0	1	1.8
PHARYNGITIS	1	2.6	11	19.3
RESPIRATORY DISORDER	2	5.3	5	8.8
RHINITIS	2	5.3	1	1.8
SINUSITIS	0	0.0	2	3.5
Skin and Appendages	4	10.5	10	17.5
ACNE	1	2.6	1	1.8
CONTACT DERMATITIS	0	0.0	1	1.8
FUNGAL DERMATITIS	0	0.0	1	1.8
MACULOPAPULAR RASH	0	0.0	2	3.5
PRURITUS	0	0.0	1	1.8
RASH	1	2.6	2	3.5
SWEATING	2	5.3	4	7.0
URTICARIA	0	0.0	1	1.8
Special Senses	5	13.2	9	15.8
ABNORMAL VISION	2	5.3	5	8.8
EAR PAIN	1	2.6	1	1.8
KERATOCONJUNCTIVITIS	0	0.0	1	1.8
MYDRIASIS	0	0.0	1	1.8
PHOTOPHOBIA	0	0.0	1	1.8
TASTE PERVERSION	1	2.6	2	3.5
TINNITUS	1	2.6	1	1.8
Urogenital System	4	10.5	5	8.8
CYSTITIS	0	0.0	1	1.8
NOCTURIA	0	0.0	1	1.8
POLYURIA	1	2.6	0	0.0
URINARY FREQUENCY	1	2.6	0	0.0
URINARY RETENTION	1	2.6	2	3.5
URINATION IMPAIRED	2	5.3	1	1.8

Table 14.10.1

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

TREATMENT GROUP: PLACEBO

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	33	100.0%	54	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	27	81.8%	42	77.8%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
Body as a Whole	20	60.6	32	59.3
ABDOMINAL PAIN	2	6.1	8	14.8
ALLERGIC REACTION	0	0.0	3	5.6
ASTHENIA	4	12.1	6	11.1
BACK PAIN	2	6.1	8	14.8
CHEST PAIN	1	3.0	1	1.9
FEVER	3	9.1	1	1.9
HEADACHE	12	36.4	22	40.7
INFECTION	5	15.2	4	7.4
PAIN	1	3.0	2	3.7
TRAUMA	3	9.1	3	5.6
Cardiovascular System	6	18.2	5	9.3
ARRHYTHMIA	1	3.0	0	0.0
AV BLOCK	0	0.0	2	3.7
BRADYCARDIA	1	3.0	0	0.0
BUNDLE BRANCH BLOCK	1	3.0	0	0.0
HEART MALFORMATION	1	3.0	0	0.0
NODAL ARRHYTHMIA	0	0.0	1	1.9
POSTURAL HYPOTENSION	0	0.0	1	1.9
SUPRAVENTRICULAR EXTRASYSTOLES	1	3.0	0	0.0
SYNCOPE	0	0.0	1	1.9
TACHYCARDIA	1	3.0	0	0.0
VASODILATATION	2	6.1	0	0.0
Digestive System	15	45.5	26	48.1
CONSTIPATION	1	3.0	3	5.6
DECREASED APPETITE	2	6.1	2	3.7
DIARRHEA	2	6.1	5	9.3
DRY MOUTH	3	9.1	9	16.7
DYSPEPSIA	2	6.1	2	3.7
GASTROINTESTINAL DISORDER	1	3.0	0	0.0
INCREASED APPETITE	0	0.0	1	1.9
NAUSEA	6	18.2	11	20.4
TOOTH DISORDER	1	3.0	1	1.9
ULCERATIVE STOMATITIS	0	0.0	1	1.9
VOMITING	1	3.0	5	9.3
Hemic and Lymphatic System	2	6.1	2	3.7
EOSINOPHILIA	1	3.0	0	0.0

Table 14.10.1

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

TREATMENT GROUP: PLACEBO

AGE	<15		>=15	
TOTAL NUMBER OF PATIENTS :	33	100.0%	54	100.0%
PATIENTS WITH ADVERSE EXPERIENCES :	27	81.8%	42	77.8%
ADECS BODY SYSTEM : PREFERRED TERM	N	%	N	%
LYMPHADENOPATHY	1	3.0	0	0.0
THROMBOCYTHEMIA	0	0.0	1	1.9
WBC ABNORMALITY	0	0.0	1	1.9
Metabolic and Nutritional Disorders	3	9.1	3	5.6
HYPERGLYCEMIA	1	3.0	0	0.0
THIRST	1	3.0	2	3.7
WEIGHT LOSS	1	3.0	1	1.9
Musculoskeletal System	2	6.1	4	7.4
ARTHRALGIA	1	3.0	3	5.6
MYALGIA	1	3.0	1	1.9
Nervous System	12	36.4	17	31.5
ABNORMAL DREAMS	0	0.0	2	3.7
ANXIETY	0	0.0	2	3.7
DEPERSONALIZATION	0	0.0	1	1.9
DEPRESSION	1	3.0	1	1.9
DIZZINESS	8	24.2	8	14.8
EMOTIONAL LABILITY	0	0.0	1	1.9
EUPHORIA	1	3.0	0	0.0
HYPERKINESIA	1	3.0	0	0.0
HYPERTONIA	1	3.0	0	0.0
INSOMNIA	1	3.0	3	5.6
MANIC REACTION	1	3.0	0	0.0
NERVOUSNESS	2	6.1	3	5.6
SOMNOLENCE	1	3.0	2	3.7
TREMOR	0	0.0	2	3.7
Respiratory System	12	36.4	17	31.5
ASTHMA	1	3.0	0	0.0
BRONCHITIS	0	0.0	4	7.4
COUGH INCREASED	3	9.1	3	5.6
DYSPNEA	1	3.0	0	0.0
PHARYNGITIS	5	15.2	3	5.6
RESPIRATORY DISORDER	4	12.1	7	13.0
RHINITIS	3	9.1	2	3.7
SINUSITIS	2	6.1	5	9.3
Skin and Appendages	3	9.1	5	9.3

Table 14.10.1

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

TREATMENT GROUP: PLACEBO

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	33	100.0%	54	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	27	81.8%	42	77.8%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
ACNE		0	0.0	1	1.9
CONTACT DERMATITIS		1	3.0	0	0.0
HERPES ZOSTER		0	0.0	1	1.9
MACULOPAPULAR RASH		0	0.0	1	1.9
RASH		1	3.0	2	3.7
SWEATING		1	3.0	0	0.0
Special Senses		1	3.0	2	3.7
ABNORMAL VISION		1	3.0	1	1.9
EYE DISORDER		0	0.0	1	1.9
Urogenital System		1	3.0	1	1.9
ALBUMINURIA		1	3.0	1	1.9
PYURIA		1	3.0	0	0.0

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Table 14.10.2

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

TREATMENT GROUP: PAROXETINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	14	100.0%	21	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%

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Table 14.10.2

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

TREATMENT GROUP: IMIPRAMINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	20	100.0%	19	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%

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Table 14.10.2

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

TREATMENT GROUP: PLACEBO

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	12	100.0%	18	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	0	0.0%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%

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Table 14.10.3

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

TREATMENT GROUP: PAROXETINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	25	100.0%	33	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	1	4.0%	3	9.1%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		1	4.0	3	9.1
AMENORRHEA		0	0.0	1	3.0
BREAST ENLARGEMENT		1	4.0	0	0.0
DYSMENORRHEA		0	0.0	2	6.1
FEMALE GENITAL DISORDERS		0	0.0	1	3.0

Table 14.10.3

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

TREATMENT GROUP: IMIPRAMINE

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	18	100.0%	38	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	0	0.0%	7	18.4%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		0	0.0	7	18.4
DYSMENORRHEA		0	0.0	5	13.2
UNINTENDED PREGNANCY		0	0.0	1	2.6
VAGINAL MONILIASIS		0	0.0	1	2.6

Table 14.10.3

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

TREATMENT GROUP: PLACEBO

AGE		<15		>=15	
TOTAL NUMBER OF PATIENTS	:	21	100.0%	36	100.0%
PATIENTS WITH ADVERSE EXPERIENCES	:	2	9.5%	2	5.6%
ADECS BODY SYSTEM : PREFERRED TERM		N	%	N	%
Urogenital System		2	9.5	2	5.6
DYSMENORRHEA		2	9.5	2	5.6

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Table 14.11

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

Treatment Group=PAROXETINE

N = 93

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Diastolic B.P. - Sitting (mmHg)	Screening	87	68.54	7.69	51.00	90.00
	Baseline	88	67.74	8.68	50.00	98.00
	Week 1	88	67.17	8.90	50.00	86.00
	Week 2	81	68.16	9.03	55.00	90.00
	Week 3	76	67.76	8.64	50.00	90.00
	Week 4	76	68.05	9.34	46.00	90.00
	Week 5	72	67.92	9.23	46.00	91.00
	Week 6	71	67.66	8.38	48.00	82.00
	Week 7	67	67.93	9.16	49.00	90.00
	Week 8	66	67.20	8.05	49.00	80.00
	Endpoint	90	67.52	7.80	49.00	80.00
	Endpoint - Change from Baseline	90	-0.54	9.01	-26.00	20.00
Systolic B.P. - Sitting (mmHg)	Screening	87	112.29	12.24	80.00	148.00
	Baseline	88	110.45	13.67	80.00	144.00
	Week 1	88	111.60	15.75	80.00	152.00
	Week 2	81	111.19	12.73	88.00	145.00
	Week 3	76	111.58	14.63	80.00	153.00
	Week 4	76	112.01	14.46	82.00	160.00
	Week 5	72	109.42	14.13	70.00	138.00
	Week 6	71	111.48	14.61	80.00	148.00
	Week 7	67	110.25	12.77	80.00	137.00
	Week 8	66	110.42	12.20	86.00	136.00
	Endpoint	90	110.38	12.47	86.00	148.00
	Endpoint - Change from Baseline	90	-0.52	12.06	-25.00	30.00
Diastolic B.P. - Standing (mmHg)	Screening	85	71.16	7.98	56.00	90.00
	Baseline	88	69.89	8.91	50.00	95.00
	Week 1	88	68.81	9.58	45.00	96.00
	Week 2	81	69.85	9.00	57.00	92.00
	Week 3	76	69.05	9.03	48.00	87.00
	Week 4	76	69.30	9.81	46.00	91.00
	Week 5	72	69.69	8.34	52.00	85.00
	Week 6	71	69.58	9.17	42.00	90.00
	Week 7	67	68.90	9.76	48.00	90.00
	Week 8	66	69.55	9.15	46.00	90.00
	Endpoint	90	70.04	8.58	46.00	90.00
	Endpoint - Change from Baseline	90	0.13	10.08	-23.00	25.00

Table 14.11

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

Treatment Group=PAROXETINE

N = 93

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Systolic B.P. - Standing (mmHg)	Screening	85	110.75	12.68	80.00	146.00
	Baseline	88	109.42	15.11	80.00	149.00
	Week 1	88	112.20	16.95	80.00	158.00
	Week 2	81	110.51	13.19	84.00	145.00
	Week 3	76	109.63	15.74	78.00	153.00
	Week 4	76	110.08	15.08	77.00	160.00
	Week 5	72	109.19	13.46	80.00	148.00
	Week 6	71	109.24	16.28	58.00	146.00
	Week 7	67	109.52	14.06	78.00	150.00
	Week 8	66	109.86	13.50	80.00	138.00
	Endpoint	90	110.18	13.48	80.00	146.00
	Endpoint - Change from Baseline	90	0.44	12.63	-30.00	30.00
Pulse - Sitting (bpm)	Screening	86	74.78	13.98	54.00	132.00
	Baseline	87	76.91	10.28	60.00	105.00
	Week 1	88	75.58	11.46	57.00	112.00
	Week 2	80	75.80	10.62	52.00	114.00
	Week 3	76	77.68	11.74	54.00	109.00
	Week 4	76	78.17	11.50	59.00	115.00
	Week 5	72	78.43	11.82	50.00	109.00
	Week 6	71	79.55	11.92	60.00	110.00
	Week 7	67	79.70	12.21	54.00	110.00
	Week 8	66	79.30	13.84	49.00	125.00
	Endpoint	90	78.12	12.93	49.00	125.00
	Endpoint - Change from Baseline	90	0.86	12.26	-35.00	22.00
Pulse - Standing (bpm)	Screening	85	81.47	13.78	54.00	115.00
	Baseline	88	84.55	13.72	62.00	132.00
	Week 1	88	82.56	13.13	60.00	133.00
	Week 2	80	80.64	13.71	45.00	126.00
	Week 3	76	85.17	14.40	58.00	135.00
	Week 4	76	85.86	13.89	59.00	120.00
	Week 5	72	87.44	13.95	60.00	125.00
	Week 6	70	87.17	16.21	60.00	133.00
	Week 7	67	85.88	14.73	62.00	128.00
	Week 8	66	86.68	14.09	56.00	125.00
	Endpoint	90	85.83	13.62	56.00	125.00
	Endpoint - Change from Baseline	90	1.07	14.63	-43.00	40.00

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Table 14.11

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

Treatment Group=PAROXETINE

N = 93

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Weight (lbs)	Screening	88	146.27	38.91	74.00	308.26
	Baseline	87	146.49	38.79	74.00	308.80
	Week 1	88	146.53	38.82	72.00	308.00
	Week 2	80	145.91	36.99	71.00	307.80
	Week 3	75	147.50	40.47	72.00	309.50
	Week 4	75	148.16	40.55	72.00	308.30
	Week 5	71	148.34	41.56	73.00	308.40
	Week 6	69	146.68	38.67	70.00	308.90
	Week 7	67	144.88	35.29	72.00	280.00
	Week 8	66	145.04	36.37	73.00	279.00
	Endpoint	90	146.88	38.16	73.00	308.90
	Endpoint - Change from Baseline	90	-0.23	4.56	-11.02	13.00

Table 14.11

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

Treatment Group=IMIPRAMINE

N = 95

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Diastolic B.P. - Sitting (mmHg)	Screening	90	67.69	8.36	45.00	90.00
	Baseline	89	66.88	9.98	40.00	88.00
	Week 1	91	68.41	9.71	44.00	100.00
	Week 2	89	69.74	8.41	50.00	90.00
	Week 3	79	70.18	9.52	49.00	90.00
	Week 4	69	70.10	9.06	50.00	85.00
	Week 5	67	71.31	10.04	50.00	98.00
	Week 6	61	72.10	8.75	46.00	91.00
	Week 7	55	72.02	9.09	53.00	90.00
	Week 8	56	71.45	8.81	52.00	90.00
	Endpoint	94	70.48	8.94	52.00	98.00
	Endpoint - Change from Baseline	94	3.59	9.26	-16.00	27.00
Systolic B.P. - Sitting (mmHg)	Screening	90	110.74	12.49	80.00	140.00
	Baseline	89	109.38	14.20	70.00	170.00
	Week 1	91	110.09	13.63	84.00	150.00
	Week 2	89	109.88	12.59	90.00	139.00
	Week 3	79	111.14	12.58	88.00	145.00
	Week 4	69	110.74	11.92	80.00	137.00
	Week 5	67	113.13	12.54	82.00	147.00
	Week 6	61	113.25	13.11	84.00	144.00
	Week 7	55	111.76	13.24	86.00	152.00
	Week 8	56	110.71	12.31	90.00	139.00
	Endpoint	94	111.27	14.34	84.00	140.00
	Endpoint - Change from Baseline	94	1.81	12.28	-50.00	31.00
Diastolic B.P. - Standing (mmHg)	Screening	88	69.14	8.75	45.00	90.00
	Baseline	88	67.49	9.67	44.00	90.00
	Week 1	91	68.51	9.80	49.00	90.00
	Week 2	89	68.56	9.75	37.00	90.00
	Week 3	77	69.45	9.64	48.00	88.00
	Week 4	69	67.93	10.40	41.00	90.00
	Week 5	66	71.29	11.76	38.00	104.00
	Week 6	61	69.95	9.56	47.00	86.00
	Week 7	55	69.62	10.34	48.00	90.00
	Week 8	56	69.63	11.27	33.00	90.00
	Endpoint	93	69.76	11.30	33.00	104.00
	Endpoint - Change from Baseline	93	2.53	10.24	-40.00	25.00

Table 14.11

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

Treatment Group=IMIPRAMINE

N = 95

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Systolic B.P. - Standing (mmHg)	Screening	88	110.93	13.09	80.00	149.00
	Baseline	88	106.26	13.90	70.00	158.00
	Week 1	91	106.48	12.64	84.00	160.00
	Week 2	89	105.37	13.58	72.00	160.00
	Week 3	78	105.91	12.16	80.00	139.00
	Week 4	69	104.61	13.23	78.00	138.00
	Week 5	66	107.48	13.45	80.00	147.00
	Week 6	61	107.39	12.76	82.00	132.00
	Week 7	55	106.69	11.58	80.00	134.00
	Week 8	56	105.25	13.71	80.00	140.00
	Endpoint	93	105.80	15.15	78.00	160.00
	Endpoint - Change from Baseline	93	-0.44	13.32	-39.00	32.00
Pulse - Sitting (bpm)	Screening	89	74.53	10.95	54.00	103.00
	Baseline	89	76.61	10.51	53.00	102.00
	Week 1	90	85.39	12.48	60.00	129.00
	Week 2	88	87.93	12.80	60.00	132.00
	Week 3	79	91.33	12.46	70.00	132.00
	Week 4	69	91.72	12.41	64.00	120.00
	Week 5	67	90.57	13.34	60.00	116.00
	Week 6	61	91.46	13.56	60.00	137.00
	Week 7	55	93.29	11.34	66.00	131.00
	Week 8	56	91.48	12.06	66.00	120.00
	Endpoint	94	92.10	13.43	66.00	132.00
	Endpoint - Change from Baseline	94	15.39	13.41	-12.00	60.00
Pulse - Standing (bpm)	Screening	88	82.82	13.01	53.00	115.00
	Baseline	88	83.41	11.31	60.00	119.00
	Week 1	90	94.14	16.85	64.00	140.00
	Week 2	88	96.19	16.45	60.00	140.00
	Week 3	77	98.00	16.58	68.00	145.00
	Week 4	69	100.20	16.33	72.00	140.00
	Week 5	64	97.61	15.83	68.00	132.00
	Week 6	61	99.20	14.27	68.00	140.00
	Week 7	55	100.47	16.24	74.00	148.00
	Week 8	56	98.25	15.01	68.00	140.00
	Endpoint	93	101.22	17.26	68.00	148.00
	Endpoint - Change from Baseline	93	17.68	17.19	-22.00	66.00

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Table 14.11

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

Treatment Group=IMIPRAMINE

N = 95

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Weight (lbs)	Screening	91	139.41	36.72	76.00	261.00
	Baseline	87	141.19	37.14	76.00	263.00
	Week 1	91	139.10	37.13	75.00	263.00
	Week 2	88	137.97	37.08	74.00	266.00
	Week 3	79	138.37	36.32	74.00	259.00
	Week 4	69	138.16	35.03	77.60	265.00
	Week 5	66	137.91	32.50	78.30	246.20
	Week 6	61	139.92	35.88	85.50	268.00
	Week 7	54	138.75	33.32	84.70	239.46
	Week 8	56	141.43	36.19	85.90	272.00
	Endpoint	93	138.46	36.76	74.00	272.00
	Endpoint - Change from Baseline	93	-0.99	4.52	-13.00	9.00

Table 14.11

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

Treatment Group=PLACEBO

N = 87

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Diastolic B.P. - Sitting (mmHg)	Screening	84	68.26	9.91	39.00	92.00
	Baseline	80	67.10	10.71	20.00	90.00
	Week 1	84	66.94	9.46	42.00	90.00
	Week 2	79	67.78	10.06	43.00	90.00
	Week 3	75	66.77	9.74	38.00	85.00
	Week 4	73	68.10	10.14	40.00	90.00
	Week 5	69	68.80	9.61	49.00	90.00
	Week 6	65	68.55	9.76	45.00	90.00
	Week 7	63	68.41	9.35	40.00	90.00
	Week 8	66	67.35	9.56	40.00	94.00
	Endpoint	87	66.85	9.94	40.00	94.00
	Endpoint - Change from Baseline	87	-0.85	10.40	-20.00	46.00
Systolic B.P. - Sitting (mmHg)	Screening	84	112.30	11.45	88.00	145.00
	Baseline	80	109.19	12.88	78.00	138.00
	Week 1	84	110.74	11.13	88.00	132.00
	Week 2	79	112.04	10.98	88.00	145.00
	Week 3	75	109.09	11.27	80.00	135.00
	Week 4	73	110.73	10.76	76.00	132.00
	Week 5	69	111.65	11.24	86.00	145.00
	Week 6	65	111.11	11.43	82.00	132.00
	Week 7	63	109.84	10.06	89.00	136.00
	Week 8	66	109.95	11.09	84.00	140.00
	Endpoint	87	110.32	11.04	84.00	140.00
	Endpoint - Change from Baseline	87	0.68	10.88	-18.00	40.00
Diastolic B.P. - Standing (mmHg)	Screening	80	70.40	9.66	49.00	98.00
	Baseline	76	66.74	9.64	44.00	95.00
	Week 1	82	68.32	9.48	43.00	90.00
	Week 2	79	69.23	8.51	50.00	90.00
	Week 3	75	69.15	9.02	47.00	88.00
	Week 4	73	68.56	9.67	46.00	95.00
	Week 5	69	68.32	9.81	48.00	90.00
	Week 6	65	68.75	8.67	46.00	82.00
	Week 7	63	70.57	9.70	52.00	94.00
	Week 8	66	68.14	10.42	44.00	94.00
	Endpoint	87	67.32	10.22	44.00	94.00
	Endpoint - Change from Baseline	86	0.22	10.43	-34.00	26.00

Table 14.11

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

Treatment Group=PLACEBO

N = 87

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Systolic B.P. - Standing (mmHg)	Screening	80	110.04	11.19	84.00	147.00
	Baseline	76	107.66	12.76	70.00	132.00
	Week 1	82	108.79	11.05	84.00	137.00
	Week 2	79	110.25	11.14	86.00	158.00
	Week 3	75	109.01	10.45	78.00	136.00
	Week 4	73	108.51	11.52	76.00	137.00
	Week 5	69	110.48	11.69	70.00	138.00
	Week 6	65	109.29	10.53	86.00	147.00
	Week 7	63	108.29	12.17	90.00	150.00
	Week 8	66	107.59	13.18	84.00	149.00
	Endpoint	87	108.32	12.75	84.00	149.00
	Endpoint - Change from Baseline	86	-0.24	13.26	-26.00	33.00
Pulse - Sitting (bpm)	Screening	82	75.44	11.08	56.00	110.00
	Baseline	79	79.32	10.61	60.00	102.00
	Week 1	84	81.23	11.43	58.00	108.00
	Week 2	78	79.69	10.54	60.00	100.00
	Week 3	75	77.43	9.44	58.00	105.00
	Week 4	73	78.63	11.69	54.00	106.00
	Week 5	69	78.54	11.30	54.00	108.00
	Week 6	65	78.91	10.31	56.00	100.00
	Week 7	63	78.14	10.28	56.00	104.00
	Week 8	66	79.35	10.58	60.00	108.00
	Endpoint	87	78.57	11.62	57.00	108.00
	Endpoint - Change from Baseline	87	0.14	13.00	-28.00	36.00
Pulse - Standing (bpm)	Screening	80	83.24	13.38	56.00	120.00
	Baseline	75	87.07	11.97	64.00	115.00
	Week 1	83	88.95	13.88	60.00	136.00
	Week 2	79	86.96	13.65	60.00	120.00
	Week 3	75	85.96	11.63	60.00	115.00
	Week 4	73	85.45	12.54	60.00	117.00
	Week 5	69	85.59	13.51	58.00	126.00
	Week 6	65	85.91	11.81	60.00	116.00
	Week 7	63	86.95	12.02	62.00	120.00
	Week 8	66	86.95	12.72	60.00	120.00
	Endpoint	87	86.72	14.01	60.00	136.00
	Endpoint - Change from Baseline	86	0.49	15.99	-50.00	48.00

Table 14.11

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

Treatment Group=PLACEBO

N = 87

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Weight (lbs)	Screening	84	145.30	40.76	80.90	287.60
	Baseline	77	144.93	41.31	80.20	299.60
	Week 1	83	147.55	42.04	80.40	296.40
	Week 2	79	147.23	41.38	81.90	288.90
	Week 3	75	149.54	42.59	83.40	292.80
	Week 4	72	145.86	39.27	83.00	257.00
	Week 5	69	149.35	43.47	83.30	294.00
	Week 6	64	151.76	43.07	83.10	287.40
	Week 7	63	151.81	43.67	84.10	293.80
	Week 8	66	150.76	43.56	82.50	296.00
	Endpoint	87	147.09	41.15	82.50	296.00
	Endpoint - Change from Baseline	87	1.19	3.95	-7.80	13.89

PAROXETINE - PROTOCOL 329

Table 14.12

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

Parameter		PAROXETINE N = 93 n	%	IMIPRAMINE N = 95 n	%	PLACEBO N = 87 n	%
Diastolic B.P. - Sitting (mmHg)	H	0	0.0	0	0.0	0	0.0
	L	1	1.1	0	0.0	2	2.3
Systolic B.P. - Sitting (mmHg)	H	0	0.0	0	0.0	0	0.0
	L	0	0.0	0	0.0	0	0.0
Diastolic B.P. - Standing (mmHg)	H	0	0.0	0	0.0	0	0.0
	L	1	1.1	1	1.1	1	1.1
Systolic B.P. - Standing (mmHg)	H	0	0.0	0	0.0	0	0.0
	L	3	3.2	2	2.1	3	3.4
Pulse - Sitting (bpm)	H	0	0.0	4	4.2	0	0.0
	L	0	0.0	0	0.0	0	0.0
Pulse - Standing (bpm)	H	1	1.1	17	17.9	1	1.1
	L	1	1.1	0	0.0	0	0.0
Weight (lbs)	H	2	2.2	0	0.0	3	3.4
	L	2	2.2	3	3.2	1	1.1

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%.

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Paroxetine

PATIENTS WITH ABNORMAL VITAL SIGNS OR BODY WEIGHT OF POTENTIAL CLINICAL CONCERN DURING THE ACUTE PHASE

329

Table 14.12a

xxxx xxxxxx, PhD*

*Clinical Research and Development

Signatory: xxxx x. xxxxxxxx
Affiliation: SmithKline Beecham

SB Document Number: BRL-029060/RSD-100TX3/1

PID 329.001.00068

Vital Sign: Pulse (standing) increased

Demography:	Age: 13 yrs	Height: 62.0 in	Sex: Female
		Weight: 129.00	Race: Caucasian

Country: United States

Medical History: Acne, fever blisters, headaches, nausea stomach upset, infection (biopsy mark right supraclavicular arm), lymph node biopsy (enlarged nodes).

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **08-Feb-95**

End: **20-Apr-95**

Concomitant Drugs	**Start**	**End**
Multiple vitamin	01-Dec-94	08-Feb-95
Rolaids (dihydroxyaluminum sodium carbonate)	01-Jun-92	08-Feb-95
Aspirin	01-Jun-93	08-Feb-95
Lysine	07-Feb-94	08-Feb-95
Tylenol (acetaminophen)	27-Feb-95	28-Mar-95

PID 329.001.00068

Adverse Experiences	Onset (Days into Study)	Duration
Dry mouth	3	Unknown
Increased appetite	22	29 days
Insomnia	8	22 days
Pharyngitis	48	2 days
Respiratory disorder	20	7 days
Urine abnormality	57	Unknown

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.001.00068

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)
0	08-Feb-95	80	86	112	120	84	80
1	15-Feb-95	72	80	116	122	72	80
2	22-Feb-95	70	84	108	112	82	88
3	01-Mar-95	78	80	116	118	104	108
4	08-Mar-95	78	80	110	120	80	100
5	15-Mar-95	70	74	116	110	84	98
6	22-Mar-95	80	84	124	118	80	88
7	29-Mar-95	80	84	110	116	110	***124***
8	05-Apr-95	80	82	120	114	104	120

This 13 year old female was randomied to paroxetine 20mg/day on 08-Feb-95. At the week 5 visit the dose was up-titrated to 30mg/day and to 40mg/day at the week 6 visit. At the week 7 visit the patient's standing pulse rate had increased to 124bpm and considered to be of potential clinical concern. Investigator did not report on adverse event associated with this increase and patient continued in study.

PID 329.002.00057

Vital Sign: Pulse (standing) increased

Demography:	Age: 15 yrs	Height: 66.5 in Weight: 162.50 lbs	Sex: Female Race: Caucasian

Country: United States

Medical History: Heartburn, occasional headaches, Scheuermann's kyphosis, stomach problems, childhood migraines, concussion, hernia operation, tonsillectomy, tubes in ears.

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **08-Sep-94**

End: **03-Nov-94**

Concomitant Drugs	**Start**	**End**
Acetaminophen, prn	01-Aug-94	continuing
Cannabis	unknown	unknown
Cannabis	30-Oct-94	30-Oct-94
Motrin (ibuprofen)	29-Sep-94	29-Sep-94
Aspirin	29-Nov-94	29-Nov-94

PID 329.002.00057

Adverse Experiences	Onset (Days into Study)	Duration
Vomiting	29	20 min.
Hyperkinesia	20	45 min.

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.002.00057

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

		SitDBP	StDBP	SitSBP	StSBP	SitPulse	StPulse	Weight
Week	**Date**	**(mmHg)**	**(mmHg)**	**(mmHg)**	**(mmHg)**	**(bpm)**	**(bpm)**	**(lb)**
0	08-Sep-94	62	61	99	92	73	89	163.00
1	15-Sep-94	60	60	90	88	88	84	160.50
2	22-Sep-94	70	60	102	94	102	***140***	158.00
3	29-Sep-94	60	60	90	94	100	100	158.00
4	06-Oct-94	68	66	112	110	96	100	157.00
5	13-Oct-94	60	50	104	88	100	102	159.50
6	20-Oct-94	62	60	100	98	100	104	159.00
7	27-Oct-94	64	62	102	94	100	102	160.00
8	03Nov-94	60	58	90	80	120	***140***	160.00

This 15 year old female was randomized to imipramine 50mg/day on 08-Sep-94. Dose was up-titrated to 300mg/day in 50mg/week increments by week 6. At weeks 2 and 8 the patient's standing pulse rate was increased at 140bpm and considered to be of potential clinical concern. Elevated pulse was not reported as an adverse experience by the investigator.

PID 329.002.00060

Vital Sign: Systolic blood pressure (standing) decreased

Demography:	Age: 14	Height: 64.0 in	Sex: Female
		Weight: 117.00 lbs	Race: Caucasian

Country: United States

Medical History: Headache, acute upper respiratory infection

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **31-Jan-95**

End: **27-Mar-95**

Concomitant Drugs
None

PID 329.002.00060

Adverse Experiences
None

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.002.00060

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	31-Jan-95	74	76	108	112	88	88	117.00
1	07-Feb-95	50	54	92	92	88	84	120.00
2	14-Feb-95	60	62	90	90	80	80	119.00
3	21-Feb-95	68	68	90	90	80	80	117.50
4	28-Feb-95	64	64	96	92	84	84	118.00
5	07-Mar-95	56	58	88	***70***	80	84	117.70
6	14-Mar-95	64	64	110	106	84	82	120.00
7	21-Mar-95	70	70	110	102	100	100	120.50
8	28-Mar-95	64	60	104	94	74	74	120.21

This 14 year old female was randomized to placebo on 31-Jan-95. At the week 5 visit, the patient's standing systolic blood pressure was low at 70mmHg. At the following visit, blood pressure returned to normal and remained normal for the remainder of the acute phase.

PID 329.002.00107

Vital Sign: Weight increase

Demography:	Age: 15 yrs	Height: 65.0 in Weight: 167.00 lbs	Sex: Female Race: Caucasian

Country: United States

Medical History: Dyspepsia, syncope and collapse, genital female disorder

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **25-Jan-96**

End: **20-Mar-96**

Concomitant Drugs	**Start**	**End**
Amoxicillin	16-Sep-96	26-Sep-96

PID 329.002.00107

Adverse Experiences
None

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.002.00107

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
Screen	18-Jan-96	74	72	112	110	70	68	167.00
1	01-Feb-96	78	76	108	106	66	60	172.00
2	08-Feb-96	76	72	110	106	64	62	174.00
3	13-Feb-96	74	76	108	110	64	80	173.00
4	20-Feb-96	68	70	110	104	68	62	174.50
5	27-Feb-96	70	66	106	100	66	62	174.00
6	05-Mar-96	74	72	114	110	70	68	***179.00***
7	15-Mar-96	72	70	106	104	64	64	***179.50***
8	21-Mar-96	72	68	94	92	70	92	178.00

This 15 year old female was randomized to placebo on 25-Jan-96. At week 6 the patient's weight was recorded at 179 lbs. This was an increase of 12 lbs over baseline and considered to be of potential clinical concern. This event was not reported as an adverse event by the investigator.

PID 329.002.00323

Vital Sign: Weight decreased

Demography:	Age: 17 yrs	Height: 63.0 in Weight: 118.00 lbs	Sex: Female Race: Caucasian

Country: United States

Medical History: Back pain, cholesterol/triglycerides elevated, cardiac murmurs

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **12-Nov-96**

End: **08-Jan-97**

Concomitant Drugs	**Start**	**End**
Unknown medication for back pain	11-Nov-96	01-Dec-96

PID 329.002.00323

Adverse Experiences	Onset (Days into Study)	Duration
Headache	49	11 days
Thirst	15	10 days
Dizziness	8	37 days
Somnolence	4	42 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.002.00323

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	12-Nov-96	68	64	92	90	84	90	118.00
1	19-Nov-96	66	64	94	98	88	80	117.00
2	26-Nov-96	78	78	102	100	84	78	***109.00***
3	05-Dec-96	70	66	96	94	80	82	112.00
4	10-Dec-96	68	66	100	96	66	64	112.00
5	17-Dec-96	60	62	98	94	90	84	114.00
6	26-Dec-96	66	64	88	88	74	76	112.00
7	02-Jan-97	72	60	102	104	80	84	112.00
8	09-Jan-97	68	66	100	100	74	80	114.50

This 17 year old female was randomized to placebo on 12-Nov-96. At the week 2 visit, it was recorded that the patient's weight had dropped to 109 lbs from a baseline weight of 118.00 lbs. This was considered to be of potential clinical concern however the investigator did not report any associated adverse events. The patient's weight had returned to 114.5 lbs by week 8 of the study.

PID 329.003.00080

Vital Sign: Diastolic blood pressure (sitting) decreased

Demography:	Age: 16 yrs.	Height: 62.6 in Weight: 177.94 lbs	Sex: Female Race: Hispanic

Country: United States

Medical History: Malaise and fatigue

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **27-Nov-95**

End: **09-Feb-96**

Concomitant Drugs	**Start**	**End**
Injectable contraceptive, nos	07-Oct-95	continuing

PID 329.003.00080

Adverse Experiences	Onset (Days into Study)	Duration
Asthenia	39	Unknown
Headache	38	Unknown
Dry Mouth	39	Unknown
Dizziness	39	Unknown
Respiratory Disorder	27	12 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.003.00080

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week*	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
1	04-Dec-95	72	80	122	110	80	96	178.61
1	07-Dec-95	64	62	124	120	94	100	179.27
3	18-Dec-95	58	66	114	110	88	100	177.50
5	29-Dec-95	***48***	60	134	112	98	106	181.03
5	04-Jan-96	58	74	128	126	86	90	179.05
6	10-Jan-96	58	48	122	110	82	88	179.71
7	17-Jan-96	68	74	122	120	82	100	181.47
8	24-Jan-96	64	60	120	110	102	112	179.27

* Visit weeks are visit window intervals

This 16 year old female was randomized to placebo on 27-Nov-95. At the week 5 visit the patient's sitting diastolic blood pressure was low at 48mmHg and considered to be of potential clinical concern. Patient's blood pressure was normal at the following visit and remained normal for the remainder of the acute phase.

PID 329.003.00292

Vital Sign: Pulse (standing) decreased

Demography:	Age: 16	Height: 60.6 in Weight: 143.10 lb	Sex: Male Race: Korean

Country: United States

Medical History: None

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **07-Aug-96**

End: **03-Oct-96**

Concomitant Drugs
None

PID 329.003.00292

Adverse Experiences
None

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.003.00292

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	07-Aug-96	56	56	126	130	80	80	143.10
1	16-Aug-96	74	62	138	142	86	88	141.56
2	21-Aug-96	80	76	112	118	80	***45***	139.36
3	30-Aug-96	50	54	122	128	80	82	139.80
4	04-Sep-96	50	46	126	116	92	106	141.12
7	25-Sep-96	58	48	128	132	95	98	142.88
8	04-Oct-96	65	70	120	120	100	96	144.43

This 16 year old male was randomized to paroxetine 20mg/day on 07-Aug-96. At the week 2 visit the patient's standing pulse was low at 45bpm and considered to be of potential clinical concern. The patient's pulse rate was normal for the remainder of the acute phase.

Lab Remarks:

This patient was also found to have an increased red blood cell count in his urine at week 8. The patient entered the study on 07-Aug-96 with urine red blood cells negative. At week 8, the urine red blood cells were 5-10 (abnormal > 8 male), which was considered to be of clinical concern by the investigator. There were no reported adverse events associated with the abnormal vital signs or abnormal laboratory value.

PID 329.004.00015

Vital Sign: Weight decreased

Demography:	Age: 16 yrs	Height: 62.6 in Weight: 116.87 lbs	Sex: Female Race: Caucasian

Country: United States

Medical History: Urinary incontinence, urinary operation

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **08-Dec-94**

End: **02-Feb-95**

Concomitant Drugs	**Start**	**End**
Polysporin (polymyxin B sulfate + bacitracin zinc) eye drops	07-Dec-94	18-Dec-94
Polysporin (polymyxin B sulfate + bacitracin zinc) eye drops	03-Jan-95	14-Jan-95
Drixoral (dexbrompheniramine maleate + pseudoephedrine sulfate)	12-Dec-94	13-Dec-94
Vitamin C	12-Dec-94	13-Dec-94
Centrum (multiple vitamin)	12-Dec-94	13-Dec-94
Tylenol (acetaminophen), prn	11-Dec-94	17-Apr-95

PID 329.004.00015

Adverse Experiences	Onset (Days into Study)	Duration
Abdominal Pain	1	12 days
Asthenia	1	43 days
Asthenia	15	11 days
Asthenia	57	ongoing
Headaches - 1 daily	4	7 days
Headache	13	3 hrs
Headache	34	1 hr
Emotional Lability	31	30 min
Tremor	3	14 days
Cough Increased	5	5 days
Cough Increased	57	ongoing
Pharyngitis	57	34 days
Rhinitis	4	10 days
Conjunctivitis	1	11 days
Dysmenorrhea	53	2 hrs

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.004.00015

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	07-Dec-94	68	70	100	96	60	80	116.87
1	14-Dec-94	60	64	90	90	96	104	***107.16***
2	21-Dec-94	60	64	100	100	88	100	***106.06***
3	28-Dec-94	70	70	100	100	82	90	***104.96***
4	04-Jan-95	60	60	90	90	74	80	***102.53***
5	11-Jan-95	70	78	110	110	76	100	***102.97***
6	18-Jan-95	60	68	98	90	80	96	***105.18***
7	25-Jan-95	78	66	110	100	94	100	***105.18***
8	03-Feb-95	68	66	104	100	80	84	***105.84***

This 16 year old female was randomized to paroxetine 20mg/day on 08-Dec-94. At baseline the patient weighed 117 lbs, however, by week 2 had lost approximately 9 pounds. This was considered to be of potential clinical concern. Patient's weight remained low through week 8 of acute phase.

Lab Remarks:

The patient entered the study with urine red blood cell count negative. At week 4, the urine red blood cells were innumerable and considered to be of potential clinical concern (abnormal > 10 female). At week 8, the urine red blood cells were again negative. The investigator did not report this event as an adverse experience.

PID 329.005.00004

Vital Sign: Weight increased

Demography:	Age: 16	Height: 68.0 in	Sex: Male
		Weight: 141.50	Race: Caucasian

Country: United States

Medical History: None

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **10-Oct-94**

End: **07-Dec-94**

Concomitant Drugs
None

PID 329.005.00004

Adverse Experiences	Onset (Days into Study)	Duration
Headache	15	2.30 hrs

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.005.00004

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	10-Oct-94	74	70	134	130	68	68	141.50
1	20-Oct-94	70	70	130	124	62	62	142.00
2	27-Oct-94	74	70	118	110	64	62	144.80
3	03-Nov-94	70	70	120	90	60	60	145.40
4	10-Nov-94	70	60	120	100	68	64	148.00
5	17-Nov-94	80	80	124	120	84	80	150.50
6	23-Nov-94	80	80	124	120	64	64	148.00
7	01-Dec-94	70	60	112	100	60	64	***152.90***
8	08-Dec-94	60	60	110	118	60	62	149.60

This 16 year old male was randomized to paroxetine 20mg/day on 10-Oct-94. Dose was up-titrated to 30mg/day at the start of week 5 and to 40mg/day the following week. At the week 7 visit, the patient's weight had increased to 153 lbs from a baseline weight of 142 lbs. This was considered to be of potential clinical concern, however, was not reported as an adverse event.

PID 329.005.00114

Vital Sign: Weight Increased

Demography:	Age: 16 yrs	Height: 70.0 in Weight: 145.20 lbs	Sex: Male Race: Caucasian

Country: United States

Medical History: Asthma

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **31-Jan-95**

End: **28-Mar-95**

Concomitant Drugs	**Start**	**End**
Tylenol (acetaminophen)	04-Feb-95	08-Feb-95
Amoxicillin	06-Feb-95	16-Feb-95

PID 329.005.00114

Adverse Experiences	Onset (Days into Study)	Duration
Infection	5	11 days
Tremor	30	22 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.005.00114

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	31-Jan-95	60	50	80	70	72	72	145.00
1	07-Feb-95	62	62	108	102	80	88	153.50
2	14-Feb-95	80	70	110	90	60	64	154.50
3	21-Feb-95	70	70	100	104	58	60	***155.89***
4	28-Feb-95	70	60	110	90	70	72	***157.00***
5	09-Mar-95	70	64	100	90	80	80	***157.00***
6	15-Mar-95	80	70	104	100	80	84	155.00
7	22-Mar-95	70	70	104	90	60	64	154.50
8	29-Mar-95	70	70	100	92	68	72	153.00

This 16 year old male was randomized to placebo on 31-Jan-95. At the week 3 visit, it was seen that the patient's weight had increased approximately 10 lbs from baseline. The patient's weight remained increased for the remainder of the acute phase and considered to be of potential clinical concern.

PID 329.005.00120

Vital Sign: Weight increased

Demography:	Age: 13	Height: 61.5 in Weight: 152.00 lbs	Sex: Male Race: Caucasian

Country: United States

Medical History: Rash on arms and chest (folliculitis)

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **30-Aug-95**

End: **26-Oct-95**

Concomitant Drugs	**Start**	**End**
Topical Cream (dermatological Nos)	Unknown	Unknown
Robitussin (guaifenesin)	17-Sep-95	19-Sep-95
Actifed (pseudoephedrine hydrochloride)	13-Sep-95	14-Sep-95
Actifed (triprolidine hydrochloride)	13-Sep-95	14-Sep-95

PID 329.005.00120

Adverse Experiences	Onset (Days into Study)	Duration
Headache	16	30 min
Eosinophilia	-8	Unknown
Eosinophilia	58	Unknown
Hyperglycemia	-8	Unknown
Hyperglycemia	58	Unknown
Euphoria	21	17 days
Nervousness	21	2 days
Nervousness	23	8 days
Cough Increased	14	8 days
Cough Increased	55	Unknown
Rhinitis	14	7 days
Kidney Function Abnormal	-8	66 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.005.00120

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	30-Aug-95	72	66	110	106	72	80	152.15
1	07-Sep-95	62	66	104	108	68	84	155.23
2	14-Sep-95	66	66	112	108	80	84	159.20
3	21-Sep-95	72	70	116	114	84	88	160.52
4	28-Sep-95	68	66	116	110	84	88	159.86
5	05-Oct-95	72	68	108	104	68	68	162.51
6	12-Oct-95	66	68	116	114	68	72	162.51
7	19-Oct-95	68	66	122	116	72	76	***164.71***
8	26-Oct-95	64	68	120	116	88	80	***166.04***

This 13 year old male was randomized to placebo on 30-Aug-95. By the week 7 visit, the patient's weight had increased approximately 12 lbs from baseline and considered to be of potential clinical concern. Weight gain was not reported as an adverse experience by the investigator.

PID 329.005.00299

Vital Sign: Diastolic blood pressure (sitting and standing) decreased

Demography:	Age: 12	Height: 63.0 in	Sex: Female
		Weight: 124.00	Race: Caucasian

Country: United States

Medical History: Headaches, knee pain (right - after running)

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **08-Jun-96**

End: **06-Aug-96**

Concomitant Drugs	**Start**	**End**
Tums (calcium carbonate)	Unknown	Unknown
Advil (ibuprofen)	Unknown	Unknown

PID 329.005.00299

Adverse Experiences	Onset (Days into Study)	Duration
Abdominal Pain	54	3 days
Headache	54	5 days
Headache (upon rising)	7	27 days
Syncope	10	1 min
Dizziness	7	27 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.005.00299

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week*	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	04-Jun-96	80	80	120	120	64	76	124.00
1	18-Jun-96	64	60	92	92	84	100	123.00
2	25-Jun-96	64	60	92	92	84	96	125.75
3	02-Jul-96	70	80	110	110	82	84	124.00
5	10-Jul-96	68	56	90	92	80	88	124.00
6	22-Jul-96	***48***	***42***	100	90	84	100	124.00
8	31-Jul-96	60	54	110	90	80	84	127.20
8	07-Aug-96	70	60	106	100	80	84	125.75

* Visit weeks are visit window intervals

This 12 year old female was randomized to paroxetine 20mg/day on 08-Jun-96. At the week 6 visit the patient's sitting diastolic blood pressure was decreased at 48mmHg as was the standing diastolic blood pressure (42mmHg). These values were of potential clinical concern. Patient's blood pressure returned to normal by the following visit.

PID 329.005.00300

Vital Sign: Systolic blood pressure (standing) decreased

Demography:	Age: 12	Height: 62.0	Sex: Male
		Weight: 96.50	Race: Caucasian

Country: United States

Medical History: None

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **19-Sep-96**

End: **Unknown**

Concomitant Drugs
None

PID 329.005.00300

Adverse Experiences	Onset (Days into Study)	Duration
Headache	55	2 hrs
Dry Mouth	6	27 days
Hostility	30	7 days
Hostility	37	Unknown
Somnolence	13	11 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.005.00300

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	19-Sep-96	50	50	80	88	60	62	96.50
1	26-Sep-96	50	60	80	84	74	78	95.50
2	03-Oct-96	60	58	88	84	64	68	94.20
3	10-Oct-96	60	50	98	104	80	86	94.75
4	17-Oct-96	60	60	90	80	60	64	97.50
5	24-Oct-96	50	60	70	90	60	62	95.70
6	31-Oct-96	60	54	80	***58***	60	60	95.50
7	07-Nov-96	60	50	80	78	60	62	95.70
8	14-Nov-96	60	58	90	80	60	64	99.00

This 12 year old male was randomized to paroxetine 20mg/day on 19-Sep-96. At week 6 the patient's standing systolic blood pressure had decreased to 58mmHg and considered to be of potential clinical concern. Blood pressure returned to normal by the following visit.

PID 329.008.00159

Vital Sign: Pulse (standing) increased

Demography:	Age: 16 yrs	Height: 62.0 in	Sex: Female
		Weight: 104.00	Race: Caucasian

Country: United States

Medical History: None

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **13-Sep-95**

End: **13-Nov-95**

Concomitant Drugs	**Start**	**End**
Tylenol (paracetamol)	Unknown	Unknown
Sleep Aid (Nos)	03-Oct-95	10-Oct-95

PID 329.008.00159

Adverse Experiences	Onset (Days into Study)	Duration
Dry Mouth	22	29 days
Dizziness	42	9 days
Insomnia	47	8 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.008.00159

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	13-Sep-95	70	65	103	100	68	80	Unknown
1	19-Sep-95	62	62	96	96	Unknown	Unknown	101.00
2	27-Sep-95	62	64	96	94	Unknown	Unknown	101.00
3	03-Oct-95	60	60	94	92	72	72	101.00
4	10-Oct-95	78	62	100	92	84	88	101.00
5	16-Oct-95	72	70	110	96	108	104	101.00
6	24-Oct-95	78	76	102	100	118	116	101.00
7	31-Oct-95	78	76	116	100	100	***122***	101.00
8	14-Nov-95	65	56	110	110	88	120	102.00

This 16 year old female was randomized to imipramine 50mg/day on 13-Sep-95. Dose was up-titrated to 250mg/day in 50mg/week increments by week 5. At day 42 the patient experienced dizziness and had an increased standing pulse of 122bpm, a valve considered to be of potential clinical concern. Patient's standing pulse was again high at 120bpm at week 8, however, patient remained in study.

Lab remarks:

The patient entered the study with a baseline urine white blood cell count of 10-15, which was considered to be of potential clinical concern (abnormal > 10). At week 8, the urine white blood cell count had increased to 25-50. This finding, however, was not reported as an adverse event by the investigator.

PID 329.008.00273

Vital Sign: Pulse (standing) increased, weight decreased

Demography:	Age: 12 yrs	Height: 72.0	Sex: Female
		Weight: 153.00	Race: Caucasian

Country: United States

Medical History: Dentofacial anomoly (temporomandibular joint pain)

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **17-May-96**

End: **18-Jul-96**

Concomitant Drugs	**Start**	**End**
Tylenol (paracetamol)	10-Apr-96	Unknown
Ansaid (flurbiprofen)	20-Mar-96	10-Apr-96

PID 329.008.00273

Adverse Experiences
None

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.008.00273

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week*	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	17-May-96	80	83	120	105	96	102	153.00
1	24-May-96	85	82	110	105	112	***136***	150.00
2	31-May-96	84	85	112	108	92	100	150.00
3	10-Jun-96	80	80	100	100	96	112	147.00
4	17-Jun-96	85	85	110	100	96	108	145.00
5	24-Jun-96	80	80	110	110	100	108	145.00
6	01-Jul-96	79	81	124	131	104	104	***140.00***
8	11-Jul-96	82	80	112	110	106	120	***138.00***
8	19-Jul-96	85	80	105	100	96	100	***140.00***

Visits at week 8 are visit window intervals

This 12 year old female was randomized to imipramine 50mg/day on 17-May-96. Dose was up-titrated to 300mg/day in 50mg/week increments by week 7. At the week 1 visit, the patient's pulse was high at 136bpm and considered to be of potential clinical concern. Pulse returned to normal through the remainder of the study. Additionally, the patient's weight had decreased 15 lbs by the week 7 visit. This too was considered to be of potential clinical concern, however, no adverse events were reported by the investigator.

PID 329.009.00136

Vital Sign: **Systolic blood pressure (standing)decreased**
Diastolic blood pressure (sitting) decreased

Demography: Age: 14 Height: 66.5 in Sex: Female
Weight: 299.60 Race: Black

Country: United States

Medical History: Headaches, menstrual cramps, sinus congestion, sprained left ankle.

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **03-Oct-95**

End: **11-Dec-95**

Concomitant Drugs	**Start**	**End**
Midol (acetylsalicylic acid, caffeine, cinnamedrine hydrochloride)	01-Jan-93	Unknown
Advil (ibuprofen)	01-Jan-95	Unknown
Drixoral (dexbrompheniramine maleate, pseudoephedrine sulfate)	01-Jan-95	

PID 329.009.00136

Adverse Experiences	Onset (Days into Study_	Duration
Headache	33	11 days
Thirst	8	15 days
Contact Dermatitis	8	15 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00136

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	03-Oct-95	76	66	119	124	102	115	299.60
1	10-Oct-95	57	63	132	***84***	81	114	296.40
2	17-Oct-95	***48***	73	124	102	90	117	288.90
3	24-Oct-95	50	56	101	114	86	115	292.80
4	03-Nov-95	54	67	109	117	54	86	Unknown
5	07-Nov-95	80	50	133	131	66	103	294.00
6	14-Nov-95	60	55	124	109	84	111	287.40
7	21-Nov-95	62	82	116	110	74	100	293.80
8	28-Nov-95	57	49	125	105	86	96	296.00

This 14 year old female was randomized to placebo on 03-Oct-95. At the week 1 visit, the patient's standing systolic blood pressure was low at 84mmHg. The following week the patient's sitting diastolic blood pressure was low at 48mmHg. Both were considered to be of potential clinical concern, however, had returned to normal through the remainder of the study.

PID 329.009.00172

Vital Sign: **Pulse (sitting) increased**
Diastolic blood pressure (standing) decreased
Systolic blood pressure (standing) decreased

Demography: Age: 13 Height: 64.0 in Sex: Female
Weight: 126.50 lbs Race: Caucasian

Country: United States

Medical History: Occasional headache, stomach ache

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **13-Nov-95**

End: **08-Jan-96**

Concomitant Drugs	**Start**	**End**
Tylenol (paracetamol)	01-Jan-94	Unknown

PID 329.009.00172

Adverse Experiences	Onset (Days into Study)	Duration
Tachycardia	2	14 days
Dry Mouth	23	Ongoing
Abnormal Dreams	36	Ongoing
Dizziness	21	Ongoing
Somnolence	17	6 days
Thinking Abnormal	40	13 days
Tinnitus	21	30 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00172

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

		SitDBP	StDBP	SitSBP	StSBP	SitPulse	StPulse	Weigh t
Week	**Date**	**(mmHg)**	**(mmHg)**	**(mmHg)**	**(mmHg)**	**(bpm)**	**(bpm)**	**(lb)**
0	13-Nov-95	63	73	129	124	84	109	126.50
1	20-Nov-95	70	57	122	115	***129***	137	123.60
2	27-Nov-95	66	58	98	104	101	92	123.00
3	04-Dec-95	81	69	126	121	92	96	125.00
4	11-Dec-95	53	67	102	129	88	100	122.50
5	21-Dec-95	67	56	117	108	108	Unknown	121.40
6	27-Dec-95	81	***47***	131	112	104	108	121.90
7	03-Jan-96	61	56	115	102	102	110	121.70
8	09-Jan-96	76	***33***	101	***85***	102	108	121.50

This 13 year old female patient was randomized to imipramine 50mg/day on 13-Nov-95. Dose wsa up-titrated to 200mg/day in 50mg/week increments by week 4. At week 1, the patient's sitting pulse was increased to 129 and of potential clinical concern. Pulse returned to normal through the remainder of the study. At the week 6 and 8 visits, the patient's standing diastolic blood pressure was decreased (47mmHg and 33mmHg respectively). At week 8, the patient's standing systolic blood pressure was also decreased to 85mmHg. All were considered to be of potential clinical concern.

PID 329.009.00197

Vital Sign: Systolic blood pressure (standing) decreased

Demography:	Age: 12 yrs	Height: 58.0 in Weight: 97.80 lbs	Sex: Male Race: Caucasian

Country: United States

Medical History: Occasional headaches, stomach pain

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **29-Dec-95**

End: **20-Feb-96**

Concomitant Drugs	**Start**	**End**
Pepcid (famotidine)	01-Nov-95	Unknown
Advil (ibuprofen)	01-Jan-95	Unknown

PID 329.009.00197

Adverse Experiences	Onset (Days into Study)	Duration
Dizziness	21	1 day

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00197

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week*	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	29-Dec-95	49	60	106	124	86	95	97.80
1	02-Jan-96	40	55	92	101	72	86	98.60
1	08-Jan-96	50	50	102	107	79	96	100.00
3	16-Jan-96	38	49	100	97	71	81	99.60
4	23-Jan-96	43	46	94	100	81	83	101.60
5	30-Jan-96	68	49	115	116	81	105	100.30
6	06-Feb-96	47	53	82	***86***	96	100	99.70
7	13-Feb-96	40	52	89	90	75	84	98.80
8	20-Feb-96	47	52	90	98	91	120	99.10

* Visit weeks are visit window intervals

This 12 year old male patient was randomized to placebo on 29-Dec-95. At the week 6 visit, the patient's standing systolic blood pressure was 86mmHg, a level of potential clinical concern. No adverse events were reported in association with this value.

PID 329.009.00239

Vital Sign: Pulse (standing) increased

Demography: Age: 16 yrs Height: 65.5 Weight: 140.40 Sex: Female Race: Caucasian

Country: United States

Medical History: Migraines, sinus arrhythmia, sinus bradycardia, allergy to penicillin, mononucleosis

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **19-Nov-96**

End: **14-Jan-97**

Concomitant Drugs
None

Adverse Experiences	Onset (Days into Study)	Duration
Tachycardia	7	ongoing (141 days)
Dry mouth	21	8 days
Dysphagia	28	8 days
Nausea	38	5 days
Vomiting	38	5 days
Insomnia	42	8 days
Somnolence	21	22 days
Respiratory Disorder	49	10 days

PID 329.009.00239

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

		SitDBP	StDBP	SitSBP	StSBP	SitPulse	StPulse	Weight
Week*	Date	(mmHg)	(mmHg)	(mmHg)	(mmHg)	(bpm)	(bpm)	(lb)
0	18-Nov-96	60	57	114	123	53	74	149.40
1	25-Nov-96	61	63	115	106	88	96	147.70
2	02-Dec-96	69	60	115	112	85	109	146.80
3	09-Dec-96	74	68	124	107	94	117	147.70
4	16-Dec-96	66	58	121	113	86	115	149.10
5	23-Dec-96	77	77	126	121	106	***121***	149.50
6	30-Dec-96	75	73	113	115	100	102	143.40
7	06-Jan-97	59	81	121	119	108	***131***	146.50
8	15-Jan-97	74	82	120	131	68	91	143.40

This 16 year old female was randomized ato imipramine 50mg/day on 19-Nov-96. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4. At the week 5 visit, the patient's standing pulse was high at 121bpm and even higher at week 7 at 131bpm. Pulse returned to 91bpm by week 8. The values at weeks 5 and 7 were concerned to be of potential clinical concern.

PID 329.009.00262

Vital Sign: **Pulse (standing) increased**
Decreased weight

Demography: Age: 13 yrs Height: 62.3 in. Sex: Male
Weight: 145.90 lbs. Race: Caucasian

Country: United States

Medical History: Encopretic, eye infection, occasional headaches, stomach aches, cronic ear infections, tubes in ears

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **17-Feb-97**

End: **26-Apr-97**

Concomitant Drugs	**Start**	**End**
Tylenol (paracetamol)	28-Mar-97	28-Mar-97
Benedryl (diphenhydramine hydrochloride)	15-Mar-97	15-Mar-97
Sulfacetamide Sodium	10-Feb-97	07-Apr-97

Adverse Experiences	**Onset (Days into Study)**	**Duration**
AV Block	19	11 days
Heart Malformation	29	15 days
Postural hypotension	57	5 min.
Dry Mouth	8	64 days
Somnolence	8	8 days
Cough Increased	27	2 days
Ear Pain	15	5 days
Eye Disorder	-7	57 days

PID 329.009.00262

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week*	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	17-Feb-97	83	79	126	131	74	84	145.90
1	24-Feb-97	63	70	129	120	77	112	141.20
2	03-Mar-97	85	72	130	120	91	119	143.60
3	07-Mar-97	75	63	131	113	90	119	141.90
4	17-Mar-97	85	65	127	119	103	***129***	139.20
5	24-Mar-97	91	84	147	147	106	112	136.70
6	31-Mar-97	83	74	143	122	96	117	136.90
7	07-Apr-97	81	76	139	116	108	***121***	***134.50***
8	14-Apr-97	74	79	139	116	102	114	135.70

This 13 year old male was randomized to imipramine 50mg/day on 17-Feb-97. Dose was up-titrated to 200mg/day in 50mg/week increments by week4. At the week 4 visit, the patient's standing pulse was increased at 129bpm, a level of potential clinical concern. At week 8, the standing pulse was again elevated at 121 bpm and the patient's weight was down to 135 lbs from 146 at baseline. These two were considered to be of potential clinical concern. The investigator reported several cardiovascular events during the study for this patient.

PID 329.009.00264

Vital Sign: **Pulse (standing) increased**
Pulse (sitting) increased

Demography: Age: 14 yrs Height: 62.5 Sex: Female
Weight: 171.00 Race: Caucasian

Country: United States

Medical History: Headaches, asthma (no problems for 2 years)

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **01-Nov-96**

End: **04-Jan-97**

Concomitant Drugs	**Start**	**End**
Aspirin (acetylsalicylic acid)	31-Oct-94	Unknown
Coadvil (ibuprofen; pseudoephedrine hydrochloride)	31-Oct-94	Unknown

PID 329.009.00264

Adverse Experiences	Onset (Days into Study)	Duration
Electrocardiogram Abnormal	53	Unknown
Tachycardia	11	Unknown
Agitation	11	8 days
Insomnia	41	6 days
Somnolence	8	25 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00264

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week*	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	01-Nov-96	72	66	109	122	102	82	171.00
1	08-Nov-96	79	Unknown	121	Unknown	108	Unknown	170.30
1	11-Nov-96	80	87	145	126	105	***140***	Unknown
2	18-Nov-96	88	68	130	130	104	***133***	168.00
3	25-Nov-96	88	73	145	120	117	***145***	168.00
4	02-Dec-96	76	57	137	104	115	***137***	169.40
6	11-Dec-96	86	61	135	123	126	***150***	165.80
6	16-Dec-96	91	72	144	125	***137***	***140***	169.60
7	23-Dec-96	66	55	128	115	131	***148***	169.10

This 14 year old female was randomized to imipramine 50mg/day on 01-Nov-96. Dose was up-titrated to 200mg/day in 50mg/week increments by week4. Beginning at week 1, the patient's pulse (standing and sitting) was elevated and at levels of potential clinical concern. Patient experienced agitation, insomnia, and somnolence during the study and was reported to have an abnormal ECG after the wee 7 visit.

PID 329.009.00301

Vital Sign: Pulse (standing) high

Demography:	Age: 17	Height: 80.0 Weight: 129.00 lbs	Sex: Male Race: Caucasian

Country: United States

Medical History: Asthma, headaches, asthma attacks (hospitalized), broken left arm (twice), broken right arm.

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **19-Mar-96**

End: **13-May-96**

Concomitant Drugs	**Start**	**End**
Theo-Dur (theophylline)	01-Jan-95	Unknown
Tylenol (paracetamol)	01-Jan-95	Unknown
Alupent (orciprenaline sulfate)	01-Jan-94	Unknown

PID 329.009.00301

Adverse Experiences	Onset (Days into Study)	Duration
Infection	22	20 min
Tachycardia	36	15 min
Dizziness	22	1 day

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00301

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	19-Mar-96	45	57	93	95	75	75	129.00
1	26-Mar-96	44	49	91	114	84	72	129.50
2	05-Apr-96	59	65	105	107	77	89	125.20
3	12-Apr-96	52	61	106	99	90	108	126.50
4	16-Apr-96	63	58	116	108	74	90	125.70
5	23-Apr-96	70	59	124	107	114	***126***	124.80
6	30-Apr-96	46	62	97	93	83	95	127.40
7	07-May-96	53	62	101	115	86	92	128.60
8	14-May-96	52	57	99	105	66	88	127.10

This 17 year old male was randomized to Imipramine 50mg/day on 19-Mar-96. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4. At week 5, the patient's standing pulse was elevated to 126bpm. This value was of potential clinical concern, however, returned to normal for the remainder of the acute phase.

PID 329.009.00304

Vital Sign: Systolic blood pressure (standing) decreased

Demography:	Age: 16 yrs	Height: 67.0 in Weight: 200.80	Sex: Male Race: Caucasian

Country: United States

Medical History: Headache (occasional)

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **09-Apr-96**

End: **03-Jun-96**

Concomitant Drugs	**Start**	**End**
Advil (ibuprofen)	01-Jan-95	Unknown

PID 329.009.00304

Adverse Experiences	Onset (Days into Study)	Duration
Headache	43	8 days
Postural Hypotension	43	30 min
Somnolence	36	15 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00304

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	09-Apr-96	59	52	118	121	80	82	200.80
1	16-Apr-96	60	57	138	139	72	73	199.90
2	23-Apr-96	59	63	138	145	74	86	195.90
3	30-Apr-96	70	83	140	145	90	102	198.10
4	07-May-96	71	73	132	139	91	100	197.20
5	14-May-96	60	74	137	139	100	102	195.20
6	21-May-96	65	56	138	***68***	91	109	198.70
7	28-May-96	64	59	137	120	69	79	200.70
8	04-Jun-96	64	60	130	128	99	102	198.70

This 14 year old male was randomized to paroxetine 20 mg/day on 09-Apr-96. Dose was up-titrated to 30mg/day at week 5 visit. At the week 6 visit, the patient's standing systolic blood pressure was decreased to 68mmHg, a level of potential clinical concern. Blood pressure was normal for remainder of the acute phase.

PID 329.009.00305

Vital Sign: Pulse (standing) increased

Demography:	Age: 14 yrs	Height: 72.3 in Weight: 135.90 lbs	Sex: Male Race: Caucasian

Country: United States

Medical History: None

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **07-May-96**

End: **02-Jul-96**

Concomitant Drugs	**Start**	**End**
Imodium A-D (loperamide hydrochloride)	02-Jul-96	02-Jul-96

PID 329.009.00305

Adverse Experiences	Onset (Days into Study)	Duration
Dry Mouth	8	22 days
Nausea	8	15 days
Nausea	22	23 days
Nausea	57	1 day
Dizziness	8	15 days
Dizziness	22	ongoing

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00305

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	07-May-96	54	53	108	107	86	89	135.90
1	14-May-96	65	65	107	108	92	98	135.10
2	21-May-96	54	37	96	99	94	98	133.80
3	28-May-96	62	64	123	106	96	96	133.70
4	04-Jun-96	76	47	126	93	100	***132***	135.60
5	11-Jun-96	72	38	123	98	96	Unknown	135.60
6	19-Jun-96	65	53	115	103	96	120	135.90
7	25-Jun-96	74	60	120	114	100	***135***	134.06
8	03-Jul-96	60	53	105	95	115	***140***	134.50

This 14 year old male was randomized to imipramine 50mg/day on 07-May-96. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4. At the week 4 visit, the patient's standing pulse was elevated to 132bpm, a level of potential clinical concern. Pulse remained elevated through end of acute phase.

PID 329.009.00306

Vital Sign: Diastolic blood pressure (standing) decreased

Demography:	Age: 14 yrs	Height: 64.0 in Weight: 120.30 lbs	Sex: Female Race: Black

Country: United States

Medical History: Non-malignant lump removed from left breast

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Placebo

Start: **11-Jun-96**

End: **19-Aug-96**

Concomitant Drugs	**Start**	**End**
Feosol Liquid (ferrous sulfate)	24-Jul-96	Unknown

PID 329.009.00306

Adverse Experiences	Onset (Days into Study)	Duration
Hot Flashes	22	50 days
Anemia	-8	Unknown

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00306

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	11-Jun-96	49	70	115	117	70	98	120.30
1	18-Jun-96	53	58	94	98	99	96	118.50
2	25-Jun-96	90	76	140	131	90	87	116.20
3	02-Jul-96	59	72	117	118	79	93	118.40
4	09-Jul-96	66	60	114	92	78	100	117.60
5	16-Jul-96	55	58	104	114	85	94	117.20
6	23-Jul-96	55	67	110	107	79	98	118.60
7	30-Jul-96	45	58	98	93	76	95	119.40
8	06-Aug-96	40	***44***	105	94	91	96	118.70

This 14 year old female was randomized to placebo on 11-Jun-96. At the week 8 visit, the patient's standing diastolic blood pressure was low at 44mmHg, a level of clinical concern. Patient experienced hot flashes throughout the study.

PID 329.009.00324

Vital Sign: Systolic blood pressure (standing) decreased

Demography:	Age: 13 yrs	Height: 61.0 in	Sex: Female
		Weight: 126.30 lbs	Race: Caucasian

Country: United States

Medical History: Headaches (occasional), seasonal allergies, sinus congestion, unconscious (age 1) resulting from hitting head in a fall.

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **28-Oct-96**

End: **08-Jan-97**

Concomitant Drugs	**Start**	**End**
Tylenol Extra Strength (paracetamol)	01-Aug-96	Unknown
Tylenol Sinus (pseudoephedrine hydrochloride)	01-Aug-96	Unknown
Advil (ibuprofen)	01-Aug-96	Unknown
Sudafed (pseudoephedrine hydrochloride)	01-Aug-96	Unknown

PID 329.009.00324

Adverse Experiences	Onset (Days into Study)	Duration
Decreased Appetite	50	Ongoing
Nausea	2	21 days
Abnormal Dreams	29	Unknown
Insomnia	15	8 days
Respiratory Disorder	43	8 days
Rash	61	Ongoing

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00324

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	28-Oct-96	64	75	130	131	82	85	126.30
1	04-Nov-96	69	55	116	115	78	86	125.10
2	11-Nov-96	66	66	114	127	86	83	126.50
3	18-Nov-96	64	67	114	106	77	67	123.40
4	25-Nov-96	59	55	119	***77***	89	94	124.80
5	02-Dec-96	65	73	115	107	85	100	127.30
6	09-Dec-96	72	57	114	106	85	86	124.90
7	16-Dec-96	73	61	122	108	88	84	123.20
8	27-Dec-96	62	68	115	132	86	89	124.00

This 13 year old female was randomized to paroxetine 20mg/day on 28-Oct-96. At week 4, the patient's standing systolic blood pressure was low at 77mmHg, a level of potential clinical concern. Blood pressure returned to normal for the remainder of the acute phase.

PID 329.009.00325

Vital Sign: Pulse (standing) increased

Demography:	Age: 15 yrs	Height: 67.0	Sex: Female
		Weight: 116.00	Race: Caucasian

Country: United States

Medical History: Asthma, Headache (occasional), menstrual cramps, nauses (stomach upset).

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Imipramine

Start: **27-Aug-96**

End: **20-Oct-96**

Concomitant Drugs	**Start**	**End**
Zantac (ranitidine hydrochloride)	01-Jan-95	Unknown
Tylenol Extra Strength (paracetamol)	01-Jan-95	Unknown
Benadryl (diphenhydramine hydrochloride)	10-Oct-96	Unknown
Desogen (dofamium chloride)	22-Sep-96	Unknown
Orudis Kt (ketoprofen_	01-Jan-90	Unknown
Benadryl (diphenhydramine)	10-Oct-96	Unknown
Ventolin Inhaler (salbutamol)	01-Jan-90	Unknown

PID 329.009.00325

Adverse Experiences	Onset (Days into Study)	Duration
Chills	45	Ongoing
Headache	45	Ongoing
Syncope	6	1 day
Dry Mouth	28	8 days
Nausea	11	11 days
Abnormal Dreams	35	11 days
Dizziness	6	16 days
Cough Increased	45	Ongoing
Dyspnea	6	16 days
Rhinitis	45	Ongoing
Keratoconjunctivitis	14	8 days

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.009.00325

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	27-Aug-96	53	55	108	96	65	97	116.00
1	03-Sep-96	73	57	107	94	88	108	114.80
2	09-Sep-96	67	65	113	100	109	114	114.44
3	16-Sep-96	53	unknown	102	90	93	115	120.39
4	23-Sep-96	56	51	112	99	103	***131***	115.32
5	30-Sep-96	61	61	123	101	74	114	116.30
6	10-Oct-96	63	59	121	107	93	119	117.40
7	14-Oct-96	70	60	149	118	94	123	117.80
8	21-Oct-96	68	58	130	128	93	119	117.20

This 15 year old female was randomized to imipramine 50mg/day on 27-Aug-96. Dose was up-titrated to 200mg/day in 50mg/week increments by week 4. At the week 4 visit, the patient's standing pulse had increased to 131bpm, a level of potential clinical concern. Pulse remained lower for the remainder of the acute phase.

PID 329.010.00182

Vital Sign: Weight decreased

Demography:	Age: 18 yrs	Height: 71.0 in	Sex: Male
		Weight: 140.50	Race: Caucasian

Country: United States

Medical History: Headaches

Study Diagnosis: **MAJOR DEPRESSIVE DISORDER**

Study Drug: Paroxetine

Start: **19-Dec-95**

End: **18-Jan-96**

Concomitant Drugs	**Start**	**End**
Aspirin (acetylsalicylic acid)	28-Dec-95	28-Dec-95
Marijuana (cannabis)	01-Jan-92	Unknown
Tylenol (paracetamol)	12-Dec-95	12-Dec-95

PID 329.010.00182

Adverse Experiences	Onset (Days into Study)	Duration
Headache	10	1 day

Vital Sign Remarks:

Individual vital sign values were regarded as being of potential clinical concern if they fell outside the normal ranges shown below and had changed from baseline by the amount shown below.

Parameter	Outside Normal Range	Increase	Decrease
Diastolic Blood Pressure (DBP)	NL range: 50 - 105 mmHg	≥ 30 mmHg	≥ 20 mmHg
Systolic Blood Pressure (SBP)	NL range: 90 - 180 mmHg	≥ 40 mmHg	≥ 30 mmHg
Pulse Rate	NL range: 50 - 120 bpm	≥ 30 bpm	≥ 30 bpm
Body Weight	-	≥ 7 %	≥ 7 %

PID 329.010.00182

This patient's vital sign data are summarized in the table below, with values of potential clinical concern indicated in bold italics.

Week	Date	SitDBP (mmHg)	StDBP (mmHg)	SitSBP (mmHg)	StSBP (mmHg)	SitPulse (bpm)	StPulse (bpm)	Weight (lb)
0	19-Dec-95	80	87	110	112	68	84	140.50
3	12-Jan-96	72	82	118	122	72	84	135.50
4	19-Jan-96	75	70	118	124	66	74	***130.00***

This 18 year old male was randomized to paroxetine 20mg/day on 19-Dec-95. By the week 4 visit the patient had lost 10 lbs since the start of study. This was of potential clinical concern. The patient did not return following week4 and was lost to follow up.

PAROXETINE - PROTOCOL 329

Table 14.13

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

Treatment Group=PAROXETINE

N = 93

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Alanine Aminotransferase (U/L)	Screening	86	13.81	8.95	4.00	69.00
	Baseline	7	11.57	6.02	4.00	20.00
	Week 1	1	4.00	.	4.00	4.00
	Week 4	1	14.00	.	14.00	14.00
	Week 7	1	23.00	.	23.00	23.00
	Week 8	64	15.09	10.19	5.00	74.00
Alkaline Phosphatase (U/L)	Screening	86	143.83	85.94	23.00	398.00
	Baseline	7	125.43	62.97	58.00	230.00
	Week 1	1	93.00	.	93.00	93.00
	Week 4	1	52.00	.	52.00	52.00
	Week 7	1	67.00	.	67.00	67.00
	Week 8	64	130.41	68.76	39.00	319.00
Aspartate Aminotransferase (U/L)	Screening	86	17.31	4.83	9.00	34.00
	Baseline	7	20.00	6.56	14.00	34.00
	Week 1	1	14.00	.	14.00	14.00
	Week 4	1	15.00	.	15.00	15.00
	Week 7	1	14.00	.	14.00	14.00
	Week 8	64	18.16	5.09	9.00	37.00
Total Bilirubin (mg/dL)	Screening	86	0.69	0.26	0.20	2.10
	Baseline	7	0.80	0.33	0.60	1.50
	Week 1	1	0.50	.	0.50	0.50
	Week 4	1	0.70	.	0.70	0.70
	Week 7	1	0.60	.	0.60	0.60
	Week 8	64	0.64	0.17	0.40	1.10
Blood Urea Nitrogen (mg/dL)	Screening	86	11.12	2.73	6.00	19.00
	Baseline	7	12.29	2.50	9.00	15.00
	Week 1	1	13.00	.	13.00	13.00
	Week 4	1	16.00	.	16.00	16.00
	Week 7	1	6.00	.	6.00	6.00
	Week 8	64	11.55	2.78	7.00	18.00
Creatinine (mg/dL)	Screening	86	1.04	1.20	0.50	12.00
	Baseline	7	0.89	0.18	0.70	1.10
	Week 1	1	1.10	.	1.10	1.10
	Week 4	1	1.30	.	1.30	1.30
	Week 7	1	0.80	.	0.80	0.80
	Week 8	64	0.89	0.14	0.60	1.20

PAROXETINE - PROTOCOL 329

Table 14.13

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

Treatment Group=PAROXETINE

N = 93

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Basophils (%)	Screening	87	0.65	0.43	0.00	2.00
	Baseline	14	0.91	0.54	0.10	1.70
	Week 4	4	0.43	0.21	0.20	0.70
	Week 5	1	0.30	.	0.30	0.30
	Week 7	1	1.30	.	1.30	1.30
	Week 8	64	0.61	0.51	0.00	2.90
Eosinophils (%)	Screening	87	4.21	2.33	1.00	11.50
	Baseline	14	3.06	1.88	0.60	6.80
	Week 4	4	3.93	1.89	2.00	6.50
	Week 5	1	9.00	.	9.00	9.00
	Week 7	1	4.40	.	4.40	4.40
	Week 8	64	4.30	2.23	0.00	9.50

PAROXETINE - PROTOCOL 329

Table 14.13

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

Treatment Group=PAROXETINE

N = 93

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Hematocrit (vol%)	Screening	82	41.22	4.58	32.70	67.30
	Baseline	14	39.25	3.59	30.90	44.00
	Week 4	4	47.75	16.56	36.60	72.40
	Week 5	1	41.10	.	41.10	41.10
	Week 7	1	39.80	.	39.80	39.80
	Week 8	62	39.78	3.54	34.10	49.90
Hemoglobin (g%)	Screening	82	14.03	1.56	10.50	22.70
	Baseline	14	13.30	1.30	10.00	15.10
	Week 4	4	16.30	5.65	12.50	24.70
	Week 5	1	14.10	.	14.10	14.10
	Week 7	1	13.70	.	13.70	13.70
	Week 8	62	13.57	1.20	11.50	17.20
Lymphocytes (%)	Screening	87	33.61	7.90	16.00	60.00
	Baseline	14	28.75	7.14	18.50	43.00
	Week 4	4	34.05	10.66	19.70	43.10
	Week 5	1	23.80	.	23.80	23.80
	Week 7	1	25.80	.	25.80	25.80
	Week 8	64	32.95	11.48	5.00	57.00
Monocytes (%)	Screening	87	7.07	2.31	2.60	16.50
	Baseline	14	6.55	1.82	4.40	11.10
	Week 4	4	5.40	1.89	3.20	7.30
	Week 5	1	3.20	.	3.20	3.20
	Week 7	1	9.00	.	9.00	9.00
	Week 8	64	6.80	2.61	0.00	12.40
Neutrophil Bands (%)	Screening	7	8.43	21.01	0.00	56.00
	Baseline	1	0.00	.	0.00	0.00
	Week 8	4	2.25	2.63	0.00	5.00
Segmented Neutrophils (%)	Screening	87	54.40	9.00	31.00	75.80
	Baseline	14	60.74	6.96	48.00	70.00
	Week 4	4	56.25	10.31	46.10	70.20
	Week 5	1	63.60	.	63.60	63.60
	Week 7	1	59.60	.	59.60	59.60
	Week 8	64	55.15	12.40	34.30	89.00
Platelets (k/mm**3)	Screening	82	298549	378922	10000.0	3640000
	Baseline	14	256000	32270.5	183000	309000

PAROXETINE - PROTOCOL 329

Table 14.13

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

Treatment Group=PAROXETINE

N = 93

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Platelets (k/mm**3)	Week 4	4	189250	117690	17000.0	271000
	Week 5	1	247000	.	247000	247000
	Week 7	1	256000	.	256000	256000
	Week 8	62	248097	74300.8	10000.0	417000
White Blood Cell Count (k/mm**3)	Screening	82	6.91	2.19	3.40	14.00
	Baseline	14	7.01	2.28	3.60	10.20
	Week 4	5	9.24	6.00	4.50	19.10
	Week 5	1	9.00	.	9.00	9.00
	Week 7	1	5.60	.	5.60	5.60
	Week 8	62	7.20	2.44	3.60	16.70

Table 14.13

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

Treatment Group=IMIPRAMINE

N = 95

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Alanine Aminotransferase (U/L)	Screening	89	14.22	10.26	5.00	78.00
	Baseline	8	11.63	2.83	8.00	15.00
	Week 2	2	9.50	2.12	8.00	11.00
	Week 3	1	26.00	.	26.00	26.00
	Week 5	1	11.00	.	11.00	11.00
	Week 7	3	27.00	23.52	11.00	54.00
	Week 8	55	16.07	8.42	4.00	43.00
Alkaline Phosphatase (U/L)	Screening	87	142.45	92.33	41.00	426.00
	Baseline	8	125.75	90.76	42.00	293.00
	Week 2	2	125.50	75.66	72.00	179.00
	Week 3	1	239.00	.	239.00	239.00
	Week 5	1	199.00	.	199.00	199.00
	Week 7	3	178.33	142.61	96.00	343.00
	Week 8	55	131.40	79.59	42.00	367.00
Aspartate Aminotransferase (U/L)	Screening	89	17.82	5.30	9.00	44.00
	Baseline	8	17.63	2.26	13.00	20.00
	Week 2	2	13.50	2.12	12.00	15.00
	Week 3	1	21.00	.	21.00	21.00
	Week 5	1	21.00	.	21.00	21.00
	Week 7	3	32.33	30.02	15.00	67.00
	Week 8	55	18.04	4.50	9.00	31.00
Total Bilirubin (mg/dL)	Screening	89	0.69	0.25	0.40	1.80
	Baseline	8	0.78	0.24	0.50	1.30
	Week 2	2	1.10	0.57	0.70	1.50
	Week 3	1	0.70	.	0.70	0.70
	Week 5	1	0.60	.	0.60	0.60
	Week 7	3	0.63	0.15	0.50	0.80
	Week 8	55	0.65	0.20	0.40	1.30
Blood Urea Nitrogen (mg/dL)	Screening	89	11.04	2.74	5.00	17.00
	Baseline	8	11.25	2.96	8.00	17.00
	Week 2	2	10.00	0.00	10.00	10.00
	Week 3	1	6.00	.	6.00	6.00
	Week 5	1	9.00	.	9.00	9.00
	Week 7	3	10.67	4.73	7.00	16.00
	Week 8	55	10.62	2.49	6.00	18.00
Creatinine (mg/dL)	Screening	89	0.91	0.14	0.60	1.40

Table 14.13

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

Treatment Group=IMIPRAMINE

N = 95

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Creatinine (mg/dL)	Baseline	8	0.95	0.12	0.70	1.10
	Week 2	2	0.90	0.14	0.80	1.00
	Week 3	1	1.00	.	1.00	1.00
	Week 5	1	0.90	.	0.90	0.90
	Week 7	3	1.03	0.23	0.90	1.30
	Week 8	55	0.95	0.11	0.80	1.20
Basophils (%)	Screening	88	0.66	0.50	0.00	2.60
	Baseline	11	0.70	0.67	0.00	2.50
	Week 1	2	0.55	0.07	0.50	0.60
	Week 2	2	0.55	0.07	0.50	0.60
	Week 3	2	1.05	0.07	1.00	1.10
	Week 5	2	0.40	0.57	0.00	0.80
	Week 6	1	2.00	.	2.00	2.00
	Week 7	3	1.20	0.56	0.70	1.80
	Week 8	55	0.57	0.34	0.00	1.20
Eosinophils (%)	Screening	88	3.66	2.66	0.40	17.70
	Baseline	11	4.63	3.40	0.00	8.90
	Week 1	2	3.00	2.26	1.40	4.60
	Week 2	2	4.50	3.39	2.10	6.90
	Week 3	2	2.65	1.20	1.80	3.50
	Week 5	2	4.50	3.54	2.00	7.00
	Week 6	1	1.00	.	1.00	1.00
	Week 7	3	2.63	1.17	1.60	3.90
	Week 8	56	3.24	2.58	0.00	9.00

Table 14.13

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

Treatment Group=IMIPRAMINE

N = 95

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Hematocrit (vol%)	Screening	86	40.75	3.16	34.60	49.10
	Baseline	11	41.10	1.60	38.60	43.50
	Week 1	2	41.00	4.24	38.00	44.00
	Week 2	2	40.60	3.25	38.30	42.90
	Week 3	2	38.65	3.32	36.30	41.00
	Week 5	2	39.15	0.21	39.00	39.30
	Week 7	3	40.77	2.91	38.70	44.10
	Week 8	54	41.13	3.35	30.40	48.70
Hemoglobin (g%)	Screening	86	13.94	1.02	11.80	16.50
	Baseline	11	14.09	0.60	13.40	15.20
	Week 1	2	14.05	1.06	13.30	14.80
	Week 2	2	13.80	0.99	13.10	14.50
	Week 3	2	13.25	1.48	12.20	14.30
	Week 5	2	13.40	0.00	13.40	13.40
	Week 7	3	14.10	1.35	13.00	15.60
	Week 8	54	14.08	1.12	10.30	16.20
Lymphocytes (%)	Screening	88	34.49	8.51	17.80	58.00
	Baseline	11	36.85	7.17	23.00	49.00
	Week 1	2	26.05	8.98	19.70	32.40
	Week 2	2	31.95	0.78	31.40	32.50
	Week 3	2	43.70	2.40	42.00	45.40
	Week 5	2	27.95	10.39	20.60	35.30
	Week 6	1	39.00	.	39.00	39.00
	Week 7	3	26.13	12.10	14.10	38.30
	Week 8	56	30.85	7.59	15.00	52.00
Monocytes (%)	Screening	88	6.92	2.34	2.00	16.20
	Baseline	11	7.32	2.03	3.00	10.00
	Week 1	2	5.30	4.81	1.90	8.70
	Week 2	2	6.25	2.62	4.40	8.10
	Week 3	2	9.05	0.07	9.00	9.10
	Week 5	2	6.35	0.64	5.90	6.80
	Week 6	1	4.00	.	4.00	4.00
	Week 7	3	6.00	2.95	4.10	9.40
	Week 8	56	6.79	1.89	3.00	12.20
Neutrophil Bands (%)	Screening	4	0.25	0.50	0.00	1.00
	Baseline	1	0.00	.	0.00	0.00
	Week 8	4	0.50	1.00	0.00	2.00

Table 14.13

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

Treatment Group=IMIPRAMINE

N = 95

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Segmented Neutrophils (%)	Screening	88	54.07	9.21	32.00	72.90
	Baseline	11	50.51	5.91	40.60	60.40
	Week 1	2	65.10	11.46	57.00	73.20
	Week 2	2	56.75	6.86	51.90	61.60
	Week 3	2	43.60	0.99	42.90	44.30
	Week 5	2	60.85	5.73	56.80	64.90
	Week 6	1	54.00	.	54.00	54.00
	Week 7	3	64.10	10.21	52.70	72.40
	Week 8	56	58.56	8.17	40.00	82.00
Platelets (k/mm**3)	Screening	86	261023	76425.4	45000.0	451000
	Baseline	11	238455	50422.9	163000	306000
	Week 1	2	215000	50911.7	179000	251000
	Week 2	2	207500	47376.2	174000	241000
	Week 3	2	279500	10606.6	272000	287000
	Week 5	2	276500	45961.9	244000	309000
	Week 7	3	280333	35076.1	244000	314000
	Week 8	54	258481	71600.0	44000.0	376000
White Blood Cell Count (k/mm**3)	Screening	86	6.64	1.84	3.50	12.30
	Baseline	11	6.06	1.85	3.10	9.10
	Week 1	2	8.20	3.25	5.90	10.50
	Week 2	2	7.30	3.82	4.60	10.00
	Week 3	2	5.45	0.78	4.90	6.00
	Week 5	2	7.35	1.48	6.30	8.40
	Week 7	3	5.90	0.92	5.10	6.90
	Week 8	54	6.65	1.71	3.10	12.90

Table 14.13

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

Treatment Group=PLACEBO

N = 87

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Alanine Aminotransferase (U/L)	Screening	80	13.95	9.42	5.00	68.00
	Baseline	9	10.56	3.43	7.00	17.00
	Week 1	2	9.50	3.54	7.00	12.00
	Week 2	1	7.00	.	7.00	7.00
	Week 4	2	6.50	2.12	5.00	8.00
	Week 5	2	8.00	1.41	7.00	9.00
	Week 8	64	14.58	9.10	4.00	54.00
Alkaline Phosphatase (U/L)	Screening	78	127.13	77.57	32.00	344.00
	Baseline	9	240.56	306.06	72.00	1028.00
	Week 1	2	218.00	165.46	101.00	335.00
	Week 2	1	69.00	.	69.00	69.00
	Week 4	2	90.50	36.06	65.00	116.00
	Week 5	2	104.00	18.38	91.00	117.00
	Week 8	64	114.39	62.84	36.00	406.00
Aspartate Aminotransferase (U/L)	Screening	80	17.36	5.12	9.00	39.00
	Baseline	9	15.78	4.49	10.00	23.00
	Week 1	2	18.00	0.00	18.00	18.00
	Week 2	1	15.00	.	15.00	15.00
	Week 4	2	13.50	3.54	11.00	16.00
	Week 5	2	16.00	2.83	14.00	18.00
	Week 8	64	17.53	6.89	8.00	58.00
Total Bilirubin (mg/dL)	Screening	80	0.72	0.20	0.40	1.50
	Baseline	9	0.74	0.19	0.50	1.10
	Week 1	2	0.90	0.14	0.80	1.00
	Week 2	1	0.60	.	0.60	0.60
	Week 4	2	0.90	0.42	0.60	1.20
	Week 5	2	0.80	0.28	0.60	1.00
	Week 8	64	0.70	0.16	0.40	1.20
Blood Urea Nitrogen (mg/dL)	Screening	80	11.71	11.18	4.00	107.00
	Baseline	9	13.22	3.80	9.00	20.00
	Week 1	2	11.50	0.71	11.00	12.00
	Week 2	1	11.00	.	11.00	11.00
	Week 4	2	14.50	3.54	12.00	17.00
	Week 5	2	10.00	0.00	10.00	10.00
	Week 8	64	11.19	2.41	5.00	18.00
Creatinine (mg/dL)	Screening	80	1.09	1.38	0.70	13.20

Table 14.13

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

Treatment Group=PLACEBO

N = 87

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Creatinine (mg/dL)	Baseline	9	0.97	0.17	0.70	1.30
	Week 1	2	0.85	0.07	0.80	0.90
	Week 2	1	0.90	.	0.90	0.90
	Week 4	2	0.90	0.00	0.90	0.90
	Week 5	2	1.00	0.00	1.00	1.00
	Week 8	64	0.93	0.16	0.60	1.40
Basophils (%)	Screening	81	0.74	0.51	0.00	2.70
	Baseline	8	0.34	0.23	0.00	0.60
	Week 1	1	1.00	.	1.00	1.00
	Week 2	1	1.00	.	1.00	1.00
	Week 4	4	0.73	0.25	0.40	1.00
	Week 5	2	1.50	0.57	1.10	1.90
	Week 8	65	0.75	0.53	0.00	2.90
Eosinophils (%)	Screening	81	3.86	2.55	0.00	12.30
	Baseline	8	3.05	2.57	1.50	9.30
	Week 1	1	7.00	.	7.00	7.00
	Week 2	1	5.80	.	5.80	5.80
	Week 4	4	3.03	0.79	2.10	4.00
	Week 5	2	2.35	0.92	1.70	3.00
	Week 8	65	3.48	2.53	0.00	12.90

Table 14.13

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

Treatment Group=PLACEBO

N = 87

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Hematocrit (vol%)	Screening	81	41.13	4.73	34.00	69.90
	Baseline	8	41.78	2.30	39.80	46.60
	Week 1	1	41.60	.	41.60	41.60
	Week 2	1	38.10	.	38.10	38.10
	Week 4	4	40.73	2.01	38.50	43.00
	Week 5	2	39.85	2.47	38.10	41.60
	Week 8	64	40.55	3.64	33.90	52.30
Hemoglobin (g%)	Screening	81	14.06	1.63	11.40	24.00
	Baseline	8	14.05	0.96	13.00	16.10
	Week 1	1	14.60	.	14.60	14.60
	Week 2	1	13.00	.	13.00	13.00
	Week 4	4	13.78	0.57	13.10	14.50
	Week 5	2	13.75	0.78	13.20	14.30
	Week 8	64	13.88	1.17	11.50	17.10
Lymphocytes (%)	Screening	81	32.67	8.50	17.00	51.00
	Baseline	8	30.66	9.43	18.70	44.40
	Week 1	1	28.60	.	28.60	28.60
	Week 2	1	37.90	.	37.90	37.90
	Week 4	4	37.63	20.54	21.20	67.00
	Week 5	2	31.80	4.67	28.50	35.10
	Week 8	65	32.21	7.11	15.80	50.70
Monocytes (%)	Screening	81	6.59	2.13	2.70	11.50
	Baseline	8	6.35	1.60	4.00	8.60
	Week 1	1	5.10	.	5.10	5.10
	Week 2	1	2.50	.	2.50	2.50
	Week 4	4	9.68	4.07	5.20	14.00
	Week 5	2	6.10	1.41	5.10	7.10
	Week 8	65	6.74	2.21	2.00	13.20
Neutrophil Bands (%)	Screening	2	1.00	1.41	0.00	2.00
	Week 8	6	0.50	1.22	0.00	3.00
Segmented Neutrophils (%)	Screening	81	56.13	9.81	32.30	74.30
	Baseline	8	59.56	12.22	41.10	75.70
	Week 1	1	58.40	.	58.40	58.40
	Week 2	1	52.80	.	52.80	52.80
	Week 4	4	49.00	24.53	14.00	70.80
	Week 5	2	58.25	7.57	52.90	63.60

Table 14.13

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

Treatment Group=PLACEBO

N = 87

Parameter	Visit	N	Mean	S.D.	Minimum	Maximum
Segmented Neutrophils (%)	Week 8	65	56.57	8.06	37.30	78.20
Platelets (k/mm**3)	Screening	81	262753	78059.2	12000.0	606000
	Baseline	8	252750	54818.5	193000	318000
	Week 1	1	253000	.	253000	253000
	Week 2	1	219000	.	219000	219000
	Week 4	4	272500	32419.1	233000	305000
	Week 5	2	277000	53740.1	239000	315000
	Week 8	64	262703	86151.3	103000	771000
White Blood Cell Count (k/mm**3)	Screening	81	6.79	2.07	3.10	19.10
	Baseline	8	6.36	1.25	5.00	9.00
	Week 1	1	8.70	.	8.70	8.70
	Week 2	1	7.60	.	7.60	7.60
	Week 4	4	6.50	1.63	4.40	8.30
	Week 5	2	7.50	0.42	7.20	7.80
	Week 8	64	6.78	1.86	4.40	11.70

PAROXETINE - PROTOCOL 329

Table 14.14

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

Parameter		PAROXETINE N = 93 n	%	IMIPRAMINE N = 95 n	%	PLACEBO N = 87 n	%
Alanine Aminotransferase	H	0	0.0	0	0.0	0	0.0
Alkaline Phosphatase	H	0	0.0	0	0.0	1	1.1
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	0	0.0	0	0.0	3	3.4
Hematocrit	L	2	2.2	3	3.2	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	1	1.1
Platelets	H	0	0.0	0	0.0	1	1.1
	L	4	4.3	2	2.1	0	0.0
White Blood Cell Count	H	2	2.2	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 14.14

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

Parameter		PAROXETINE N = 93 n	%	IMIPRAMINE N = 95 n	%	PLACEBO N = 87 n	%
Urine Protein - Dipstick	H	0	0.0	0	0.0	0	0.0
Urine Red Blood Cells/HPF	H	5	5.4	1	1.1	2	2.3
Urine White Blood Cells/HPF	H	1	1.1	1	1.1	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.

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SmithKline Beecham

Paroxetine

BRL-029060

Clinically Significant Abnormal Laboratory Values Patient Narratives

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Table 14.14a

SB Document Number: BRL-029060/RSD-100TX2/1

PID 329.001.00121

Laboratory Parameters: **Decreased hematocrit**

Demography: Age: 15 years Height: 74.0 in. Sex: Male
Weight: 143.50 lbs. Race: Caucasian

Country: **United States**

Medical History: **Decreased white blood cell count, birthmark removed, chicken pox, cyst removed from chest**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 04-Apr-95

Stop Date: 29-May-95

Lab Remarks:
The patient entered the study on 04-Apr-95 with a baseline hematocrit of 40.2% which was slightly below the reference range of 41-50%. At week 8, the hematocrit had decreased to 36.2% (abnormal ≤ 37.0 male) which was considered to be of clinical concern by the investigator; however, this was not reported as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Hematocrit	Baseline	40.2	%	41-50
Hematocrit	8	36.2	%	41-50

Adverse Experiences:	Onset (Days into Study)	Duration
Nausea	3	27 days
Weight loss	8	22 days
Dizziness	50	20 min.
Acne	9	20 days

Concomitant Drugs:
None

PID 329.002.00058

Laboratory Parameters: **Increased urine white blood cells**

Demography: Age: 16 years Height: 62.6 in. Sex: Female
Weight: 203.50 lbs. Race: Caucasian

Country: **United States**

Medical History: **Headaches, attention deficit disorders**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 20-Sep-94

Stop Date: 16-Nov-94

Lab Remarks:
This patient entered the study on 20-Sep-94 with urine white blood cells reading of negative. At week 8, the urine white blood cells were 15-25 (abnormal >10) which was considered of clinical concern by the investigator; however, this was not reported as an adverse experience. The patient had a throat infection at week 8 with a positive culture for beta hemolytic streptococcus Group A.

Lab Test Code/Name	Week	Lab Value
Urine white blood cells	8	15-25

Adverse Experiences:	Onset (Days into Study)	Duration
Infection (strep throat)	58	3 days

Concomitant Drugs:
None

PID 329.003.00074

Laboratory Parameters: **Increased alkaline phosphatase**

Demography:	Age: 13 years	Height: 61.4 in. Weight: 94.20 lbs.	Sex: Male Race: Columbian/ Yugoslavic

Country: **United States**

Medical History: **Appendicitis 1994**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Placebo**

Start Date: 25-Jan-95

Stop Date: 21-Mar-95

Lab Remarks:
The patient entered the study on 25-Jan-95 with a baseline alkaline phosphatase of 344.0 D/L which was within normal limits. At week 8, the alkaline phosphatase had increased to 406.0 D/L which was flagged as above the level of clinical concern (≥ 390). This finding, however, was not reported as an adverse experience by the investigator.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Alkaline phosphatase	Baseline	344.0	D/L	44-400
Alkaline phosphatase	8	406.0	D/L	44-400

Adverse Experiences:	Onset (Days into Study)	Duration
Headaches	16	1.30 hours
Constipation	25	12 days

Concomitant Drugs:
None

PID 329.003.00289

Laboratory Parameters: **Decreased hematocrit**

Demography: Age: 16 years Height: 63.0 in. Sex: Female
Weight: 119.07 lbs. Race: Hispanic

Country: **United States**

Medical History: **Allergic Rhinitis, Dysmenorrhea, Headaches, Asthma**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Imipramine**

Start Date: 28-Feb-96

Stop Date: 23-Apr-96

Lab Remarks:
The patient entered the study on 28-Feb-96 with a hematocrit at screening of 35.3% which was within the normal reference range of 35-46% for female patients. At week 8, the hematocrit had decreased to 30.4% (abnormal ≤ 32.0% females). However, this was not reported as an adverse experience by the investigator.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Hematocrit	Baseline	35.3	%	35-46
Hematocrit	8	30.4	%	35-46

Adverse Experiences:	Onset (Days into Study)	Duration
Headaches	1	ongoing (85 days)
Dry mouth	13	31 days
Insomnia	15	ongoing (129 days)

Concomitant Drugs:	Start	End
Pamprin (mepyramine maleate)	unknown	unknown
Tylenol (paracetamol)	unknown	unknown

PID 329.003.00316

Laboratory Parameters: **Increased platelets**

Demography: Age: 16 years Height: 65.8 in. Sex: Female
Weight: 135.00 lbs. Race: Caucasian

Country: **United States**

Medical History: **None**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Placebo**

Start Date: 17-Dec-96

Stop Date: 18-Feb-97

Lab Remarks:
The patient entered the study on 17-Dec-96 and had a baseline platelet count of 606,000 which exceeded the normal range of 130,000-400,000 per cumm. At week 8, the platelets had increased to 771,000 and this value was flagged as above the level of clinical concern. Creatinine was within normal range (0.8-1.5 mg/DL) at baseline (0.8 mg/DL) and was flagged as low at week 8 (0.7 mg/DL). The investigator considered the increased platelets as an adverse experience, which was reported as thrombocythemia of mild intensity, probably unrelated to study drug, required no corrective therapy, and did not result in the drug being stopped. No other adverse experiences were reported.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Platelets	Baseline	606,000	per cumm	130,000 - 400,000
Platelets	8	771,000	per cumm	130,000 - 400,000

Adverse Experiences:	Onset (Days into Study)	Duration
Thrombocytopenia	57	unknown

Concomitant Drugs:
None

PID 329.005.00007

Laboratory Parameters: **Decreased platelets**

Demography: Age: 15 years Height: 64.0 in. Weight: 132.30 lbs. Sex: Female Race: Caucasian

Country: **United States**

Medical History: **Questionable ovarian cyst**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Imipramine**

Start Date: 09-Nov-94

Stop Date: 10-Jan-95

Lab Remarks:
The patient entered the study on 09-Nov-94 and had a baseline platelet count of 307,000 which was within normal range. At week 8, the platelet count had decreased to 44,000 and was flagged as below the level of clinical concern (≤ 75,000). The platelet count was recorded as low due to in vitro clumping of the platelets. The investigator did not report the finding as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Platelets	Baseline	307,000	per cumm	130,000 - 400,000
Platelets	8	44,000	per cumm	130,000 - 400,000

Adverse Experiences:	Onset (Days into Study)	Duration
Infection	32 days	4 days
Postural hypotension	23 days	14 days
Dry mouth	42 days	ongoing (151 days)
Tremor	42 days	6 days
Urticaria	2 days	5 days

PID 329.005.00007

Concomitant Drugs:	**Start**	**End**
Caladryl lotion (calamine)	10-Nov-94	14-Nov-94
Birth control pills (oral contraceptive)	04-Apr-94	Unknown

PID 329.005.00009

Laboratory Parameters: **Decreased platelets**

Demography: Age: 16 years Height: 63.0 in. Weight: 145.00 lbs. Sex: Female Race: Mixed

Country: **United States**

Medical History: **Headache, hay fever**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Imipramine**

Start Date: 12-Dec-94

Stop Date: 22-Feb-95

Lab Remarks:
The patient entered the study on 12-Dec-94 and had a baseline platelet count of 211,000 which was within the normal range. At week 8, the platelets had decreased to 54,000 which was flagged as below the level of clinical concern. The week 8 platelet count was low due to in vitro clumping. The investigator did not report the finding as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Platelets	Baseline	211,000	per cumm	130,000 - 400,000
Platelets	8	54,000	per cumm	130,000 - 400,000

Adverse Experiences:	Onset (Days into Study)	Duration
Headache	5	4 days
Headache	21	4 hours
Headache	11	6 days
Dry mouth	5	unknown
Dyspepsia	29	3 hours
Dyspepsia	6	unknown
Leukocytosis	-5	1 day

PID 329.005.00009

Leukopenia	-5	1 day
Hyperglycemia	59	1 day
Tremor	32	unknown
Dysmenorrhea	40	5 days
Haematuria	-5	1 day

Concomitant Drugs:	**Start**	**End**
Tylenol (paracetamol)	01-Dec-94	07-Dec-94

PID 329.005.00011

Laboratory Parameters: **Platelets decreased**

Demography: Age: 16 years Height: 69.0 in. Sex: Female
Weight: 122.00 lbs. Race: Caucasian

Country: **United States**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 13-Dec-94

Stop Date: 06-Feb-95

Lab Remarks:
The patient entered the study on 13-Dec-94 with a baseline platelet count of 235,000, which was within the normal range. At week 8, the platelet count had decreased to 51,000 (abnormal ≤ 75,000) which was considered to be of clinical concern by the investigator. However, this was not reported as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Platelets	Baseline	235,000	per cumm	130,000 - 400,000
Platelets	8	51,000	per cumm	130,000 - 400,000

Adverse Experiences:	Onset (Days into Study)	Duration
Asthenia	47 days	Unknown
Headache	8 days	10 days
Dizziness	21 days	34 days

Concomitant Drugs:	Start	End
Tylenol (paracetamol)	20-Dec-94	03-Jan-95

PID 329.005.00112

Laboratory Parameters: **Platelets decreased**

Demography: Age: 13 years Height: 61.0 in. Sex: Male
Weight: 115.00 lbs. Race: Caucasian

Country: **United States**

Medical History: **Burning stomach**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 26-Jan-95

Stop Date: 21-Mar-95

Lab Remarks:
The patient entered the study on 26-Jan-95 with a baseline platelet count of 245,000 which was within the normal range. At week 8, the platelet count had decreased to 10,000 (abnormal≤75,000) which was flagged to be of clinical concern. The reason the platelet count was low was due to in vitro clumping. This was not reported as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Platelets	Baseline	245,000	per cumm	130,000 - 400,000
Platelets	8	10,000	per cumm	130,000 - 400,000

Adverse Experiences:	Onset (Days into Study)	Duration
Fever	-2	3 days
Headache	-2	3 days
Infection (flu)	47	2 days
Tooth disorder	32	10.30 hours

PID 329.005.00112

Concomitant Drugs:	**Start**	**End**
Tylenol (paracetamol)	24-Jan-95	26-Jan-95

PID 329.005.00116

Laboratory Parameters: **Platelets decreased**

Demography: Age: 16 years Height: 71.0 in. Weight: 206.50 lbs. Sex: Female Race: Caucasian

Country: **United States**

Medical History: **None**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 07-Feb-95

Stop Date: 05-Apr-95

Lab Remarks:
The patient entered the study on 07-Feb-95 with a baseline platelet count of 284,000 which was within the normal range. At week 8, the platelet count was 71,000 (abnormal ≤ 75,000). This low reading was due to in vitro clumping of the platelets. The reading at week 8 was flagged to be of clinical concern, but was not reported as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Platelets	Baseline	284,000	per cumm	130,000 - 400,000
Platelets	8	71,000	per cumm	130,000 - 400,000

Adverse Experiences:	Onset (Days into Study)	Duration
Infection (flu)	28	24 hours
Dry mouth	4	ongoing (152 days)
Dyspepsia	2	6 days
Increased appetite	9	ongoing (162 days)
Myalgia	30	2 days
Tremor	26	29 days

PID 329.005.00116

Bronchitis	26	25 days
Otite's Media	26	25 days

Concomitant Drugs:	**Start**	**End**
Amoxicillin	04-Mar-95	14-Mar-95
Augmentin (amoxicillin trihydrate)	03-Mar-95	13-Mar-95
Tylenol (paracetamol)	03-Mar-95	04-Apr-95
Ventolin inhaler (salbutomol)	04-Mar-95	14-Mar-95
Ear drops (Nos)	03-Mar-95	04-Apr-95

PID 329.005.00257

Laboratory Parameters: **Platelets decreased**
White blood cell count increased

Demography: Age: 12 years Height: 63.0 in. Sex: Female
Weight: 112.50 lbs. Race: Caucasian

Country: **United States**

Medical History: **Acne**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 11-Mar-96

Stop Date: 05-May-96

Lab Remarks:
The patient entered the study on 11-Mar-96 with a baseline platelet count of 136,000 which was within normal range and a white blood cell count of 7, also within normal range. At week 4, the platelet count had decreased to 17,000 which was due to in vitro clumping of the sample. The white blood cell count at week 4 had increased to 19.1 (abnormal > 10) and was reported to be of clinical concern. At week 8, the platelets had increased to 214,000, well within normal range and the white blood cell count had decreased to 11.4, also within normal range.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Platelets	Baseline	136,000	per cumm	130,000 - 400,000
Platelets	4	17,000	per cumm	130,000 - 400,000
Platelets	8	214,000	per cumm	130,000 - 400,000
White blood cell count	Baseline	7	thou/MCL	4.5-13
White blood cell count	4	19.1	thou/MCL	4.5-13
White blood cell count	8	11.4	thou/MCL	4.5-13

PID 329.005.00257

Adverse Experiences:	**Onset (Days into Study)**	**Duration**
Respiratory disorder (cold symptoms)	8	9 days
Sinusitis	14	7 days

Concomitant Drugs:	**Start**	**End**
Vitamin C (ascorbic acid)	13-Mar-96	unknown
Ceclor (cefaclor)	25-Mar-96	05-Apr-96
Slo-Bid (theophylline)	03-May-96	10-May-96
Flonase (fluticasone propionate)	22-Apr-96	28-Apr-96
Accutane (isotretinoin)	11-Nov-95	unknown
Semprex-D (acrivastine)	24-Mar-96	24-Mar-96
Rynatan (chlorphenamine)	25-Mar-96	27-Mar-96
Albuterol (salbutamol)	22-Apr-96	06-May-96

PID 329.005.00258

Laboratory Parameters: **Increased urine red blood cells**

Demography: Age: 14 years Height: 64.0 in. Sex: Female
Weight: 171.70 lbs. Race: Caucasian

Country: **United States**

Medical History: **Hematuria, proteinuria**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 12-Mar-96

Stop Date: 06-May-96

Lab Remarks:
The patient entered the study on 12-Mar-96 with a baseline urine red blood cells 5-10. At week 8, the urine red blood cells were 15-25 and the value was flagged as above the level of clinical concern (abnormal > 10 female). This finding was not reported as an adverse experience by the investigator.

Lab Test Code/Name	Week	Lab Value
Urine red blood cells	Baseline	5-10
Urine red blood cells	8	15-25

Adverse Experiences:	Onset (Days into Study)	Duration
Abdominal pain	10	2 hours
Abdominal pain	25	4 days
Headache	10	4 days
Headache	25	4 days
Tooth disorder	21	3.30 hours
Tooth disorder	28	2.40 hours
Cough increased	-4	8 days
Urine abnormality	57	unknown

PID 329.005.00258

Concomitant Drugs:	**Start**	**End**
Tylenol (paracetamol)	01-Apr-96	01-Apr-96
Robitussin (quaifenesin)	13-Mar-96	13-Mar-96

PID 329.007.00140

Laboratory Parameters: **Decreased hematocrit**

Demography: Age: 11 years Height: 54.0 in. Sex: Male
Weight: 74.00 lbs. Race: Caucasian

Country: **United States**

Medical History: **Occasional headaches, vesicular dyshidrosis, tonsillectomy**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 15-Sep-95

Stop Date: 08-Nov-95

Lab Remarks:
The patient entered the study on 15-Sep-95 with a baseline hematocrit of 37.5% which was below the reference range of 41-50%. At week 8, the hematocrit had decreased to 36.7% (abnormal ≤ 37.0 male) which was considered to be of clinical concern by the investigator. However, this was not reported as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Hematocrit	Baseline	37.5	%	41-50
Hematocrit	8	36.7	%	41-50

Adverse Experiences:	Onset (Days into Study)	Duration
Ringworm	29 days	21 days

Concomitant Drugs:	Start	End
Triamcinalone	18-Oct-95	22-Oct-95
Tylenol (paracetamol)	01-Jan-94	unknown
Clotrimazole	23-Oct-95	24-Oct-95
Gris-Peg (griseofulvin)	25-Oct-95	03-Nov-95

PID 329.007.00311

Laboratory Parameters: **Increased eosinophils**

Demography: Age: 15 years Height: 65.0 in. Sex: Male
Weight: 122.00 lbs. Race: Caucasian

Country: **United States**

Medical History: **Protein in urine, bronchitis, concussion, eustachian tubes in both ears**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Placebo**

Start Date: 03-Oct-96

Stop Date: 01-Dec-96

Lab Remarks:
The patient entered the study on 03-Oct-96 with a baseline eosinophil value of 9.7% which exceeded the normal range of 0-5%. At week 8, the eosinophil value had increased to 11.0% and was flagged as above the level of clinical concern (≥ 10%). This finding, however, was not reported as an adverse experience by the investigator.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Eosinophils	Baseline	9.7	%	0-5
Eosinophils	8	11.0	%	0-5

Adverse Experiences:	Onset (Days into Study)	Duration
Abdominal pain	7	1.00 hour
Diarrhea	16	2.00 hours
Nausea	16	2.00 hours
Arthralgia	47	5 days
Bronchitis	20	12 days
Sinusitis	21	31 days

Concomitant Drugs:	Start	End

PID 329.007.00311

Dulcolax (bisacodyl)	09-Oct-96	09-Oct-96
Bactrim (sulfamethoxazole)	06-Sep-96	20-Sep-96
Effexor (venlafaxine hydrochloride)	01-May-96	27-Sep-96
Flonase (fluticasone propionate)	23-Oct-96	23-Nov-96
Naprosyn (naproxen)	18-Nov-96	22-Nov-96
Entex La (gueifenesin)	23-Oct-96	24-Oct-96
Proventil (salbutamol)	06-Sep-96	13-Sep-96

PID 329.008.00160

Laboratory Parameters: **Increased urine red blood cells**

Demography: Age: 14 years Height: 76.0 in. Sex: Female
Weight: 159.00 lbs. Race: Caucasian

Country: **United States**

Medical History: **Epiglottitis**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 01-Nov-95

Stop Date: 05-Jan-96

Lab Remarks:
The patient entered the study on 01-Nov-95 with a baseline urine red blood cell value of 25-50 which was flagged as above the level of clinical concern. At week 8, the urine red blood cell value had decreased to 10-15, but remained above the level of clinical concern (abnormal > 10 female). This finding was not reported as an adverse experience by the investigator.

Lab Test Code/Name	Week	Lab Value
Urine red blood cells	Baseline	25-50
Urine red blood cells	8	10-15

Adverse Experiences:	Onset (Days into Study)	Duration
Nervousness	20 days	8 days
Dyspnea	20 days	8 days
Breast enlargement	27 days	unknown

Concomitant Drugs:	Start	End
Doxycycline	20-Nov-95	unknown
Ventolin inhaler (salbutamol)	20-Nov-95	unknown

PID 329.009.00134

Laboratory Parameters: **Increased urine red blood cells**

Demography: Age: 15 years Height: 66.0 in. Sex: Female
Weight: 122.50 lbs. Race: Caucasian

Country: **United States**

Medical History: **Dermatological fungus, menstrual cramps, occasional stomach aches, sprained arm muscles**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Imipramine**

Start Date: 06-Jul-95

Stop Date: 09-Sep-95

Lab Remarks:
The patient entered the study on 06-Jul-95. The urine red blood cell count at baseline was negative. At week 8, the urine red blood cell count was 50-100 which was above the level of clinical concern (>10 female). This finding was not reported as an adverse experience by the investigator.

Lab Test Code/Name	Week	Lab Value
Urine red blood cells	Baseline	Negative
Urine red blood cells	8	50-100

Adverse Experiences:	Onset (Days into Study)	Duration
Asthenia	5	65 days
Headache	38	unknown
Postural hypotension	37	33 days
OT Interval Prolonged	55	15 days
Syncope	37	33 days
Tachycardia	37	33 days
Dry Mouth	22	48 days
Dizziness	37	33 days
Somnolence	5	65 days
Sweating	22	48 days

PID 329.009.00134

Concomitant Drugs:	Start	End
Nizoral (ketoconazole)	05-Jul-95	10-Jul-95
Aspirin (acetylsalicylic acid)	12-Aug-95	unknown
Midol (cinnamedrine hydrochloride)	01-Jan-92	unknown
Triphasil (ethinylestradial)	01-Jan-92	unknown
Naproxen	02-Jun-95	09-Jun-95
Anaprox (naproxen sodium)	01-Jan-93	unknown

PID 329.009.00137

Laboratory Parameters: **Decreased hematocrit**

Demography: Age: 14 years Height: 62.0 in. Sex: Male
Weight: 88.30 lbs. Race: Caucasian

Country: **United States**

Medical History: **None**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Imipramine**

Start Date: 10-Oct-95

Stop Date: 16-Dec-95

Lab Remarks:
The patient entered the study on 10-Oct-96 with a baseline hematocrit of 38.6% which was flagged as below the normal range. At week 8, the hematocrit had decreased to 35.7% which was below the level of clinical concern (male ≤ 37.0%). However, the investigator did not report this finding as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Hematocrit	Baseline	38.6	%	41-50
Hematocrit	8	35.7	%	41-50

Adverse Experiences:	Onset (Days into Study)	Duration
Asthenia	36	22 days
Headache	39	4 days
Somnolence	16	42 days
Increased urination	8	8 days

Concomitant Drugs:
None

PID 329.009.00194

Laboratory Parameters: **Decreased hematocrit**

Demography: Age: 12 years Height: 56.8 in. Sex: Male
Weight: 91.40 lbs. Race: Caucasian

Country: **United States**

Medical History: **Allergies to milk, ankle pain (secondary to surgical correction right foot), headache, myalgia (unspecified)**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Imipramine**

Start Date: 05-Dec-95

Stop Date: 29-Jan-96

Lab Remarks:
The patient entered the study on 05-Dec-95 with a baseline hematocrit of 36.0% which was flagged as below the level of clinical concern (≤ 37% male). At week 8, the hematocrit had decreased to 35.9% and again was below the level of clinical concern. However, the investigator did not report this finding as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Hematocrit	Baseline	36.0	%	41-50
Hematocrit	8	35.9	%	41-50

Adverse Experiences:	Onset (Days into Study)	Duration
Abdominal pain	15 days	ongoing (181 days)
Nausea	43 days	ongoing (153 days)
Abnormal dreams	3 days	34 days
Respiratory disorder	29 days	15 days

PID 329.009.00194

Concomitant Drugs:	**Start**	**End**
Tagamet (cimetidine)	01-Jan-96	unknown
Tylenol (paracetamol)	01-Jan-94	unknown
Tylenol sinus (pseudoephedrine hydrochloride)	02-Jan-96	16-Jan-96
Cough syrup (Nos)	02-Jan-96	16-Jan-96

PID 329.009.00196

Laboratory Parameters: **Increased white blood cell count**
Increased urine red blood cells

Demography: Age: 17 years Height: 65.0 in. Sex: Female
Weight: 232.40 lbs. Race: Black

Country: **United States**

Medical History: **Allergy to aspirin and sulfa drugs, anemia, asthma, headaches, menstrual cramps, obesity**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Paroxetine**

Start Date: 18-Dec-95

Stop Date: 25-Feb-96

Lab Remarks:
The patient entered the study on 18-Dec-95 with a baseline white blood cell count of 10.3 which was within normal range. At week 8, the white blood cell count was 16.7 which was above the level of clinical concern (high ≥ 16.0). At baseline, the urine red blood cell value was 1-3 and within normal range, but increased to 10-15 at week 8, which was above the level of clinical concern (> 10 female). These finding were not reported as adverse experiences by the investigator.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
White blood cell count	Baseline	10.3	thou/MCL	4.5 - 13
White blood cell count	8	16.7	thou/MCL	3.8 - 10.8*
Urine red blood cells	Baseline	1-3		
Urine red blood cells	8	10-15		

* Normal range is 4.5-13 for ages 12-17 and 3.8-10.8 for 18 and above. The patient turned 18 during the study.

PID 329.009.00196

Adverse Experiences:	**Onset (Days into Study)**	**Duration**
Constipation	3	unknown
Decreased appetite	2	2 days
Dry mouth	17	6 days
Heartburn	41	unknown
Nausea	2	21 days
Insomnia	2	21 days
Asthma	43	unknown
Sinus infection	43	unknown

Concomitant Drugs:	**Start**	**End**
Rolaids (dihydroxyaluminum sodium carbonate)	27-Dec-95	unknown
Pepcid AC (famotidine)	27-Dec-95	unknown
Cefixime	11-Feb-96	unknown
Tylenol (paracetamol)	01-Jan-94	unknown
Tylenol Sinus (pseudoephedrine hydrochloride)	10-Feb-96	unknown
Ibuprofen	01-Jan-94	unknown
Rondec Dm (carbinoxamine)	11-Feb-96	unknown
Entex (quaifenesin)	09-Feb-96	09-Feb-96
Prednisone	11-Feb-96	unknown
Albuterol (salbutamol)	01-Jan-93	unknown
Albuterol Inhaler	01-Jan-93	unknown
Prednisone	11-Feb-96	unknown

PID 329.009.00327

Laboratory Parameters: **Increased urine red blood cells**

Demography: Age: 16 years Height: 60.1 in. Sex: Female
Weight: 94.40 lbs. Race: Oriental

Country: **United States**

Medical History: **Headache, insect bites, menstrual cramps**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Placebo**

Start Date: 16-Sep-96

Stop Date: 04-Nov-96

Lab Remarks:
The patient entered the study on 16-Sep-96 and did not have a baseline red blood cell count. At week 5, the urine red blood cell count was 10-15 which was flagged as above the level of clinical concern (> 10 female). The investigator did not report this finding as an adverse experience.

Lab Test Code/Name	Week	Lab Value
Urine red blood cell count	Baseline	No value
Urine red blood cell count	5	10-15

Adverse Experiences:
None

Concomitant Drugs:	Start	End
Mylanta Double Strength (aluminum hydroxide)	01-Jan-95	unknown
Dicyclomine (dicycloverine)	01-Jan-95	unknown
Zantac (ranitidine)	01-Jan-95	unknown
Tylenol (paracetamol)	01-Jan-94	unknown

PID 329.009.00327

Benadryl (diphenhydramine hydrochloride)	01-Jan-96	unknown
Midol Ib (ibuprofen)	01-Jan-94	unknown
Codimal La (chlorphenamine maleate)	01-Jan-96	unknown

PID 329.012.00027

Laboratory Parameters: **Decreased segmented neutrophils**

Demography: Age: 15 years Height: 71.7 in. Sex: Male
Weight: 158.76 lbs. Race: Caucasian

Country: **Canada**

Medical History: **Asthma, otitis media, tension headaches**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Placebo**

Start Date: 06-Dec-95

Stop Date: 11-Jan-96

Lab Remarks:
The patient entered the study on 06-Dec-95 and had a segmented neutrophil value of 41.1% which was within the normal range. At week 8, the value for segmented neutrophils had decreased to 14.0% which was flagged as being below the level of clinical concern (≤ 15%). The investigator did not report this finding as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Segmented neutrophils	Baseline	41.1	%	30-70
Segmented neutrophils	4	14.0	%	30-70

Adverse Experiences:	Onset (Days into Study)	Duration
Back pain	16	unknown
Anxiety	16	unknown
Respiratory disorder (cold)	10	13 days
Otitis Media	-10	12 days

PID 329.012.00027

Concomitant Drugs:	**Start**	**End**
Erythromycin	28-Nov-95	08-Dec-95
Entrophen (acetylsaticylic acid)	24-Dec-95	unknown
Lorazepam	21-Dec-95	26-Dec-95
Tylenol (paracetamol)	01-Jan-93	unknown
Erythromycin	28-Nov-95	08-Dec-95
Anaprox (naproxen sodium)	11-Nov-95	17-Nov-95
Becloforte (beclomethasone)	01-Aug-95	20-Nov-95
Intal (cromoglicate sodium)	01-Sep-95	unknown
Neo-Citran (paracetamol)	15-Dec-95	17-Dec-95
Sudafed (pseudoephedrine)	15-Dec-95	17-Dec-95
Ventolin (salbutamol)	01-Sep-94	17-Nov-95
Ventolin (salbutamol)	15-Dec-95	unknown
Garasone (betamethasone sodium phosphate)	27-Nov-95	08-Dec-95

PID 329.012.00218

Laboratory Parameters: **Increased eosinophils**
Increased urine red blood cells

Demography: Age: 17 years Height: 65.7 inc. Sex: Female
Weight: 118.41 lbs. Race: Caucasian

Country: **United States**

Medical History: **Anxiety, asthma**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Placebo**

Start Date: 16-Jun-96

Stop Date: 12-Aug-96

Lab Remarks:
The patient entered the study on 16-Jun-96 with a baseline eosinophil value of 7.0% which exceeded the normal range of 0-5%. The urine red blood cell count at baseline was negative. At week 8, the eosinophil value had increased to 12.6% which was flagged as above the level of clinical concern (≥ 10%). The urine red blood cell count at week 8 had increased to 50-100 and was flagged as above the level of clinical concern (≥ 10 females). Neither of these findings, however, was reported as an adverse experience by the investigator.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Eosinophils	Baseline	7.0	%	0-5
Eosinophils	8	12.6	%	0-5
Urine red blood cells	Baseline	5-10		
Urine red blood cells	8	50-100		

Adverse Experiences:	Onset (Days into Study)	Duration
Headache	-8	2.00 hours

PID 329.012.00218

Concomitant Drugs:	**Start**	**End**
Clonazepam	13-May-96	16-May-96
Tylenol (paracetamol)	08-Jun-96	11-Jul-96

PID 329.012.00224

Laboratory Parameters: **Increased eosinophils**

Demography: Age: 14 years Height: 63.8 in. Sex: Female
Weight: 113.78 lbs. Race: Caucasian

Country: **Canada**

Medical History: **None**

Study Diagnosis: **Major Depressive Disorder**

Study Drug: **Placebo**

Start Date: 16-Sep-96

Stop Date: 20-Nov-96

Lab Remarks:
The patient entered the study on 16-Sep-96 with a baseline eosinophil value of 9.2%, which exceeded the normal range of 0-5%. At week 8, the eosinophils had increased to 12.9%, which was flagged as above the level of clinical concern (≥ 10%). The investigator, however, did not report this finding as an adverse experience.

Lab Test Code/Name	Week	Lab Value	Units	Normal Range
Eosinophils	Baseline	9.2	%	0-5
Eosinophils	8	12.9	%	0-5

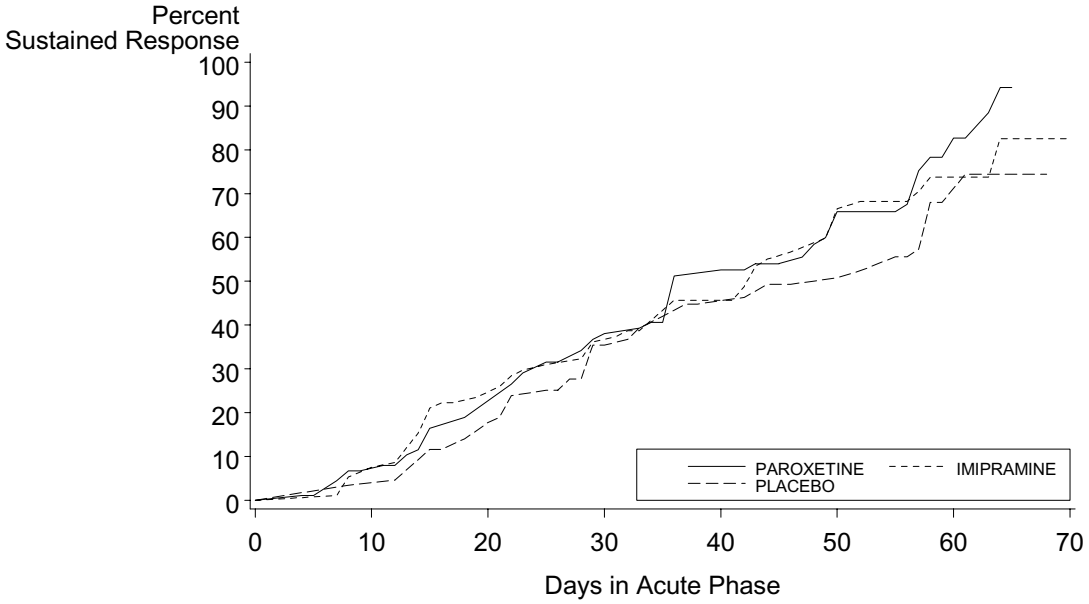
Adverse Experiences:	Onset (Days into Study)	Duration
Tooth disorder	16	1 day
Arthralgia	18	18.00 hours
Respiratory disorder	7	11 days
Dysmenorrhea	24	unknown

Concomitant Drugs:	Start	End
Tylenol (paracetamol)	01-Oct-96	10-Oct-96

13 Data Source Figures

Figure 1

Kaplan Meier Survival Curves for Time to Sustained Response
During Acute Phase
Paroxetine - Protocol 329
Intent to Treat Population



Sustained Response = HAMD Total Score less than or equal to 8 OR decrease from baseline of 50% or greater (lasting until endpoint).