Studie 046

(M/2020/0046)

Studienbericht

Reboxetine, Placebo, and Paroxetine Comparison in Patients With Major Depressive Disorder

A phase III, randomized, double-blind, placebo- and active-treatment-controlled, parallel-group, 8-week study of reboxetine, given orally twice daily to adult patients with major depressive disorder

Final Report of the Study
Protocol M/2020/0046

Previous Reports of the Study: None

It is the policy of Pharmacia & Upjohn to conduct clinical trials in compliance with company SOPs and Standards which incorporate the requirements of the ICH Guideline for Good Clinical Practice. These include trial conduct and archiving of essential documents. Protocol deviations are described in this report.

Trial Initiation Date	18 May 2000
Trial Completion Date	27 October 2000
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Development Phase of Trial	III
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1 SIGNATURE PAGE

(Appendix 1 contains the scanned image of the approval signatures for this document. All original paper signature pages are retained in the paper document and kept in the paper document archive.)

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2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 96 principal investigators participated in this trial: 72 principal investigators participated at 70 centers in the United States and 24 principal investigators participated at 24 centers in Canada. Appendix 2 lists the investigators and their affiliations and provides a curriculum vitae for each principal investigator. Appendix 3 contains the signature of the sponsor's responsible medical officer.

Laboratory tests were performed at a central laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, CA). Electrocardiogram (ECG) results were analyzed by eResearchTechnology (Philadelphia, PA).

3 SYNOPSIS

Name of Company: Pharmacia & Upjohn **Name of Finished Product:** VESTRA **Name of Active Ingredient:** Reboxetine mesylate	**Individual study table**	(For National authority use only)

Title of study: Reboxetine, Placebo, and Paroxetine Comparison in Patients With Major Depressive Disorder; A phase III, randomized, double-blind, placebo- and active-treatment-controlled, parallel-group, 8-week study of reboxetine, given orally twice daily to adult patients with major depressive disorder

Protocol number: M/2020/0046

Investigators and Study Centers: This multicenter study was conducted by 96 principal investigators at 70 study centers in the United States and at 24 study centers in Canada.
The following 24 principal investigators participated at 24 study centers in Canada: David Bakish (Ottawa, ON), Vernon Bennett (Saskatoon, SK), Dorothea Bergen (White Rock, BC), P. Chokka (Edmonton, AB), Mary Connolly (Victoria, BC), Murray Enns (Winnipeg, MB), Peter Faux (Toronto, ON), Herman Gelber (Scarborough, ON), Sunny Johnson (Mississauga, ON), Paul Latimer (Kelowna, BC), R. Milev (Regina, SK), Shaila Misri (Vancouver, BC), Autar Munshi (Sydney, NS), Richard Payeur (Hull, PQ), Nabil Philips (Mississauga, ON), Robin Reesal (Calgary, AB), Ronald Remick (Vancouver, BC), Doron Sagman (Toronto, ON), Bishan Saxena (Burlington, ON), Rustom Sethna (Markham, ON), Sanjay Siddhartha (Miramichi, NB), Amarendra Singh (Kingston, ON), Stephen Stokl (Newmarket, ON), V. Velamoor (London, ON).

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Pharmacia & Upjohn a0089691

Name of Company: Pharmacia & Upjohn **Name of Finished Product:** VESTRA **Name of Active Ingredient:** Reboxetine mesylate	**Individual study table**	(For National authority use only)

Publication (reference): none

Studied period (years): **Phase of development**: III

Date of first enrollment: 18 May 2000
Date of last patient visit: 27 October 2000

Objectives

Primary: The primary objective of this study was to demonstrate that the antidepressant efficacy of reboxetine, administered at a dose of 4 mg/day during the first week and at a dose of 8 to 10 mg/day during the following 7 weeks, is superior to that of placebo, as determined by a 2-way analysis of variance (ANOVA) of the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at day 56 in the intent-to-treat (ITT) patient population.

Secondary: One secondary objective was to further demonstrate that the antidepressant efficacy of reboxetine is superior to that of placebo, as determined by a 2-way ANOVA of the continuous antidepressant-efficacy endpoints and a Cochran-Mantel-Haenszel test of the categorical antidepressant-efficacy endpoints at day 56 in the ITT patient population. Another secondary objective of this study was to demonstrate that reboxetine produces an improvement in energy and social function that is superior to the improvement produced by placebo, as determined by a 2-way ANOVA of the energy and social function endpoints at day 56 in the ITT patient population.

Methodology: This was a phase III, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study of 787 patients aged 18 to 65 years who suffered from major depressive disorder (MDD) without psychotic features, as diagnosed using criteria defined by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV). Patients who had a prescreening score of ≥20 on the 17-Item Hamilton Rating Scale for Depression (HAM-D; administered via an interactive voice response system [IVRS]) were scheduled for a screening visit, at which time they signed the informed consent form and underwent screening evaluations. Eligible patients were randomized to receive 8 weeks of treatment with reboxetine (4 mg/day, days 0-6; 8 mg/day, days 7-27; 8-10 mg/day, days 28-56), paroxetine (20 mg/day, days 0-27; 20-40 mg/day, days 28-56), or placebo. The optional dose increase to 10 mg/day of reboxetine or to 40 mg/day of paroxetine was allowed after 4 weeks of therapy in those patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. Efficacy measures were assessed every 2 weeks; safety measures were assessed at each visit (weekly during the first 4 weeks of treatment and every 2 weeks during the last 4 weeks of treatment).

Number of patients (planned and analyzed): The planned enrollment in the study was 645 patients (215 patients in each of the 3 treatment groups). The actual enrollment was 787 patients. The ITT population, which includes all patients who were randomized into the trial and who received at least one dose of study medication, includes 264 reboxetine-treated patients, 254 placebo-treated patients, and 262 paroxetine-treated patients, for a total of 780 patients in the ITT population.

Diagnosis and main criteria for inclusion: Patients of either sex and any race, aged 18 to 65 years, who had a diagnosis of MDD without psychotic features (as defined by DSM-IV) and a total score of ≥20 on the 17-Item HAM-D (administered via the IVRS prior to screening) were enrolled in the study. Patients were otherwise healthy and had no other significant psychiatric condition.

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Test product, dose and mode of administration, batch number
Reboxetine mesylate tablets (2 or 4 mg) were inserted into gelatin capsules for use in this randomized study. During the first week (days 0-6) of treatment, reboxetine was administered orally in twice-daily doses of 2 mg (lot number 38,593), for a total daily dose of 4 mg of reboxetine. During weeks 2 through 4 (days 7-27), reboxetine was administered in twice-daily doses of 4 mg (lot numbers 38,414 or 38,504), for a total daily dose of 8 mg of reboxetine. After 4 weeks of treatment, the reboxetine dose was increased to 10 mg/day, administered as a 4-mg capsule in the morning and a 6-mg capsule (lot numbers 38,415 or 38,505) in the late afternoon, in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose.

Duration of treatment: 8 weeks

Reference therapy, dose and mode of administration, batch number: The paroxetine (Paxil™, SmithKline Beecham Pharmaceuticals, Philadelphia, PA) comparator was commercially available and was inserted into gelatin capsules by Pharmacia & Upjohn.

During weeks 1 through 4 (days 0-27), paroxetine was administered as a morning dose of 20 mg of paroxetine (lot numbers 38,506 or 38,416). After 4 weeks of treatment, the paroxetine dose was increased to 40 mg/day (administered as a morning dose of 40 mg of paroxetine, lot numbers 38,417, 38,507 or 38,529) in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. A placebo capsule was administered in the late afternoon to maintain the study blind.

In placebo-treated patients, placebo capsules (lot numbers 38,413 or 38,503) were administered orally, twice daily.

Criteria for evaluation:
Efficacy: The primary efficacy endpoint was the mean change from baseline in the MADRS total score. The secondary endpoints were as follows: (a) continuous measures of antidepressant efficacy, including the mean change from baseline in the 21-Item HAM-D total score, in the HAM-D Item 1 (Depressed Mood) score, in the HAM-D Retardation Cluster (Items 1, 7, 8, and 14) score, and in the Clinical Global Impression (CGI) Severity of Illness score; (b) categorical measures of antidepressant efficacy, including the MADRS response rate, the MADRS remission rate, the HAM-D response rate, the HAM-D remission rate, the CGI Global Improvement score, and the CGI Global Improvement response rate; (c) continuous measures of energy, including the mean change from baseline in the General Fatigue subscale of the Multidimensional Fatigue Inventory (MFI) and in the Vitality scale of the Medical Outcomes Study Short-Form Health Survey (MOS SF-36); and (d) continuous measures of social function, including the mean change from baseline in the total scores for the Social Adaptation Self-evaluation Scale (SASS) and the Social Functioning scale of the MOS SF-36.

Safety: The safety of the study medication was assessed by evaluation of adverse events, vital signs, laboratory assays, and electrocardiograms.

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Statistical methods:

The ITT data set, which includes all patients who were randomized into the trial and who received at least one dose of study medication, was used for all of the analyses. Two types of analyses were performed for all efficacy variables: "last observation carried forward" (LOCF) and "observed cases" (OC). The LOCF analyses used the last valid assessment as an estimate for all subsequent missing values. The OC analysis did not replace missing data. The LOCF analyses were the primary analyses and the OC analyses were the secondary analyses. Comparisons were based on a 2-sided test at an alpha level of 0.05, unless otherwise specified. Although comparisons were made at each visit, the primary endpoint was day 56.

For the primary efficacy measure (the mean change from baseline in the MADRS total score), differences among the 3 treatment groups were assessed at each visit using a 2-way ANOVA with investigator, treatment, and treatment-by-investigator interaction as factors. If a statistically significant ($p \leq 0.05$) treatment effect was observed among the 3 treatment groups based on the 2-way ANOVA, then pairwise comparisons between reboxetine and placebo were performed. Differences among the 3 treatment groups in the mean change from baseline in the MADRS total score were also assessed using a 2-way analysis of covariance (ANCOVA), with baseline severity as a covariate and with investigator, treatment, and treatment-by-investigator interaction as factors.

In addition to the endpoint analyses described above, a generalized estimating equation (GEE) analysis of the mean change from baseline in the MADRS total score was performed as an additional secondary analysis.

For the continuous secondary efficacy endpoints, differences among the 3 treatment groups were assessed at each visit using a 2-way ANOVA, with investigator, treatment, and treatment-by-investigator interaction as factors. For the categorical secondary efficacy endpoints, differences among the 3 treatment groups were assessed at each visit using the Cochran-Mantel-Haenszel test, stratified by investigator. In either of the analyses, if a statistically significant ($p \leq 0.05$) difference was observed among the 3 treatment groups, then pairwise comparisons between reboxetine and placebo were performed.

For all efficacy endpoints, the comparison between the reboxetine and placebo groups was the primary comparison; the comparison between the paroxetine and placebo groups was included as a positive control. No comparisons were made between the reboxetine and paroxetine groups.

SUMMARY

EFFICACY RESULTS:

This study failed to meet the protocol-specified primary objective, which was to demonstrate that the antidepressant efficacy of reboxetine, administered at a dose of 4 mg/day during the first week and at a dose of 8 to 10 mg/day during the following 7 weeks, is superior to that of placebo, as determined by a 2-way ANOVA of the mean change from baseline in the MADRS total score at day 56 in the ITT patient population.

Although the margin of effect did not attain statistical significance, reboxetine efficacy values were numerically greater than or equal to placebo at endpoint (day 56) on all primary and secondary measures of antidepressant efficacy. In no case did placebo exceed reboxetine in effect size. As shown in the table, statistically significant differences were observed among the 3 treatment groups on the majority of the antidepressant efficacy endpoints at day 56 in the LOCF analysis. In the pairwise comparison, statistically significant differences, favoring paroxetine over placebo, were observed on the primary efficacy endpoint and on a number of secondary efficacy endpoints.

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Summary of Antidepressant Efficacy Measures at Day 56 (LOCF Analysis)

	Results by Treatment Group			P Values		
	RBX N=264	PBO N=254	PAR N=262	Overall	RBX vs PBO	PAR vs PBO
Primary Endpoint						
MADRS total score, mean change from baseline	-14.7	-14.4	-16.8	0.0422*	0.5512	0.0155*
Secondary Endpoints						
Mean Change from Baseline						
HAM-D Item 1	-1.4	-1.4	-1.6	0.0128*	0.8390	0.0077*
HAM-D Retardation Cluster	-3.7	-3.6	-4.1	0.1214	--	--
CGI Severity of Illness	-1.5	-1.5	-1.8	0.0177*	0.8352	0.0103*
HAM-D Total Score	-11.5	-11.5	-12.5	0.2265	--	--
% Responders or Remitters						
MADRS Response	55.8	53.4	64.8	0.0178*	0.6038	0.0088*
MADRS Remission	50.8	49.0	60.2	0.0189*	0.7075	0.0105*
HAM-D Response	57.1	55.1	64.2	0.0739	--	--
HAM-D Remission	52.4	50.2	62.6	0.0079*	0.6027	0.0041*
CGI Global Improvement Response	55.0	50.6	66.3	0.0007*	0.3282	0.0003*

* $p \leq 0.05$

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference was observed among the 3 treatment groups ($p \leq 0.05$ for overall comparison).

Abbreviations: LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine

The results from the secondary measures of energy and social function indicate that quality of life improved in all treatment groups during the study. Statistically significant differences were observed among the 3 treatment groups on the mean change from baseline in the SASS total score on days 28, 42, and 56 in both the LOCF and OC analyses, with reboxetine producing a significantly greater increase in the SASS total score than placebo on days 42 (LOCF analysis) and 56 (LOCF and OC analyses) and paroxetine producing a significantly greater increase in the SASS total score than placebo on days 28, 42, and 56 (LOCF and OC analyses).

On the other secondary measures of energy and social function, including the MOS SF-36 Social Functioning and Vitality scales and the MFI General Fatigue subscale, no statistically significant differences were observed among the 3 treatment groups at endpoint (day 56). However, on the MOS SF-36 Social Functioning scale, reboxetine produced a significantly greater increase than placebo on day 42 (OC analysis) and paroxetine produced a significantly greater increase than placebo on days 28 (LOCF and OC analyses) and 42 (OC analysis).

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SAFETY RESULTS:

Treatment-emergent signs and symptoms were reported in a similar percentage of patients in each of the treatment groups (90.5% in the reboxetine group, 81.9% in the placebo group, and 88.2% in the paroxetine group).

Overall, the adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. The most frequently reported TESS (reported in at least 5% of reboxetine-treated patients and at least 2 times more frequently in the reboxetine-treated patients than in the placebo-treated patients) were dry mouth, constipation, anorexia, insomnia, asthenia, chills, sweating, and vasodilatation. In the paroxetine group, the most frequently reported TESS (reported in at least 5% of paroxetine-treated patients and at least 2 times more frequently in the paroxetine-treated patients than in the placebo-treated patients) were constipation, nausea, anorexia, somnolence, asthenia, reaction unevaluable, accidental injury, and sweating.

No deaths were reported during this study. Serious TESS were reported in a similar percentage of patients in each of the 3 treatment groups: 1.5% (4/264) of reboxetine-treated patients, 0.4% (1/254) of placebo-treated patients, and 1.5% (4/262) of paroxetine-treated patients.

The percentage of patients who discontinued treatment due to TESS at any time during the treatment period was higher in the reboxetine (9.8%; 26/264) and paroxetine (8.4%; 22/262) groups than in the placebo (3.5%; 9/254) group. The most frequently reported TESS that led to discontinuation of reboxetine treatment was insomnia, which led to discontinuation of treatment in 2.3% of reboxetine-treated patients. The most frequently reported TESS that led to discontinuation of paroxetine treatment was headache, which led to discontinuation of treatment in 1.5% of paroxetine-treated patients.

The rates of discontinuation due to TESS that were observed in this study were much lower than the rates that were observed in earlier US studies of reboxetine (protocols 049 and 050). In the reboxetine group, the rate of discontinuations due to TESS decreased from 19.5% (50/256) in the earlier studies (combined data from protocols 049 and 050) to 9.8% (26/264) in this study. In the placebo group, the rate of discontinuations due to TESS decreased from 6.7% (17/254) in the earlier studies to 3.5% (9/254) in this study.

During the first week of treatment in this study, when reboxetine was administered at a dose of 4 mg/day (half of the usual recommended dose of 8 mg/day), the rate of discontinuations due to TESS in the reboxetine group (1.9%; 5/264) was substantially lower than the rate that was observed during the first week of studies 049 and 050 (7.0%; 18/256). The rate of discontinuations due to TESS in this study decreased slightly during week 2 (1.5%; 4/264) and increased slightly during week 3 (2.3%; 6/264). However, these rates remained lower than the rates that were observed during weeks 2 (2.7%; 7/256) and 3 (3.5%; 9/256) of studies 049 and 050. These results indicate that the 1-week dose-escalation period for reboxetine was successful in reducing the rate of discontinuations due to TESS. The lower rate of discontinuation during weeks 2 and 3 of this study may indicate that the patients became acclimated to the effects of the drug during the 1-week dose-escalation period, or it may reflect improved management of symptoms by the site personnel, compared with earlier studies.

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In addition to the improvements that were observed in the rate of discontinuation due to TESS in the reboxetine group in this study, improvements in the number and severity of TESS were also observed during the 1-week dose-escalation period for reboxetine. A total of 490 TESS were reported in the reboxetine group (N=264) during the first week of this study (when reboxetine was administered at a dose of 4 mg/day), whereas 726 TESS were reported in the reboxetine group (N=256) during the first week of studies 049 and 050 (when reboxetine was administered at a dose of 8 mg/day). In addition, the percentage of TESS that were severe in intensity was reduced during the first week of this study (5.5%; 27/490), compared with studies 049 and 050 (11.7%; 85/726). The 1-week dose-escalation period for reboxetine is the most likely reason for the improvements that were observed in the profile of TESS during the first week of treatment in this study.

Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline values for sitting diastolic blood pressure at each visit. At the end of the study (day 56), the mean change from baseline diastolic blood pressure was +1.8 mmHg in the reboxetine group, -1.1 mmHg in the placebo group, and +0.2 mmHg in the paroxetine group.

Consistent with the results of previous studies, the mean change from baseline values for pulse rate and ECG heart rate were significantly greater in the reboxetine group than in the placebo group throughout the study. At the end of the study (day 56), the mean change from baseline pulse rate was +8.0 beats per minute in the reboxetine group, +0.5 beats per minute in the placebo group, and –2.3 beats per minute in the paroxetine group, whereas the mean change from baseline ECG heart rate was +15.0 beats per minute in the reboxetine group, +1.9 beats per minute in the placebo group, and +1.5 beats per minute in the paroxetine group. However, few reboxetine-treated patients (1.6%; 4/251) had postbaseline values for pulse rate that were above the predefined limit (≥120 beats/min), and no reboxetine-treated patients had postbaseline values for ECG heart rate that were above the predefined limit (≥120 beats/min).

CONCLUSION:
In conclusion, this phase III, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study failed to demonstrate that the antidepressant efficacy of reboxetine is superior to that of placebo, as determined by the mean change from baseline in the MADRS total score at day 56 in the ITT patient population, the primary endpoint. The adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. No new safety concerns associated with the use of reboxetine were identified.

Date of the report: 26 April 2001

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4 ABBREVIATIONS AND DEFINITION OF TERMS

ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
CGI	Clinical Global Impression
CI	confidence interval
COSTART	Coding Symbols and Thesaurus of Adverse Reaction Terms
CRF	case report form
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECG	electrocardiogram
GEE	generalized estimating equations
HAM-D	Hamilton Rating Scale for Depression
IRB	Institutional Review Board
ITT	intent to treat
IVRS	interactive voice response system
LOCF	last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	major depressive disorder
MFI	Multidimensional Fatigue Inventory
MOS SF-36	Medical Outcomes Study Short-Form Health Survey (36 items)
OC	observed cases
P&U	Pharmacia & Upjohn
SASS	Social Adaptation Self-evaluation Scale
SSRI	selective serotonin reuptake inhibitors
TCA	tricyclic antidepressants
TESS	treatment-emergent signs and symptoms

5 ETHICS

5.1 Institutional Review Board (IRB)

The protocol and all amendments for this trial were reviewed by an Institutional Review Board (IRB). Appendix 4 contains a copy of the protocol and its amendments,* Appendix 5 contains copies of the unique pages of the case report forms (CRFs), and Appendix 6 lists the IRBs that were consulted.

5.2 Ethical Conduct of the Study

Monitoring and audit procedures performed prior to, during, and upon completion of this trial have verified that this trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Appendix 14 lists the protocol deviations.

5.3 Patient Information and Consent

Prior to inclusion in the study, each patient was given adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. All patients gave signed informed consent prior to inclusion in the study. Appendix 7 contains a copy of a sample informed consent form.

6 INTRODUCTION

Major depression is a common disorder, with a lifetime prevalence of 2% to 12% in men and 5% to 26% in women [1]. A diagnosis of depression depends on the presence of significant depressed mood and associated affects, but loss of interest, loss of energy, and impaired social function are also inherent components of major depression [2].

Depression can be treated effectively by a range of antidepressant agents [3]. Approximately 50% to 70% of patients in clinical trials will respond to antidepressants but will fail to go into remission [4], whereas 25% to 35% will experience full remission after treatment with an effective antidepressant agent [4, 5]. Recent meta-analytic reviews have suggested that the selective serotonin reuptake inhibitors (SSRIs) offer equal efficacy to some of the older antidepressant agents (eg, the tricyclic antidepressants [TCAs]), with the advantage of greater tolerability, as assessed by attrition due to adverse events [6, 7, 8]. Other reviewers have suggested that SSRIs may be of more limited utility in more severely depressed patients and in patients with melancholic symptoms. For example, non-SSRI antidepressants, such as venlafaxine and clomipramine, have been found to be significantly more effective than

* Because of the extensive changes that were made to the protocol before any patients were enrolled in the study (changes detailed in Amendments A, 1, 2, and 3), a "working protocol," which incorporates Amendments A, 1, 2, and 3, was provided to the investigators. The original protocol, the protocol amendments, and the working protocol are provided in Appendix 4.

fluoxetine for the treatment of patients with severe depression [9]. However, the studies that have found approximately equal outcomes on general measures of depression symptoms (eg, the Hamilton Rating Scale for Depression [HAM-D] total scores) do not provide any perspective on whether select agents offer superior treatment on a specific domain of depression symptoms. Even for approved, effective antidepressants, pivotal-sized clinical trials commonly fail to demonstrate efficacy, as shown by a review of clinical trial data for approved antidepressants from the FDA database [10].

Norepinephrine, one of the fundamental neurotransmitters of the brain, has been implicated in the neuronal systems that are important in vigilance, mood, and cognition. Modern neurochemical models of depression focus on the concept that norepinephrine is particularly important in the brain subsystems that underlie energy, interest, and motivation, whereas serotonergic systems have particular importance in modulating impulsivity. Both systems may overlap in modulating mood, sleep, anxiety, and appetite [11]. Current theories on depression have suggested that there are potential underlying genetic variations in the noradrenergic or serotoninergic systems. The suggestion has been made that a proportion of depressions relate predominantly to noradrenergic problems, a proportion to serotoninergic problems, and that the remaining depressions relate to a mixture of these problems or other issues. This theory may explain why the SSRIs in general are associated with approximately one third full responses (normalization of HAM-D), one third partial responses (improvement but not normalization), and one third non-responses [4]. This conceptualization of depression implies the need for agents that are capable of specifically modifying brain norepinephrine systems. As such, this model is consistent with the original monoamine hypothesis of depression, which was first published by Schildkraut [12].

Reboxetine methanesulphonate (reboxetine mesylate, PNU-155950E, FCE 20124) is a highly selective norepinephrine reuptake inhibitor that has antidepressant activity. The affinity of reboxetine to bind to the norepinephrine reuptake transporter (1.1 nM) is similar to that of desipramine (1.2 nM) and higher than that of imipramine (24 nM), venlafaxine (1060 nM), fluoxetine (1015 nM), sertraline (420 nM), paroxetine (40 nM), or citalopram (4070 nM) [13, 14]. At clinically relevant doses, reboxetine does not block serotonin or dopamine reuptake, affect anticholinergic or antihistaminergic receptors, or affect cardiac conduction in the manner underlying the cardiotoxicity of the TCAs.

The currently available agents that affect the norepinephrine system have less receptor specificity than reboxetine and, more importantly, affect other pervasive neurotransmitter systems that produce histaminergic and anticholinergic symptoms, among others. This nonspecific binding to other receptors is expected to produce increased adverse events that are unrelated to the therapeutic effect. The high level of norepinephrine-uptake selectivity and receptor specificity (ie, the relative lack of activity of reboxetine on other neurotransmitter systems) implies the potential utility of reboxetine as an antidepressant, particularly in depressions that are associated with underlying perturbations of the norepinephrine system and in patients who have symptoms that are associated with reduced energy, interest, and motivation.

The efficacy of reboxetine has been independently demonstrated in multiple short-term, randomized, double-blind, placebo-controlled studies (protocols 008 [15], 014 [16], and 091 [17]) and in a long-term, double-blind, placebo-controlled study (protocol 013 [18]). The analyses of the trial endpoints from the placebo-controlled studies indicates that a clinically relevant benefit is obtained from a short course of treatment with reboxetine.

In addition to improvements in depressive symptoms, treatment-associated improvements in social behavior (measured using the Social Adaptation Self-Evaluation Scale [SASS] [19]) were noted in one study [16]. In this study, reboxetine was statistically and clinically superior to both placebo and fluoxetine in improving social functioning. The improvement was evident in both the patients who were and were not in remission from their depressive symptoms and indicated a better quality of remission for social adaptation in the reboxetine-treated patients.

The most frequently reported adverse events associated with the administration of reboxetine, as determined from combined safety data from controlled and uncontrolled studies in which 2140 patients have been treated with reboxetine, are dry mouth, constipation, nausea, insomnia, dizziness, headache, and sweating. However, these events were usually mild to moderate in severity, and only a small proportion of patients discontinued treatment with reboxetine for these reasons.

This study (protocol M/2020/0046) was conducted to test the hypothesis that reboxetine is effective for the treatment of depression in a US and Canadian population. In addition, this study was conducted to test the hypothesis that a noradrenergic-specific agent, such as reboxetine, is effective for improving the energy and social functioning of patients with depression.

7 OBJECTIVES

7.1 Primary Objective

The primary objective of this study was to demonstrate that the antidepressant efficacy of reboxetine, administered at a dose of 4 mg/day during the first week and at a dose of 8 to 10 mg/day during the following 7 weeks, is superior to that of placebo, as determined by a 2-way analysis of variance (ANOVA) of the mean change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at day 56 in the intent-to-treat (ITT) patient population.

7.2 Secondary Objectives

One secondary objective of this study was to further demonstrate that the antidepressant efficacy of reboxetine, administered at a dose of 4 mg/day during the first week and at a dose of 8 to 10 mg/day during the following 7 weeks, is superior to that of placebo, as determined by a 2-way ANOVA of the continuous antidepressant-efficacy endpoints and a Cochran-Mantel-Haenszel test of the categorical antidepressant-efficacy endpoints at day 56 in the

ITT patient population. The continuous measures of antidepressant efficacy included the mean change from baseline in the 21-Item HAM-D total score, in the HAM-D Item 1 (Depressed Mood) score, in the HAM-D Retardation Cluster (Items 1, 7, 8, and 14) score, and in the Clinical Global Impression (CGI) Severity of Illness score. The categorical measures of antidepressant efficacy included the MADRS response rate, the MADRS remission rate, the HAM-D response rate, the HAM-D remission rate, the CGI Global Improvement score, and the CGI Global Improvement response rate.

Another secondary objective was to demonstrate that reboxetine, administered at a dose of 4 mg/day during the first week and at a dose of 8 to 10 mg/day during the following 7 weeks, produces an improvement in energy and social function that is superior to the improvement produced by placebo, as determined by a 2-way ANOVA of the energy and social function endpoints at day 56 in the ITT patient population. The energy endpoints included the mean change from baseline in the General Fatigue subscale of the Multidimensional Fatigue Inventory (MFI) and in the Vitality scale of the Medical Outcomes Study Short-Form Health Survey (MOS SF-36), whereas the social function endpoints included the mean change from baseline in the SASS total score and in the Social Functioning scale of the MOS SF-36.

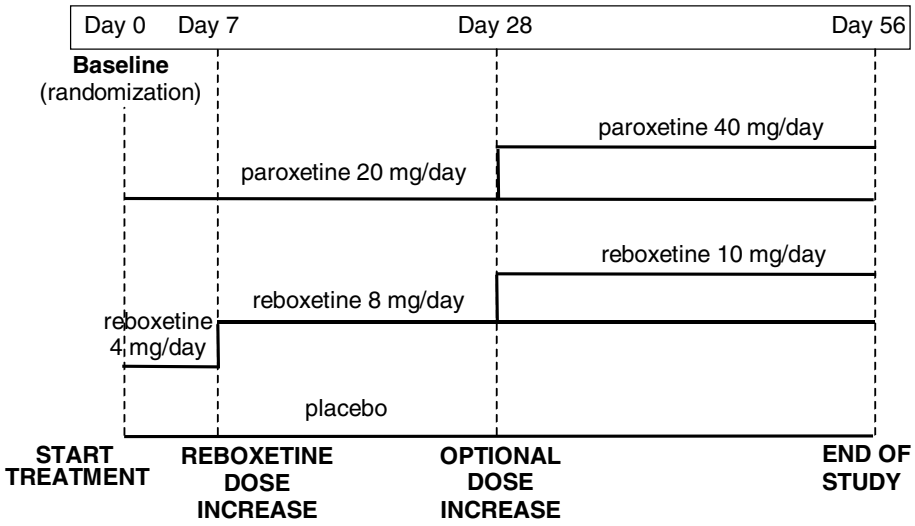
8 METHODS

8.1 Overall Study Design and Plan

This phase III, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study was conducted in 787 patients (780 ITT patients) aged 18 to 65 years who suffered from major depressive disorder (MDD) without psychotic features, as diagnosed using criteria defined by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) [2]. Patients who had a prescreening score of ≥20 on the 17-Item HAM-D (administered via an interactive voice response system [IVRS] [20]) were scheduled for a screening visit, at which time they signed the informed consent form and underwent screening evaluations. Eligible patients were randomized to receive 8 weeks of treatment with reboxetine (4 mg/day, days 0-6; 8 mg/day, days 7-27; 8-10 mg/day, days 28-56), paroxetine (20 mg/day, days 0-27; 20-40 mg/day, days 28-56), or placebo. The optional dose increase to 10 mg/day of reboxetine or 40 mg/day of paroxetine was allowed after 4 weeks of therapy in those patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. Study visits were conducted weekly during the first 4 weeks of treatment and every 2 weeks during the last 4 weeks of treatment. Efficacy measures were assessed every 2 weeks (days 0, 14, 28, 42, and 56); safety measures were assessed at each visit (days 0, 7, 14, 21, 28, 42, and 56).

The study design is presented in Figure 1.

Figure 1. Study Design and Timeline



8.2 Discussion of Study Design

The double-blind, randomized, parallel-group design that was used in this study is generally recognized as one that provides an unbiased assessment of the efficacy and safety of an experimental drug. The active comparator, paroxetine, was included only as a positive control. Paroxetine was chosen because it is one of the most commonly prescribed SSRIs in the United States and because investigators are familiar with it as a first-line medication for the treatment of MDD. This study was not powered or designed to directly compare the efficacy of reboxetine and paroxetine.

The MADRS was chosen as the primary efficacy measure in this study because the questions that it comprises are more focused on the core symptoms and signs of depression, such as depressed mood and depressed affect, and are less focused on secondary effects, such as sleepiness, than are the questions that comprise the HAM-D. In the MADRS, categories of degree are precisely described, items are restricted to representing only those symptoms that are considered to be the core symptoms of depressive syndromes, and items representing somatic complaints have been reduced [21]. The ability of the MADRS to differentiate between responders and non-responders to antidepressant treatment and to distinguish between subjects who are likely to experience somatic adverse events from treatment and those who are less likely has been demonstrated in several studies [22, 23, 24, 25].

The 1-week dose-escalation period for reboxetine (escalation from 4 mg/day, administered on days 0-6, to 8 mg/day, starting on day 7) was included in the study design to assess whether the relatively high rate of early discontinuations due to adverse events that had been observed in earlier US studies of reboxetine (protocols 97-CRBX-049 [26] and 97-CRBX-050 [27]) could be reduced by reducing the starting dose of reboxetine.

The automated prescreening assessment (17-Item HAM-D, administered via the IVRS) was used to reduce potential bias in the prescreening evaluation of depressive symptoms.

8.3 Study Population

8.3.1 Inclusion Criteria

To be included in the study, patients must have met all of the following criteria:

- Diagnosis of MDD without psychotic features, as defined by DSM-IV.
- Male or female, of any race, between the ages of 18 and 65 years.
- If female, must have been postmenopausal or must have met all of the following criteria:
    - agreed to avoid pregnancy during the study
    - had a negative serum pregnancy test at screen
    - used an accepted means of birth control (as determined by the investigator), such as abstinence, oral contraceptive, implantable or injectable contraceptive, intrauterine device, or barrier method, or have been surgically sterilized
- Total score of ≥20 on the 17-Item HAM-D, which was administered via the IVRS prior to the screening visit.
- General good health, as confirmed by routine clinical laboratory safety findings.
- Voluntary consent to participate in the study, documented in a written Patient Informed Consent Form that was signed prior to the start of any study procedures at the screening visit.

8.3.2 Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

- DSM-IV diagnosis of the following concomitant psychiatric disorders: MDD with psychotic features, cyclothymic disorder, bipolar I or bipolar II disorders, substance-related disorders (within the preceding 12 months), schizophrenia, or other psychotic disorders.
- Resistance to antidepressive treatment, defined as a lack of response to at least 2 previous courses of antidepressant medications administered at full doses for more than 1 month.
- Participation in a previous clinical trial of reboxetine or lack of response to previous treatment with paroxetine, administered at a dose of ≥20 mg/day for more than 1 month.
- Use of antidepressant medication for the treatment of depression in the 2 months preceding the start of the study.

- History of MDD associated with endocrine disorders: hypo- or hyper-thyroidism tested by thyroid-stimulating hormone and thyroxine, adrenal insufficiency, or Cushing's syndrome.
- Positive pregnancy test for females of childbearing potential.
- Breast-feeding by female patients.
- Refusal by female patients of childbearing age to use an effective contraceptive method during the study.
- Participation in any clinical study with an investigational compound in the 4 weeks preceding the study.
- History or presence of gastrointestinal, liver, or kidney disease or other conditions known to interfere with the absorption, distribution, metabolism, and excretion of drugs.
- History of seizures or brain injury; current evidence of clinically important hematopoietic, respiratory, or cardiovascular diseases; current evidence of urinary retention or glaucoma.
- Clinically significant illness in the 4 weeks preceding the study that might have interfered with the conduct of the trial.
- Clinically relevant abnormal findings in the physical examination, laboratory tests, or ECG at admission.
- Positive urine drug screen for amphetamines, barbiturates, marijuana metabolites, cocaine metabolites, methadone, methaqualone, opiates, phencyclidine, or propoxyphene. A positive urine drug screen for benzodiazepines did not exclude the patient.
- Treatment with electroconvulsive therapy in the 6 months preceding the study.
- Major risk of suicide as assessed by the investigator, a score of ≥3 on Item 3 of the HAM-D at screen or baseline, or a history of suicide attempt during the current depressive episode.
- History of hypersensitivity to reboxetine or paroxetine.
- Use of the following medications, which are potent inhibitors of the drug-metabolizing enzyme cytochrome p450-3A4: azole antifungals, macrolide antibiotics (such as erythromycin), or fluvoxamine.
- Use of the following medications, which are known to be substrates or inhibitors of the drug-metabolizing enzyme cytochrome p450-2D6: Type 1C antiarrhythmics (such as flecainide, encainide, or propafenone), quinidine, or cimetidine.
- Use of oral anticoagulants (such as warfarin or coumadin) that are known to inhibit vitamin K-dependent coagulation factors.
- Use of concomitant psychotropic medications other than the protocol-specified sedatives/hypnotics, which could be taken on an as-needed basis for sleep.

- Inability of the patient to comply with the conditions of the study, based on the investigator's assessment.

8.3.3 Removal of Patients From Therapy or Assessment

Patients were withdrawn from the study medication if the investigator judged it to be medically necessary or if it was the wish of the patient. The reasons for the withdrawal of a patient from study medication were noted. Regardless of the reason for withdrawal, the patient was examined as soon as possible. Relevant samples (eg, laboratory tests, ECGs, and any diagnostic procedures that were considered necessary to define the event that led to patient withdrawal) were obtained and relevant assessments were completed according to the schedule of final assessments. The CRFs were completed and forwarded to Pharmacia & Upjohn (P&U).

8.4 Treatments

8.4.1 Trial Products

The study medications (reboxetine, paroxetine, or placebo) were provided as identically appearing capsules. Study medications were administered orally, twice daily.

During the first week (days 0-6) of treatment, reboxetine was administered in twice-daily doses of 2 mg, for a total daily dose of 4 mg of reboxetine. During weeks 2 through 4 (days 7-27), reboxetine was administered in twice-daily doses of 4 mg, for a total daily dose of 8 mg of reboxetine. After 4 weeks of treatment, the reboxetine dose was increased to 10 mg/day (administered as a 4-mg capsule in the morning and a 6-mg capsule in the late afternoon) in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose.

During weeks 1 through 4 (days 0-27), paroxetine was administered as a morning dose of 20 mg of paroxetine. After 4 weeks of treatment, the paroxetine dose was increased to 40 mg/day (administered as a morning dose of 40 mg of paroxetine) in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. A placebo capsule was administered in the late afternoon to maintain the study blind.

During weeks 1 through 8 (days 0-56), placebo treatment consisted of twice-daily administration of placebo capsules.

8.4.2 Identity of Investigational Products

Study medications for the randomized treatments consisted of identically appearing capsules that contained reboxetine, paroxetine, or placebo. The reboxetine and placebo supplies were manufactured and supplied by P&U. Placebo capsules consisted of lactose-filled gelatin capsules. The paroxetine (Paxil, SmithKline Beecham Pharmaceuticals, Philadelphia, PA)

comparator was commercially available and was inserted into gelatin capsules by P&U. Information about the study medications is summarized in Table 1.

Table 1. Study Medications: Capsule Strength, Suppliers, and Batch Numbers

Study Medication	Capsule Strength	Supplier	Lot Number*
Reboxetine	2 mg (one 2-mg tablet)	P&U	38,593
Reboxetine	4 mg (one 4-mg tablet)	P&U	38,414 38,504
Reboxetine	6 mg (one 2-mg tablet and one 4-mg tablet)	P&U	38,415 38,505
Paroxetine	20 mg (one 20-mg tablet)	SmithKline Beecham, (repackaged by P&U)†	38,416 38,506
Paroxetine	40 mg (one 40-mg tablet or two 20-mg tablets in Canada)	SmithKline Beecham, (repackaged by P&U)†	38,417 38,507 38,529
Placebo	--	P&U	38,413 38,503

* Appendix 8 lists the patient numbers according to the lot number of study medication that each patient received.

† Paxil tablets, supplied by SmithKline Beecham Pharmaceuticals, were inserted into gelatin capsules by P&U.

Abbreviation: P&U=Pharmacia & Upjohn

The study medications were provided in product packages, which were labeled with the protocol number, the patient number, and the study week (1 through 8). Each product package contained 2 bottles that provided the study medication for 1 week; 1 bottle contained capsules for the morning dose, and 1 bottle contained capsules for the evening dose. Three extra capsules (for a total of 10 capsules) were included in each bottle, to allow for possible loss.

To allow for the optional dose increase after week 4 (day 28), 2 sets of color-coded product packages were provided for each patient for weeks 5 through 8. The product packages that contained the regular dose (8 mg/day of reboxetine, 20 mg/day of paroxetine, or placebo) were marked with a blue border, whereas the packages that contained the escalated dose (10 mg/day of reboxetine, 40 mg/day of paroxetine, or placebo) were marked with a red border that was labeled with upward arrows.

Medications were dispensed to patients at each visit during the treatment period (baseline, weeks 1-4, and week 6). At the same visit, the patients returned the bottles that had been dispensed at the previous visit. All unused medications and empty bottles were returned to P&U.

Drug supplies were stored at room temperature. All drug supplies were handled under the direct responsibility of the investigator. The study field monitor assessed the drug storage conditions during site visits.

Appendix 8 lists patient numbers according to the batch number of study medication that each patient received.

8.4.3 Method of Assigning Patients to a Treatment Group

P&U prepared a randomization list for assignment of the patients to 1 of the 3 treatment groups. Study medication for each treatment group was prepared on this basis by P&U and was labeled with the corresponding patient number. At the baseline visit, the investigator assigned each patient to a treatment group based on the patient's temporal entry into the study (ie, by assigning the lowest patient number available). A list of patient numbers and medication assignments was provided only after the data for the study had been analyzed. Appendix 9 contains the randomization code.

8.4.4 Selection of Doses in the Study

The 8- to 10-mg/day doses of reboxetine that were administered in this study were chosen based on the results of previously conducted phase II and phase III studies in which these doses were shown to provide maximal response rates with the most acceptable adverse-event profile. The 1-week dose-escalation period for reboxetine (escalation from 4 mg/day, administered on days 0-6, to 8 mg/day, starting on day 7) was included in the study design to assess whether the relatively high rate of early discontinuations due to adverse events that had been observed in earlier US studies of reboxetine (protocols 049 [26] and 050 [27]) could be reduced by reducing the starting dose of reboxetine.

The starting dose of paroxetine that was administered in this study (20 mg/day) has been shown to be the minimal-effective dose and the optimal dose for most patients. The optional dose increase to 40 mg/day of paroxetine is consistent with the recommended increase in patients who do not respond to treatment with 20 mg/day [28].

8.4.5 Selection and Timing of Dose for Each Patient

Throughout the 8-week study period, patients in each of the treatment groups took one capsule in the morning and one capsule in the late afternoon, at an approximately fixed time (eg, between 8 and 9 AM and between 5 and 6 PM).

The reboxetine dose was escalated from 4 mg/day, administered during the first week of treatment (days 0-6), to 8 mg/day, administered during weeks 2 through 4. Paroxetine was administered at a dose of 20 mg/day during the first 4 weeks of treatment.

An optional dose increase (to 10 mg/day of reboxetine or 40 mg/day of paroxetine) was permitted for weeks 5 through 8 if the investigator believed that the patient would benefit in terms of response and would adequately tolerate the increased dose (ie, in patients who had shown little or no improvement in the objective measures of depressive symptoms but who had no significant difficulty in tolerating the initial doses of study medication). A patient whose dose was escalated at the 4-week evaluation (day 28) continued with the higher dose until treatment was completed (day 56), unless the patient was unable to tolerate the

increased dose, in which case she/he resumed the regimen that was used during weeks 2 through 4 of the study.

8.4.6 Blinding

Patients were randomized to a treatment in a double-blind fashion in order to minimize potential bias in the evaluation of clinical response and safety. The randomized medication consisted of identically appearing capsules containing reboxetine, paroxetine, or placebo. The capsules were provided in clinical supply packages that were labeled with the protocol number, patient number, treatment period, dosing directions, and storage conditions.

Investigators were given sealed drug-disclosure sheets that contained information about each patient's treatment. These sheets were opened only in case of emergency, when knowledge of the treatment was necessary for proper management of the patient. If the treatment code was opened, the reason and the date were recorded on the serious adverse event report form, which was signed by the investigator. The investigator immediately (within 24 hours) informed the study monitor and reported a full description of the reason for opening the code on the Adverse Event Form of the CRF. When the treatment code was opened, the patient was withdrawn from the study.

The sealed disclosure sheets were returned to P&U at the end of the study.

8.4.7 Prior and Concomitant Therapy

No concomitant psychotropic medications other than temazepam, lorazepam, zolpidem, or oxazepam, which could be administered as sleep inducers on an as-needed basis, were allowed during the study. The administration of other psychotropic drugs was considered to be a protocol violation. Use of St. John's Wort was not allowed during the study.

Other therapy that was considered to be necessary for the patient's welfare was permitted at the investigator's discretion. All such therapy was recorded on the Concomitant Medication CRF.

No other investigational drug was allowed to be taken concomitantly with the study medication, and patients were not allowed to participate concurrently in any other clinical study. Over-the-counter medications were allowed as needed for symptomatic treatment; these were recorded along with other medications on the Concomitant Medication CRF.

8.4.8 Treatment Compliance

The investigator maintained a record of the study medications that were received from the sponsor, those that were dispensed, and those that were returned. Discrepancies between dispensed and returned study medications were recorded.

Treatment compliance was monitored by the investigators and was recorded on the appropriate CRF (eg, Medication Record CRF, Concomitant Medication CRF) at each visit.

8.4.9 Continuation of Treatment

Patients who were randomized and who received at least one dose of study medication during this study (protocol M/2020/0046) were eligible to enroll in an open-label continuation study of reboxetine (protocol 950E-CNS-0005-087) after they completed or discontinued from this study. However, patients who discontinued early from this study were required to wait at least 56 days from the date of randomization before they could be enrolled in the continuation study.

8.5 Efficacy and Safety Variables

8.5.1 Study Schedule

The schedule of study activities is summarized in Table 2.

Table 2. Schedule of Activities

Study Activity	Study Day								
	Prescreen	Screen -7	Baseline 0	7	14	21	28	42	56
IVRS 17-Item HAM-D	X								
Informed Consent		X							
Inclusion / Exclusion Criteria		X	X						
Admission Checklist		X							
Medical history		X							
History of Mental Disorder		X							
Demographics		X							
Physical examination		X							
Randomization			X						
Medication Record			X	X	X	X	X	X	X
ECG		X					X		X
Laboratory Safety Assays		X					X		X
Pregnancy test (serum)		X							X
Urine drug screen		X							
Pharmacokinetic assays					X		X	X	X
Platelet serotonin assay		X					X		X
Vital signs		X	X	X	X	X	X	X	X
MADRS			X		X		X	X	X
21-Item HAM-D		X	X		X		X	X	X
CGI			X		X		X	X	X
SASS			X		X		X	X	X
MFI			X		X		X	X	X
MOS SF-36 Social Functioning			X		X		X	X	X
MOS SF-36 Vitality			X		X		X	X	X
Treatment/Study Completion									X
Concomitant Medication		X	X	X	X	X	X	X	X
Compliance				X	X	X	X	X	X
Adverse Events Query				X	X	X	X	X	X

Abbreviations: CGI = Clinical Global Impression, ECG = electrocardiogram, HAM-D = Hamilton Rating Scale for Depression, IVRS = interactive voice response system, MADRS = Montgomery-Asberg Depression Rating Scale, MFI = Multidimensional Fatigue Inventory, MOS SF-36 = Medical Outcomes Study Short-Form Health Survey (36-item), SASS = Social Adaptation Self-evaluation Scale

8.5.2 Efficacy Variables

Efficacy was evaluated every 2 weeks (days 0, 14, 28, 42, and 56) using the results of both clinician- and patient-rated assessment instruments (Table 3).

Table 3. Efficacy Measures

Domain	Assessment Instrument	Endpoint	Rater
Depression	MADRS	Primary	Clinician
	21-Item HAM-D	Secondary	Clinician
	CGI Global Improvement	Secondary	Clinician
	CGI Severity of Illness	Secondary	Clinician
Energy	MFI General Fatigue subscale	Secondary	Patient
	MOS SF-36 Vitality scale	Secondary	Patient
Social Function	SASS	Secondary	Patient
	MOS SF-36 Social Functioning scale	Secondary	Patient

Abbreviations: CGI = Clinical Global Impression, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, MFI = Multidimensional Fatigue Inventory, MOS SF-36 = Medical Outcomes Study Short-Form Health Survey (36-item), SASS = Social Adaptation Self-evaluation Scale

8.5.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the mean change from baseline in the MADRS total score.

8.5.2.2 Secondary Efficacy Endpoints

The secondary endpoints of this study were as follows:

Antidepressant efficacy (continuous endpoints)

- 21-Item HAM-D, mean change from baseline in the total score
- HAM-D Item 1 (Depressed Mood), mean change from baseline
- HAM-D Retardation Cluster (Items 1, 7, 8 and 14), mean change from baseline
- CGI Severity of Illness, mean change from baseline

Antidepressant efficacy (categorical endpoints)

- MADRS response rate, defined as the percentage of patients who had a decrease of ≥50% from baseline in the MADRS total score
- MADRS remission rate, defined as the percentage of patients who had a MADRS total score of ≤12
- HAM-D response rate, defined as the percentage of patients who had a decrease of ≥50% from baseline in the 21-Item HAM-D total score
- HAM-D remission rate, defined as the percentage of patients who had a total score of ≤10 on the 21-Item HAM-D

- CGI Global Improvement score
- CGI Global Improvement response rate, defined as the percentage of patients who had a CGI Global Improvement score of ≤2 (corresponding to "very much improved" or "much improved")

Energy

- General Fatigue subscale of the MFI [29], mean change from baseline in the total score
- Vitality scale of the MOS SF-36, mean change from baseline in the total score

Social function

- SASS, mean change from baseline in the total score
- Social Functioning scale of the MOS SF-36, mean change from baseline in the total score

8.5.2.3 Description of Efficacy Scales

8.5.2.3.1 Montgomery-Asberg Depression Rating Scale

The MADRS [22], which is based on a clinical interview, has been shown to satisfactorily distinguish between 5 grades of depression. In the MADRS, categories of degree are precisely described, items are restricted to representing only those symptoms that are considered to be the core symptoms of depressive syndromes, and items representing somatic complaints have been reduced [21]. The ability of the MADRS to differentiate between responders and non-responders to antidepressant treatment and to distinguish between subjects who are likely to experience somatic adverse events from treatment and those who are less likely has been demonstrated in several studies [22, 23, 24, 25]. The MADRS consists of 10 items, each of which is scored on a 7-point scale on which 0 corresponds to the absence of the symptom and 6 corresponds to the most extreme form of the symptom. The MADRS total score ranges from 0 to 60. Remission is defined as a MADRS total score of ≤12. Response to study medication is defined as a decrease of ≥50% from baseline in the MADRS total score at the postbaseline assessment.

8.5.2.3.2 Hamilton Depression Rating Scale

The 21-Item HAM-D [30] is an observer-rated scale that is based on both a clinical interview and on observations of behavior made by an experienced clinician. This scale is well standardized and is intended to assess the state of the patient's condition at the time of the interview and over the preceding few days. The individual items on the HAM-D are graded according to severity on 0- to 2-point or 0- to 4-point scales. The HAM-D total score ranges from 0 to 62; scores of ≥25 are associated with severe depression, scores between 18 and 24 are associated with moderate depression, and scores between 8 and 17 are associated with mild depression. Scores of ≤10 are often used as the definition of disease remission. Response to study medication is defined as a decrease of ≥50% from baseline in the HAM-D total score at the postbaseline assessment.

8.5.2.3.3 Clinical Global Impression

The CGI [31] consists of the following 3 parts: Severity of Illness, Global Improvement, and Efficacy Index; only the Severity of Illness and Global Improvement portions of the scale were used in this study. A mean decrease from baseline on the CGI Severity of Illness score represents patient improvement. The questions from the Global Improvement index refer to changes since the beginning of the study, as evaluated at each postbaseline visit, and are not asked at baseline. Lower scores on the CGI Global Improvement index indicate patient improvement; a responder is defined as a patient who has a score of ≤2 (corresponding to "very much improved" or "much improved").

8.5.2.3.4 The Social Adaptation Self-Evaluation Scale

The SASS [19] is a 21-question self-evaluation questionnaire that explores the domains of work and leisure, relationships, and patient perception of his/her ability to manage the environment. The scale was validated using data from 4000 individuals in a general population survey and data from 549 depressed patients who were enrolled in clinical studies that compared reboxetine with placebo and/or fluoxetine [19]. Each item of SASS is scored on a scale of 0 to 3, with a higher score indicating better social functioning. A total score in the range of 35 to 52 points is considered to be normal (ie, this range was observed in 80% of the general population) [19]. The SASS represents a useful tool for the evaluation of social functioning in depression because it is relatively simple to use and because it may help to differentiate the effects of different classes of antidepressants (eg, serotonergic agents regulating mood, noradrenergic agents sustaining drive) in a way that syndromic clinical rating scales are unable to do.

8.5.2.3.5 Multidimensional Fatigue Inventory

The MFI [29], a validated, 20-item, self-administered instrument, is used to measure fatigue. The MFI addresses the following dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. The general fatigue subscale of the MFI was the key measure of energy in this study. The score for the general fatigue subscale of the MFI ranges from 4 to 20, with a higher score indicating more fatigue.

8.5.2.3.6 Medical Outcomes Study Short-Form Health Survey (36-item)

The MOS SF-36 [32, 33] is a general, self-administered, health-related, quality of life instrument, which is composed of 8 scales that each address a different aspect of quality of life. Each scale is scored separately; only the Vitality and Social Functioning scales were used in this study. The reliability and validity of the MOS SF-36 scales are well established. General population norms exist on thousands of individuals and can be broken out for age and sex comparisons with almost any population sample. This instrument has also been used extensively in patients with clinical depression.

8.5.3 Safety Variables

8.5.3.1 Safety Assessments

The following safety variables were assessed in this study:

- Standard medical history, obtained at screen.
- Standard clinical and physical examination, obtained at screen.
- Blood pressure and pulse, measured at each visit in the sitting position.
- Adverse events, recorded at each visit.
- ECG, obtained at screen, day 28, and day 56 (end of treatment). The ECG results were analyzed by eResearchTechnology (Philadelphia, PA). Abnormal ECG patterns were assessed and the heart rate, PR, QRS, and QT intervals were measured.
- Safety laboratory assays: hematology and serum chemistries were performed at screen and on days 28 and 56, serum pregnancy tests for females of childbearing potential were performed at screen and on day 56, and thyroid-function tests and a urine drug test were performed at screen. Laboratory tests were performed at a central laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, CA).
- Additional laboratory assays: pharmacokinetic assessments were performed by P&U on samples that were collected on days 14, 28, 42, and 56 at all study sites. A platelet serotonin assay was performed by an independent private laboratory on samples that were collected at screen and on days 28 and 56; samples were collected at only those sites in the United States and Canada that were able to process the samples appropriately for this assay. The results of both the pharmacokinetic assessments and the platelet serotonin assay will be summarized in separate study reports.

The specific laboratory tests that were evaluated are summarized in Table 4.

Table 4. Laboratory Assays

Category	Assay
Hematology	Hematocrit Hemoglobin White blood cell count Differential Neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelet count Red blood cell count
Serum Chemistries	Electrolytes Sodium Potassium Chloride Carbon dioxide content Blood urea nitrogen Creatinine Glucose Uric acid Total bilirubin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Thyroid stimulating hormone (TSH) and thyroxine (T_4) – screen only Pregnancy test (for all females of childbearing potential) – screen and day 56
Urinalysis	Drug screen (screen only)
Additional Laboratory Assays*	Pharmacokinetic assessments Platelet serotonin assay (selected sites)

* The results of the pharmacokinetic assessments and the platelet serotonin assay will be summarized in separate study reports and are not included in this report.

8.5.3.2 Adverse Events

8.5.3.2.1 Definition of Adverse Events

For this study, an adverse event was defined as any untoward medical event that occurred during the protocol-specified adverse event reporting period (from baseline until the final clinic visit) regardless of whether it was considered to be related to study medication. In addition, any known untoward event that occurred subsequent to the adverse event reporting period and that the investigator assessed as possibly related to the investigational medication was also considered to be an adverse event.

Adverse events included all suspected adverse medication reactions; all reactions from medication abuse, withdrawal, sensitivity, or toxicity; apparently unrelated illnesses, including the worsening of a preexisting illness; any injury or accident; and any abnormality in physical examination or laboratory test results that required clinical intervention or further investigation (beyond ordering a repeat confirmatory test). If a medical condition was known to have caused the injury or accident (eg, a fall secondary to dizziness), then the medical condition (dizziness) and the accident (fall) were reported as 2 separate adverse events. The outcome of the accident (eg, hip fracture secondary to the fall) was recorded in the comments section of the CRF. Laboratory abnormalities that were associated with a clinical event (eg, elevated liver enzymes in a patient with jaundice) were described in the comments section of the CRF, rather than listed as a separate adverse event.

Diagnostic and therapeutic procedures, such as surgery, were not reported as adverse events. However, the medical condition for which the procedure was performed was reported if it met the definition of an adverse event (eg, an acute appendicitis that began during the adverse event reporting period would have been reported as an adverse event; the resulting appendectomy would have been noted in the comments section of the CRF).

Except for worsening of depressed mood (which would be reflected in a change in the HAM-D Item 1 score), an increase in the intensity of other symptoms of depression (eg, sleep difficulties, somatic symptoms, genital symptoms, weight change, anxiety, other psychiatric symptoms) was to be considered an adverse event if the intensity of the event increased during the treatment period.

8.5.3.2.2 Eliciting Adverse Event Information

Investigators reported all directly observed adverse events and all adverse events that were spontaneously reported by the patients. In addition, each patient was questioned about adverse events at each clinic visit following initiation of treatment, as follows: "Since your last clinic visit," (or "Since you began taking the investigational medication,") "have you had any health problems?"

8.5.3.2.3 Adverse Events Reporting Period

The adverse event reporting period began with the administration of the first dose of study medication (at the baseline [day 0] visit) and ended at the final clinic visit (day 56). An adverse event that occurred during the protocol-specified adverse event reporting period was reported, regardless of whether it was considered to be related to the study medication. A disorder that was present before the adverse event reporting period started and that was noted on the pretreatment medical history/physical examination form was not reported as an adverse event unless the condition worsened or episodes increased in frequency during the adverse event reporting period. Any known untoward event that occurred subsequent to the adverse event reporting period and that the investigator assessed as possibly related to the study medication was considered to be an adverse event.

8.5.3.2.4 Assessment of Gravity and Intensity

Each adverse event was classified by the investigator as serious or nonserious. A serious adverse event was one that was fatal or life-threatening (ie, resulted in immediate risk of death), required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly. Any other important adverse event that did not meet the preceding criteria was classified as serious if, based upon appropriate medical judgment, the event was considered to jeopardize the patient or if medical or surgical intervention was required to prevent the occurrence of one of the outcomes listed above. Serious adverse events also included any other adverse event that the investigator or company judged to be serious or that was defined as serious by the regulatory agency in the country in which the adverse event occurred.

Investigators characterized the intensity of adverse events as mild (did not interfere with subject's usual function), moderate (interfered to some extent with subject's usual function), or severe (interfered significantly with subject's usual function). The assessment of intensity was made independently of the assessment of gravity. It should be noted that severity is a measure of intensity, whereas seriousness is a measure of gravity. (A severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.)

8.5.3.2.5 Assessment of Drug-Relatedness

Investigators assessed the possible relationship between the adverse event and the study medication.

8.5.3.2.6 Follow-up of Unresolved Events

All adverse events were followed until they resolved or until the patient's participation in the study ended (ie, until a final report was completed for that patient). In addition, all serious adverse events and those nonserious events that were assessed by the investigator as possibly related to the study medication were followed after the patient's participation in the study was over, until the events resolved or until the investigator assessed them as "chronic" or "stable."

8.5.3.2.7 Exposure In Utero

If a patient became, or was found to be, pregnant while receiving or within 30 days of discontinuing study medication, then the investigator submitted an adverse event CRF that included the anticipated date of birth or pregnancy termination. The patient was followed by the investigator until the completion of the pregnancy. The following pregnancy outcomes were to be reported as serious adverse events: spontaneous abortion (including miscarriage and missed abortion), stillbirth, neonatal death within 1 month of birth, infant death that occurred after 1 month of birth and that the investigator assessed as possibly related to the in utero exposure, or congenital anomaly (including that in an aborted fetus). In the case of a live birth, the “normality” of the newborn was assessed at the time of birth (ie, there was no required minimum follow-up of a presumably normal infant). The “normality” of an aborted

fetus was assessed by gross visual inspection unless pre-abortion laboratory findings were suggestive of a congenital anomaly.

8.6 Data Quality Assurance

The following procedures were implemented to ensure the quality of data that were collected:

- An investigator's meeting was held to familiarize the investigators with the protocol and with the assessment instruments.
- A reference manual was given to each investigator.
- An automated prescreening assessment (17-Item HAM-D, administered via the IVRS) was used to reduce potential bias in the prescreening evaluation of depressive symptoms.
- Data were collected on standard CRFs that were provided to each investigator by the sponsor.
- Investigators and institutions guaranteed access to source documents for quality assurance audits by P&U personnel and the appropriate regulatory agencies.
- Monitoring visits were made periodically during the study to ensure that all aspects of the protocol were followed.
- Source documents were reviewed to verify their agreement with the data on the patient CRFs.
- All safety laboratory measurements were conducted by SmithKline Beecham Clinical Laboratories, Van Nuys, CA, a central laboratory that is certified by the Clinical Laboratory Improvement Act and the College of American Pathologists. (Documentation is provided in Appendix 11.)
- Laboratory data were entered at SmithKline Beecham Clinical Laboratories and were transmitted electronically to P&U for analysis.
- ECGs were evaluated by eResearchTechnology, Philadelphia, PA; the ECG data were then transmitted electronically to P&U for analysis.
- Data (ie, MADRS scores, HAM-D scores, and adverse events) in the clinical database were reviewed to verify their agreement with the data on the patient CRFs.
- P&U's Standard Operating Procedures were followed in the conduct and analysis of the study.

P&U is responsible for independent quality assurance audits of the clinical trial processes at company sites worldwide. Audits of selected clinical investigator sites were conducted to assess and help assure compliance with Good Clinical Practice and applicable regulatory requirements. A copy of the audit certificate is provided in Appendix 10.

8.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

8.7.1 Statistical and Analytical Plans

8.7.1.1 Data Sets Analyzed

The ITT population includes all patients who were randomized into the trial and who received at least one dose of study medication. All analyses were based on the ITT population. Efficacy analyses were based on the population of ITT patients who had at least one postbaseline evaluation for the specified efficacy measure (eg, MADRS, HAM-D).

Information regarding visit number or study day was based on the visit numbers that were preprinted on the CRFs. For purposes of data analysis, the day of first dose of study medication was considered to be study day 1.

Two types of analyses were performed for all efficacy variables: "last observation carried forward" (LOCF) and "observed cases" (OC). The LOCF analyses used the last valid assessment as an estimate for all subsequent missing values. The OC analysis did not replace missing data. The LOCF analyses were the primary analyses, and the OC analyses were the secondary analyses. Comparisons were based on a 2-sided test at an alpha level of 0.05, unless otherwise specified.

8.7.1.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics (eg, age, sex, race) of the patients in each treatment group were compiled. Categorical variables were summarized using frequency counts. The association between treatment groups and categorical variables was assessed using the chi-square test. Continuous variables were summarized using treatment group means, standard deviations, and ranges. The association between treatment groups and continuous variables was assessed using a one-way ANOVA with treatment as a factor.

8.7.1.3 Primary Efficacy Endpoint

8.7.1.3.1 Primary Analysis of the Primary Endpoint

Summary statistics of the data for the MADRS total score, including the mean, mean change from baseline, standard deviation of the change from baseline, and the minimum and maximum values, were presented.

Differences among the 3 treatment groups in the mean change from baseline in the MADRS total score at each visit were assessed using a 2-way ANOVA with investigator, treatment, and treatment-by-investigator interaction as factors. Investigators who had low numbers of patients were grouped by geographical region for purposes of analysis. If a statistically significant ($p \leq 0.05$) treatment effect was observed among the 3 treatment groups based on the 2-way ANOVA, then pairwise comparisons between reboxetine and placebo were performed. Although comparisons were made at each visit, the primary endpoint was day 56. The comparison between reboxetine and placebo was the primary comparison; the

comparison between paroxetine and placebo was included as a positive control. No comparisons were made between reboxetine and paroxetine.

8.7.1.3.2 Secondary Analyses of the Primary Endpoint

Differences among the 3 treatment groups in the mean change from baseline in the MADRS total score were assessed at each visit using a 2-way analysis of covariance (ANCOVA) with baseline severity as a covariate and with investigator, treatment, and treatment-by-investigator interaction as factors. Two categories of baseline severity were used: patients who had a baseline CGI Severity of Illness score of 5 to 7 (corresponding to "markedly to extremely ill") were categorized as "severely ill patients," whereas all other patients were categorized as "non-severely ill patients." If a statistically significant ($p \leq 0.05$) treatment effect was observed among the 3 treatment groups based on the 2-way ANCOVA, then pairwise comparisons between the reboxetine and placebo groups were performed. Although comparisons were made at each visit, the primary endpoint was day 56. The comparison between the reboxetine and placebo groups was the primary comparison; the comparison between the paroxetine and placebo groups was included as a positive control. No comparisons were made between the reboxetine and paroxetine groups.

In addition to the endpoint analyses described above, a generalized estimating equation (GEE) analysis [34] of the mean change from baseline in the MADRS total score was performed. The GEE analysis estimates the average rate of change per day over the entire study duration by regressing the change from baseline on the number of days in the study. This methodology uses all observed data and incorporates correlation among the multiple observations within a subject. This is in contrast to the ordinary regression methodology, which often treats the multiple observations within a subject as independent. Under the GEE analysis, treatment effects can be compared by examining the average rates of change, estimated for the 3 treatment groups. However, one can also obtain an estimate for the total change at the last visit. The latter is obtained by multiplying the average rate of change per day by the number of study days for each treatment group. The advantage of the GEE method is that the inference is based on the complete data that were collected at all time points. In contrast, in the LOCF and OC analyses, the inference is based only on data that were collected at endpoint (LOCF) or at day 56 (OC).

The GEE analysis was performed only on the OC data (ie, missing data were not replaced). The GEE analysis was used to compare the reboxetine and placebo groups and the paroxetine and placebo groups. No comparisons were made between the reboxetine and paroxetine groups.

8.7.1.4 Secondary Efficacy Endpoints

8.7.1.4.1 Continuous Endpoints

For the continuous, secondary efficacy endpoints, summary statistics—which include the mean, mean change from baseline, standard deviation of the change from baseline, and the minimum and maximum values—were presented.

Differences among the 3 treatment groups in the mean change from baseline in the continuous secondary efficacy endpoints were assessed at each visit using a 2-way ANOVA with investigator, treatment, and treatment-by-investigator interaction as factors. If a statistically significant ($p \leq 0.05$) treatment effect was observed among the 3 treatment groups based on the 2-way ANOVA, then pairwise comparisons between reboxetine and placebo were performed. Although comparisons were made at each visit, the primary endpoint was day 56. The comparison between the reboxetine and placebo groups was the primary comparison; the comparison between the paroxetine and placebo groups was included as a positive control. No comparisons were made between the reboxetine and paroxetine groups.

8.7.1.4.2 Categorical Endpoints

For the categorical efficacy endpoints, differences among the 3 treatment groups were assessed at each visit using the Cochran-Mantel-Haenszel test, stratified by investigator. If a statistically significant ($p \leq 0.05$) difference was observed among the 3 treatment groups based on the Cochran-Mantel-Haenszel test, then pairwise comparisons between reboxetine and placebo were performed. Although comparisons were made at each visit, the primary endpoint was day 56. The comparison between the reboxetine and placebo groups was the primary comparison; the comparison between the paroxetine and placebo groups was included as a positive control. No comparisons were made between the reboxetine and paroxetine groups.

8.7.1.5 Safety Evaluations

The original terms that were used by investigators to identify adverse events on the CRFs were translated according to the Coding Symbols and Thesaurus of Adverse Reaction Terms (COSTART) and were grouped according to COSTART body systems and preferred terms.

Each adverse event was counted once, according to the date of onset. If the adverse event began prior to the first dose of study medication and did not increase in severity after the first dose of study medication, then the adverse event was considered to be a pretreatment event and was not counted in the adverse event frequency tables. If the onset was prior to the first dose of study medication and the severity increased after baseline, then the event was considered to be an adverse event and was included in the adverse event frequency tables. This rule was consistent with the treatment-emergent signs and symptoms (TESS) convention for counting adverse events.

The incidence of TESS was summarized as follows: (1) by body system and preferred term; (2) by maximum severity; (3) by relationship to study medication; and (4) by gender. The relationship of an adverse event to study medication was based on the investigator's judgment. Summary tables were also presented for adverse events that resulted in termination of study medication, for serious adverse events, and for serious adverse events that resulted in termination of study medication. Corresponding patient data listings were prepared to support each of the above summaries.

For each vital sign, laboratory test, and ECG measure, differences among treatment groups in the change from baseline at each postbaseline evaluation were analyzed using a one-way

ANOVA. Differences between each treatment group and placebo were analyzed using a pairwise t-test. The incidence of abnormal postbaseline vital signs, laboratory tests, and ECG results were summarized and corresponding patient data listings were prepared to support each of the summaries.

8.7.2 Determination of Sample Size

The adequacy of the sample size was determined based on the calculated power to detect a difference between the reboxetine and placebo treatment groups on the mean change from baseline in the MADRS total score. As described in Amendments 2 and 4 of the protocol, the power calculation was based on the results of a previously conducted study (protocol 97-CRBX-049 [26]) in which the mean change from baseline in the MADRS total score at week 6 was significantly greater in the reboxetine group (mean change of 10.6 points) than in the placebo group (mean change of 7.1 points; $p = 0.019$). Based on this information, it was determined that 215 patients would be required per treatment group (total sample size of 645 patients) to detect a treatment effect of 3.5 points with a power of 97% and a 2-sided alpha equal to 0.05. The sample size of 215 patients per arm would still provide 90% power in the observed-cases analyses if 30% of the patients failed to complete the study.

Calculations were made using nQuery Advisor Release 3.0, Statistical Solutions Ltd., Cork, Ireland.

8.8 Changes in the Conduct of the Study or Planned Analyses

8.8.1 Protocol Amendments

Changes to protocol M/2020/0046 were detailed in 5 amendments. The protocol and protocol amendments are in Appendix 4.* Amendment A and Amendments 1 through 3 were implemented before any patients were enrolled in the study. Amendment 4 was implemented after enrollment was completed but before the study blind was broken. The protocol amendments, along with the reasons for each, are briefly summarized below.

8.8.1.1 Amendment A (16 August 1999)

The protocol was amended to specify that the 40-mg capsules of paroxetine that are administered at Canadian sites will contain two 20-mg tablets rather than one 40-mg tablet, since the 40-mg tablet is not approved for marketing in Canada.

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* Because of the extensive changes that were made to the protocol before any patients were enrolled in the study (changes detailed in Amendments A, 1, 2, and 3), a "working protocol," which incorporates Amendments A, 1, 2, and 3, was provided to the investigators. The original protocol, the protocol amendments, and the working protocol are provided in Appendix 4.

8.8.1.2 Amendment 1 (7 October 1999)

The protocol was amended to add cimetidine to the list of excluded medications. Cimetidine is a potent inhibitor of the drug-metabolizing enzyme cytochrome p450-2D6 and is contraindicated for use with paroxetine.

8.8.1.3 Amendment 2 (7 March 2000)

With Amendment 2, the protocol was changed substantially in order to redesign the study from a multiple-endpoint evaluation of quality-of-life parameters to a single-endpoint evaluation of antidepressant efficacy. The following specific changes were made:

- The primary and secondary objectives of the study were changed, and the number of secondary quality-of-life endpoints was reduced.
- The study timeline was shortened by eliminating the placebo washout period and the posttreatment follow-up period and by shortening the targeted enrollment period. The number of investigator sites was increased in order to meet the shortened enrollment period.
- An automated prescreening assessment (17-Item HAM-D, administered via the IVRS) was added to the protocol. This change was made to facilitate rapid patient enrollment and to reduce potential bias in the prescreening assessment.
- The planned number of patients to be enrolled in the study was reduced based on the power calculation to support the new primary and secondary objectives. The inclusion and exclusion criteria were also modified to support patient selection for the revised primary and secondary objectives.
- A dose escalation during the first week of the study was added for the reboxetine treatment group (ie, reboxetine was administered at a dose of 4 mg/day during days 0-6 and 8 mg/day during days 7-56, with an optional dose increase to 10 mg/day starting at day 28).
- The background and the statistics sections of the protocol were rewritten to support the new primary and secondary objectives of the study.

8.8.1.4 Amendment 3 (15 March 2000)

The qualifications section of the sample informed consent form (provided in Appendix 2 of the protocol) was changed to correct an error in item 17, which incorrectly stated that patients "must not have participated in any study with an investigational compound in the last 4 months" (this time period was corrected to "4 weeks").

8.8.1.5 Amendment 4 (19 September 2000)

The protocol was amended to change the statistical analysis plan and to clarify several items in the protocol. For the primary efficacy endpoint, the planned repeated-measures ANOVA was changed to a 2-way ANOVA. The 2-way ANOVA was designated as the primary analysis and 2 additional analyses—a 2-way ANCOVA and a GEE analyses—were added to

the protocol as secondary analyses. The analysis plan for the secondary, continuous efficacy endpoints was also changed from a repeated-measures ANOVA to a 2-way ANOVA.

The analysis plan for the secondary, categorical efficacy endpoints was changed from the chi-square test to the Cochran-Mantel-Haenszel test. For all efficacy endpoints, the protocol was changed to specify that the comparison between the reboxetine and placebo groups would be the primary comparison, the comparison between the paroxetine and placebo groups would be included as a positive control, and no comparisons would be made between the reboxetine and paroxetine groups.

8.8.2 Additional Analyses

An additional subset analysis was conducted to assess the pattern of response among patients who discontinued early from the study. Patients were placed in independent subsets, based on their day of last assessment (days 14, 28, or 42). The mean change from baseline in the MADRS total score was evaluated by visit for each of these subsets. Because of the small number of patients who discontinued at each visit, the change from baseline values were described using summary statistics only; no statistical testing was performed.

Although not planned in the protocol, the corrected QT intervals (QTc) were calculated using both Fridericia's and Bazett's correction methods.

In November 2000 (after all patients had been enrolled and had completed the study), P&U received notification that Western IRB had suspended enrollment privileges at Investigator J. Apter's site (Investigator No. 40051) while allegations that had been made against him were investigated. To determine whether the data collected at this site affected the outcome of the study, the primary endpoint (mean change from baseline in the MADRS total score) was reanalyzed, excluding the data from the 7 patients who had been enrolled at his site.

9 RESULTS

Key data displays are included in the text. More detailed, supportive tables are included in Section 13; references to these tables are included in the text.

9.1 Study Patients

9.1.1 Disposition of Patients

A total of 787 patients were enrolled in the study and were randomized to receive treatment with reboxetine (265 patients), placebo (257 patients), or paroxetine (265 patients). The ITT population includes all patients who were randomized and who received at least one dose of study medication. A total of 780 patients, including 264 reboxetine-treated patients, 254 placebo-treated patients, and 262 paroxetine-treated patients, were included in the ITT population.

The percentage of patients who completed the 8-week treatment period was higher in the placebo group (84.4%; 217/257) than in the paroxetine (78.1%; 207/265) or reboxetine (74.7%; 198/265) groups. The reasons for study discontinuation are summarized in Table 5.

Table 5. Patient Disposition

	RBX		PBO		PAR	
	n	%*	n	%*	n	%*
Number of patients						
Randomized	265	100.0	257	100.0	265	100.0
Intent to treat†	264	99.6	254	98.8	262	98.9
Completed study	198	74.7	217	84.4	207	78.1
Discontinued study	67	25.3	40	15.6	58	21.9
Reason for discontinuation						
Adverse event	28	10.6	8	3.1	22	8.3
Protocol violation	3	1.1	1	0.4	4	1.5
Consent withdrawn	11	4.2	12	4.7	16	6.0
Lost to follow-up	16	6.0	12	4.7	15	5.7
Protocol-specific withdrawal criteria	2	0.8	0	0	0	0
Lack of efficacy	4	1.5	6	2.3	1	0.4
Progression of disease	3	1.1	1	0.4	0	0

* Percentages are based on the number of patients who were randomized.

† The intent-to-treat population includes all patients who were randomized and who received at least one dose of study medication.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Table 1.1

In the active treatment groups, the most common reasons for discontinuation of study medication were adverse events, which led to discontinuation of treatment in 10.6% (28/265) of reboxetine-treated patients, 8.3% (22/265) of paroxetine-treated patients, and 3.1% (8/257) of placebo-treated patients*. (Discontinuations due to adverse events are discussed in Section 9.4.2.3.)

Section 13, Table 1.2, summarizes patient enrollment by investigator. The patients who prematurely discontinued from the study are listed in Appendix 13, Table 9.1. The 7 patients who were randomized for treatment but who were not included in the ITT group are listed in Appendix 15, Table 11.1.

* The information regarding discontinuations due to adverse events that is reported in Table 30 and in Table 38 was taken from the adverse event forms, whereas the information in Table 5 was taken from the treatment termination record. Two reboxetine-treated patients (patient nos. 1024 and 1112) were included in Table 5 but not in Table 30 or in Table 38 because the adverse events that led to discontinuation of treatment were not considered to be treatment-emergent. One placebo-treated patient (patient no. 1742) who was not included in Table 5 was incorrectly included in Table 30 and in Table 38 because of a CRF error.

9.1.2 Protocol Deviations

The occurrences of the following protocol deviations were assessed in each treatment group: (1) use of disallowed psychotropic medications, (2) patient age greater than 65 years, (3) administration of a dose of study medication that exceeded the protocol-specified dosing regimen (ie, patients who had an average daily dose of >10 mg/day of reboxetine or >40 mg/day of paroxetine), (4) positive urine drug screen, or (5) positive serum pregnancy test at screen. As shown in Table 6, these protocol deviations occurred in a comparable number of patients in the 3 treatment groups.

Table 6. Protocol Deviations

	RBX		PBO		PAR	
	N*	n (%)	N*	n (%)	N*	n (%)
Use of disallowed psychotropic medications	264	20 (7.6)	254	13 (5.1)	262	25 (9.5)
Patient age >65 years	264	0	254	0	262	0
Dose of study medication exceeding the protocol-specified dosage regimen						
>10 to <12 mg/day RBX or >40 to <50 mg/day PAR	264	30 (11.4)			262	21 (8.0)
≥12 mg/day RBX or ≥50 mg/day PAR	264	9 (3.4)			262	6 (2.3)
Positive urine drug screen†	262	8 (3.1)	252	2 (0.8)	258	6 (2.3)
Positive serum pregnancy test at screen‡	125	0§	133	0	135	0

* The percentages of patients who had a positive urine drug test or pregnancy test at screen were based on the number of ITT patients who had at least one test performed. All other percentages in this table were based on the number of ITT patients.

† The urine drug screen tested for the presence of the following: amphetamines, barbiturates, benzodiazepines, marijuana metabolites, cocaine metabolites, methadone, methaqualone, opiates, phencyclidine, and propoxyphene. However, because the protocol specified that a positive urine drug screen for benzodiazepines did not exclude the patient from the study, positive results for benzodiazepines are not counted in this table.

‡ The number of patients who had a positive pregnancy test at screen is shown; Appendix 14, Table 10.4A, summarizes the number of patients who had a positive pregnancy test at any visit.

§ One patient (patient no. 1024) was retrospectively found to have been pregnant at the start of the study; no serum pregnancy test was performed on this patient at screen due to site error.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Appendix 14, Tables 10.1A, 10.2A, 10.3A, 10.4A, 10.4B

The protocol specified that female patients who had a positive serum pregnancy test at screen were to be excluded from the study. However, one reboxetine-treated patient (patient no. 1024) was retrospectively found to have been pregnant at the start of the study. No serum pregnancy test had been performed on this patient at screen due to site error. A narrative summary for this patient is provided in Section 9.4.6, Exposure in Utero.

As indicated in Table 6, data from the medication record CRFs indicated that 39 reboxetine-treated patients and 27 paroxetine-treated patients had received an average daily dose that exceeded the protocol-specified dosing regimen (ie, >10 mg/day of reboxetine or >40 mg/day of paroxetine) at any time during the treatment period. (An average daily dose was

calculated for each time period during the study when the dose changed for any patient.) For the majority of these patients, the dose represented a minor elevation above the protocol-specified dose. More substantial elevations in dose (defined as ≥12 mg/day of reboxetine or ≥50 mg/day of paroxetine) were reported in 9 reboxetine-treated patients and in 6 paroxetine-treated patients. Data for these 15 patients are summarized in Table 7.

Table 7. Patients Who Received ≥12 mg/day of Reboxetine or ≥50 mg/day of Paroxetine

Treatment	Patient No.	Study Day	Average Daily Dose* (mg/day)
Reboxetine	2024	37-54	12.1
	1680	23-26	14.0
	1029	47-59	12.1
	1009	30-36	12.9
	1423	32-45	27.7
	1081	29-43	12.5
	2100	28	13.7
		29-41	17.7
		42-55	18.0
	2067	45-57	12.1
	1066	49	15.4
		50-63	17.7
Paroxetine	1020	31-43	60.0†
		44-55	80.0†
	2019	37-43	85.7
	2098	29-42	65.7
		43-55	58.5
	2099	31-45	66.7
	1271	36-40	80.0
	1404	46-56	50.9

* An average daily dose was calculated for each time period during the study when the dose changed for any patient.

† Corrected average daily dose; because of errors in the way in which the medication record CRF was completed for patient no. 1020, the source table incorrectly lists the average daily dose as 80.0 mg/day for days 31-43 and as 106.7 mg/day for days 44-55. According to comments on the CRF, the actual doses were 60.0 mg/day for days 31-43 and 80.0 mg/day for days 44-55.

Source: Appendix 14, Table 10.2B

Only 4 patients reported adverse events that occurred for the first time, or increased in intensity, during the time period in which the elevated dose was taken: patient no. 1029 in the reboxetine group reported pharyngitis, patient no. 1423 in the reboxetine group reported skin disorder (increase in the size of a skin tag on the neck), patient no. 1020 in the paroxetine group reported impaired urination, and patient no. 2019 in the paroxetine group reported conjunctivitis. In a fifth patient (patient no. 1271 in the paroxetine group), adverse

events of asthenia, dry mouth, and flatulence were reported during the month in which the elevated dose was taken, although the exact start dates for the adverse events are unknown. No clinically significant abnormalities in blood pressure, heart rate, ECGs, or laboratory assays were noted during the time period in which the elevated dose was taken.

Patients who met the criteria for protocol deviations are listed in Appendix 14, Tables 10.1B, 10.2B, 10.3B, and 10.4B: Appendix 14, Table 10.1B, lists the patients who used disallowed psychotropic medications; Appendix 14, Table 10.2B, lists the patients who received an average daily dose of >10 mg/day of reboxetine or >40 mg/day of paroxetine; Appendix 14, Table 10.3B, lists the patients who had positive results on the urine drug screen; and Appendix 14, Table 10.4B, lists the patients who had positive results on the serum pregnancy test.

9.1.3 Data Sets Analyzed

The ITT population includes all patients who were randomized into the trial and who received at least one dose of study medication. Of the 787 patients who were randomized into the study, 780 patients (264 reboxetine-treated, 254 placebo-treated, and 262 paroxetine-treated patients) satisfied this criterion and were, therefore, included in the ITT population (Section 13, Table 1.1).

All analyses were based on the ITT population. Efficacy analyses were based on the population of ITT patients who had at least one postbaseline evaluation for the specified efficacy measure (eg, MADRS, HAM-D).

9.1.4 Demographic and Other Baseline Characteristics

9.1.4.1 Demographic Characteristics

No statistically significant differences were noted among the treatment groups in the age, sex, or race of patients at screen. Overall, the patient population in this study was reflective of the general population of patients with depression [35]. The patients in the study ranged in age from 18 to 65 years, and the majority of the patients were female and white. Selected demographic characteristics are compared by treatment group in Table 8.

Table 8. Patient Demographics at Screen

Variable		RBX N=264	PBO N=254	PAR N=262	P Value*
Age, years	Mean ± SD	39.9 ± 11.1	39.0 ± 11.6	39.8 ± 11.8	0.6431
	Range	18 - 65	18 - 65	18 - 65	
Sex: n (%)	Male	78 (29.5%)	77 (30.3%)	81 (30.9%)	0.9429
	Female	186 (70.5%)	177 (69.7%)	181 (69.1%)	
Race: n (%)	White	235 (89.4%)	212 (83.5%)	223 (85.1%)	0.5600
	Black	18 (6.8%)	27 (10.6%)	26 (9.9%)	
	Asian	4 (1.5%)	8 (3.1%)	5 (1.9%)	
	Other	6 (2.3%)	7 (2.8%)	8 (3.1%)	

* P values for continuous variables are based on a one-way ANOVA with treatment as the main effect; p values for categorical variables are based on a chi-square test.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 2.1, 2.2

Statistically significant differences were noted among the treatment groups in the mean pulse rate at screen, which was higher in the paroxetine group (75.3 beats/min) than in the reboxetine (74.9 beats/min) or placebo (73.2 beats/min) groups (p=0.039).

Statistically significant differences were also noted among the treatment groups in the distribution of patients by occupational group and living situation. However, although these differences were statistically significant, they were generally small and are unlikely to be clinically relevant. No statistically significant differences were noted among the treatment groups in the other continuous (eg, height or weight) or categorical (eg, patient's educational background or current employment status) demographic characteristics that were assessed at screen (Section 13, Tables 2.1, 2.2).

Likewise, no statistically significant differences were noted among the treatment groups in the proportion of patients who had normal or abnormal physical examinations (Section 13, Table 2.7). Although statistical testing was not performed, the findings for medical histories were generally similar among the 3 treatment groups (Section 13, Table 2.8).

9.1.4.2 Psychiatric History

9.1.4.2.1 Previous History of Depression

No statistically significant differences were noted among the treatment groups in the mean age of patients at the onset of their first depressive episode, in the mean number of previous depressive episodes, in the mean duration of the previous episode, or in the history of previous hospitalization for depression. Patients in each treatment group tended to have been in their late twenties at the time of onset of their illness and to have had a mean of 5 to 9 previous depressive episodes. The mean duration of the last depressive episode was 49 weeks in the reboxetine group, 52 weeks in the placebo group, and 42 weeks in the paroxetine group (Table 9).

Table 9. Previous History of Depression

Variable	RBX N=264	PBO N=254	PAR N=262	P Value*
Age (years) at onset of major depression				
Mean ± SD	28.8 ± 13.2	28.0± 12.7	28.6 ± 13.3	0.7788
Range	0 - 62	2 - 62	0 - 63	
Number of previous episodes				
Mean ± SD	7.3 ± 19.2	8.5 ± 64.0	5.1 ± 11.3	0.6016
Range	0 - 120	0 - 1000	0 - 99	
Approximate duration of last episode (weeks)				
Mean ± SD	49.1 ± 112.1	52.0 ± 117.0	42.3 ± 82.7	0.5955
Range	0 - 884	0 - 1040	0 - 624	
Previous hospitalization for depression				
No. (%) of patients who were ever hospitalized	28 (10.6)	33 (13.0)	33 (12.6)	0.6685
No. of hospitalizations				0.8969
Mean ± SD	1.6 ± 1.1	1.5 ± 1.2	1.6 ± 1.0	
Range	1 - 5	1 - 7	1 - 5	
Age at first hospitalization				0.3031
Mean ± SD	29.3 ± 10.4	27.4 ± 10.3	24.9 ± 12.2	
Range	13 - 47	13 - 47	10 - 56	

* P values for continuous variables are based on a one-way ANOVA with treatment as the main effect; p values for categorical variables are based on a chi-square test.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 2.3, 2.5, 2.6

9.1.4.2.2 Previous Use of Psychotropic Medication Other Than Antidepressants

No statistically significant differences were noted among treatment groups in the previous use of psychotropic medications other than antidepressants. The most commonly used psychotropic medications other than antidepressants were benzodiazepines, which were previously used by 14.4% (38/264) of reboxetine-treated patients, 14.2% (36/254) of placebo-treated patients, and 14.5% (38/262) of paroxetine-treated patients (Table 10).

Table 10. Previous Use of Psychotropic Medication Other Than Antidepressants

	RBX N=264		PBO N=254		PAR N=262	
	n	%*	n	%*	n	%*
Any psychotropic medication other than antidepressants	**52**	**19.7**	**50**	**19.7**	**54**	**20.6**
Benzodiazepines	38	14.4	36	14.2	38	14.5
Anxiolytics other than benzodiazepines	5	1.9	5	2.0	5	1.9
Anti-psychotics	2	0.8	2	0.8	3	1.1
Lithium	3	1.1	1	0.4	0	0
Other	2	0.8	7	2.8	8	3.1

* Percentages are based on the number of ITT patients.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Table 2.6

9.1.4.2.3 Characteristics of the Present Depressive Episode

As specified in the protocol, patients who had used antidepressant medication for the treatment of depression in the 2 months preceding the start of the study were to be excluded from the study. Consistent with this provision, the majority of patients (>87%) in each treatment group were receiving no treatment immediately prior to screen (Table 11).

No statistically significant differences were noted among the treatment groups at screen in the other characteristics of the present depressive episode (Table 11). The mean duration of the present depressive episode was 76 weeks in the reboxetine group, 98 weeks in the placebo group, and 108 weeks in the paroxetine group. For the majority of patients in each group, the present episode was diagnosed as a recurrent episode (70% in the reboxetine group, 71% in the placebo group, and 68% in the paroxetine group). Most patients (≥67%) in each group had precipitating stress associated with their present episode.

Table 11. Characteristics of the Present Depressive Episode

	RBX N=264	PBO N=254	PAR N=262	P Value*
No. (%)† of patients by treatment status immediately prior to screen				
No treatment	245 (92.8)	234 (92.1)	230 (87.8)	0.2671@
Outpatient treatment only	19 (7.2)	18 (7.1)	29 (11.1)	
Partial hospitalization (day treatment)	0	0	1 (0.4)	
Inpatient treatment	0	2 (0.8)	2 (0.8)	
Approximate duration of present episode				
Mean ± SD (weeks)	76.4 ± 151.0	98.4 ± 241.0	108.0 ± 240.2	0.2229
Range (weeks)	0 - 1612	1 - 2392	0 - 1976	
No. (%)† of patients whose present episode was diagnosed as:				
Single episode	80 (30.3)	73 (28.9)	85 (32.4)	0.6727
Recurrent episode	184 (69.7)	180 (71.1)	177 (67.6)	
No. (%)† of patients whose present episode was best characterized as:				
Exacerbation of chronic condition	44 (16.7)	46 (18.2)	53 (20.2)	0.6657
Recurrence of similar previous conditions	139 (52.7)	131 (51.8)	122 (46.6)	
Significantly different from any previous conditions	8 (3.0)	9 (3.6)	14 (5.3)	
First occurrence, no previous psychiatric diagnosis	73 (27.7)	67 (26.5)	73 (27.9)	
No. (%)† of patients for whom precipitating stress was:				
Absent	77 (29.2)	83 (32.8)	76 (29.1)	0.7472
Probably present	96 (36.4)	92 (36.4)	91 (34.9)	
Definitely present	91 (34.5)	78 (30.8)	94 (36.0)	

@ The statistical test may not be valid because of the low number of observations in certain categories.

* P values for continuous variables are based on a one-way ANOVA with treatment as the main effect; p values for categorical variables are based on a chi-square test.

† Percentages are based on the number of patients for whom data were reported in each category.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 2.3, 2.4, 2.6

9.1.4.2.4 Severity of Depression at Baseline

No statistically significant differences were noted among the treatment groups in the severity of depression at baseline, as judged by the mean total scores for the MADRS, the HAM-D, the CGI Severity of Illness, or the SASS (Table 12).

Table 12. Severity of Depression at Baseline

Variable	RBX N=264	PBO N=254	PAR N=262	P Value*
MADRS total score				
No. of patients	263	254	262	0.9379
Mean ± SD	28.7 ± 6.4	28.9 ± 6.3	28.9 ± 6.1	
Range	13 - 47	13 - 50	12 - 46	
21-Item HAM-D total score				
No. of patients	264	254	262	0.8455
Mean ± SD	23.0 ± 5.5	23.0 ± 5.2	22.8 ± 5.4	
Range	5 - 37	9 - 39	7 - 38	
CGI Severity of Illness score				
No. of patients	264	253	262	0.8529
Mean ± SD	4.3 ± 0.6	4.3 ± 0.7	4.3 ± 0.6	
Range	3 - 6	2 - 6	3 - 6	
SASS total score				
No. of patients	264	252	261	0.5571
Mean ± SD	29.2 ± 7.6	28.8 ± 7.6	28.4 ± 7.5	
Range	6 - 52	7 - 48	6 - 58	

* P values are based on a one-way ANOVA with treatment as the main effect.

Abbreviations: CGI = Clinical Global Impression, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, PAR = paroxetine, PBO = placebo, RBX = reboxetine, SASS = Social Adaptation Self-evaluation Scale

Source: Section 13, Table 2.9

9.1.5 Concomitant Medications

9.1.5.1 Prior to the Study

At the screening evaluation, similar percentages of patients in each treatment group were taking at least one medication: 72.0% (190/264) of patients in the reboxetine group, 78.3% (199/254) of patients in the placebo group, and 72.9% (191/261) of patients in the paroxetine group. The therapeutic classes of medications that were taken most frequently (≥5% in any treatment group) included the following: acetaminophen, antianxiety medications, systemic antihistamines, oral calcium, estrogens, multivitamins, combination nonnarcotic analgesics, nonsteroidal anti-inflammatory agents, oral contraceptives, salicylates, thyroid hormones, vitamin C, and vitamin E. Medications that were taken prior to the study are summarized in Section 13, Table 3.1.

9.1.5.2 During the Treatment Period

Non-investigational medications were taken concomitantly with the study medication by similar percentages of patients in each treatment group: 84.1% (222/264) of patients in the reboxetine group, 85.8% (218/254) of patients in the placebo group, and 84.4% (221/262) of patients in the paroxetine group (Section 13, Table 3.2). Likewise, the pattern of medication use was comparable among treatment groups. The therapeutic classes of medications that were taken most frequently (≥5% in any treatment group) during the study included the following: acetaminophen, antianxiety medications, antidiarrheals, systemic antihistamines, oral calcium, estrogens, multivitamins, nonbarbiturate sedatives and hypnotics, combination nonnarcotic analgesics, nonsteroidal anti-inflammatory agents, oral contraceptives, salicylates, thyroid hormones, vitamin C, and vitamin E.

The concomitant use of psychotropic medications other than temazepam, lorazepam, zolpidem, or oxazepam was not allowed during the study. The use of disallowed concomitant medications during the study is presented in Section 9.1.2, Protocol Deviations.

9.2 Dosage Information

9.2.1 Extent of Exposure

The mean daily doses of study medication are presented by visit in Table 13. These mean-dosing data suggest that most patients complied with the dosing regimens that were specified in the protocol for the reboxetine group (4 mg/day, days 0-6; 8 mg/day, days 7-27; 8-10 mg/day, days 28-56) and for the paroxetine group (20 mg/day, days 0-27; 20-40 mg/day, days 28-56). The mean-dosing data at day 42 imply that the doses of approximately 50% of the reboxetine-treated patients and 45% of the paroxetine-treated patients who remained in the study were escalated during days 28 to 42 of the study.

Table 13. Mean Daily Dose by Visit

Study Day	Reboxetine		Paroxetine	
	Number of Patients†	Mean Dose* (mg/day)	Number of Patients†	Mean Dose* (mg/day)
7	256	4.0	254	18.1
14	243	7.6	239	19.4
21	237	7.7	230	19.4
28	227	7.9	226	19.8
42	216	9.0	214	28.9
56	203	8.7	203	29.3

* Mean daily dose was based on the average dose for all patients who took the study medication between the preceding visit and the specified visit.

† Number of patients who completed the specified visit.

Source: Section 13, Table 3.3

9.2.2 Treatment Compliance

Patients whose average daily dose of study medication exceeded the protocol-specified dosing regimen (ie, patients who had an average daily dose of >10 mg/day of reboxetine or >40 mg/day of paroxetine) are summarized in Section 9.1.2, Protocol Deviations.

9.3 Efficacy Results

9.3.1 Primary Efficacy Measure

9.3.1.1 Endpoint Analyses

Significant differences were observed among the 3 treatment groups in the mean change from baseline in the MADRS total score at each postbaseline evaluation (days 14, 28, 42, and 56) in both the LOCF and OC analyses. In the pairwise comparison, the mean change from baseline in the MADRS total score was significantly greater in the paroxetine group than in the placebo group at each postbaseline evaluation in both the LOCF and OC analyses. However, no significant differences were observed between the reboxetine and placebo groups in either the LOCF or OC analyses (Table 14). It should be noted that the investigator-by-treatment interaction was not significant at day 56 in the LOCF (p=0.524) or OC analyses (p=0.169) (Section 13, Tables 4.1A and 4.1B).

Table 14. Mean Change From Baseline in the MADRS Total Score

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	263	28.7	250	-7.3	251	-9.9	251	-12.9	251	-14.7
		PBO	254	28.9	241	-7.6	246	-10.3	246	-12.6	247	-14.4
		PAR	262	28.9	240	-9.1	243	-13.0	243	-15.2	244	-16.8
	P Values‡	Among Treatments	0.8998		0.0404*		0.0014*		0.0079*		0.0422*	
		RBX vs. PBO	--		0.9575		0.9023		0.5382		0.5512	
		PAR vs. PBO	--		0.0261*		0.0013*		0.0031*		0.0155*	
Observed Cases	Mean Change From Baseline	RBX	263	28.7	250	-7.3	229	-10.4	210	-13.9	205	-16.2
		PBO	254	28.9	241	-7.6	236	-10.5	225	-13.5	222	-15.5
		PAR	262	28.9	240	-9.1	225	-13.8	209	-16.7	211	-18.6
	P Values‡	Among Treatments	0.8998		0.0404*		0.0005*		0.0018*		0.0116*	
		RBX vs. PBO	--		0.9575		0.6222		0.2626		0.1121	
		PAR vs. PBO	--		0.0261*		0.0003*		0.0004*		0.0029*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.1A, 4.1B, and 4.1C

When the results of the mean change from baseline in the MADRS total score were adjusted for baseline severity as a covariate, the results were similar to the results that were observed in the LOCF and OC analyses (Section 13, Tables 4.4A, 4.4B, and 4.4C).

When the mean change from baseline in the MADRS total score was reanalyzed to exclude the data from the 7 patients who were enrolled at Investigator J. Apter's site (Investigator No. 40051), the results were similar to the results that were observed in the original analysis (Section 13, Tables 4.1F, 4.1G, and 4.1H).

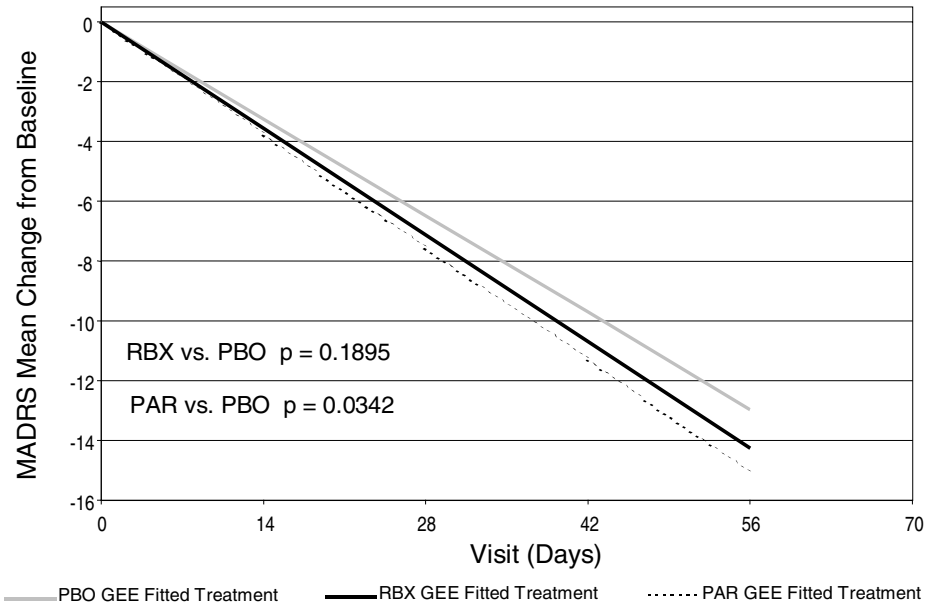
9.3.1.2 Analysis by Generalized Estimating Equations (GEE)

In addition to the LOCF and OC analyses described above, a GEE analysis of the mean change from baseline in the MADRS total score was performed. The GEE analysis estimates the average rate of change per day over the entire study duration by regressing the change from baseline on the number of days in the study. This methodology uses all observed data and incorporates correlation among the multiple observations within a subject. This is in contrast to the ordinary regression methodology, which often treats the multiple observations within a subject as independent. The advantage of the GEE method is that the inference is

based on the complete data that were collected at all time points. In contrast, in the LOCF and OC analyses, the inference is based only on data that were collected at endpoint (LOCF) or at day 56 (OC).

Figure 2 summarizes the results of the GEE analysis by comparing the fitted-treatment effect for the mean change from baseline in the MADRS total score in the active treatment groups to the fitted-treatment effect for the mean change from baseline in the MADRS total score in the placebo group.

Figure 2. GEE Analysis of the Mean Change From Baseline in the MADRS Total Score



Fitted Treatment Effect = $t*\beta + \gamma_k*t$
where t = visit in days, β = rate of change due to time (placebo effect), and
γ_k = the therapy-by-time interaction for the treatment k
Abbreviations: GEE = generalized estimating equations; PAR = paroxetine, PBO = placebo; RBX = reboxetine

As in the endpoint analyses, the results of the GEE analysis showed that the improvements in the MADRS total score were greater in each of the active treatment groups than in the placebo group. However, the differences between the active treatments and placebo were statistically significant for the paroxetine group but not for the reboxetine group.

9.3.1.3 Last Assessment for Patients Who Discontinued Early

As shown in Table 15, patients in the reboxetine group who discontinued early from the study were experiencing an improvement in their symptoms when they discontinued

treatment, as demonstrated by a mean decrease in the MADRS total score at last assessment that was greater in the reboxetine group than in the placebo group for patients whose last assessment was on days 28 or 42. Patients in the paroxetine group who discontinued early also were experiencing an improvement in their symptoms when they discontinued treatment, as demonstrated by a mean decrease in the MADRS total score at last assessment that was greater in the paroxetine group than in the placebo group for patients whose last assessment was on day 42.

Table 15. Mean Change From Baseline in the MADRS Total Score at Last Assessment for Patients Who Discontinued Early

Day of Last Assessment*	RBX N=264		PBO N=254		PAR N=262	
	n	Mean Change	n	Mean Change	n	Mean Change
Day 14	20	-5.2	7	-4.3	16	-3.5
Day 28	17	-10.2	10	-4.2	11	-3.3
Day 42	9	-10.6	8	-6.4	6	-14.2

* Patients are included only in the row that represents the day of their last assessment (ie, patients who completed the day-14 and day-28 visits but discontinued before their day-42 visit are counted only in the day-28 row).

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Table 4.1D

9.3.2 Continuous Secondary Measures of Antidepressant Efficacy

9.3.2.1 HAM-D Total Score

No statistically significant differences were observed among the 3 treatment groups on the mean change from baseline in the HAM-D total score at day 56 in either the LOCF or OC analyses (Table 16).

Table 16. Mean Change From Baseline in the HAM-D Total Score

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	264	23.0	251	-5.8	252	-7.8	252	-10.0	252	-11.5
		PBO	254	23.0	241	-6.4	246	-8.5	246	-10.3	247	-11.5
		PAR	262	22.8	238	-7.2	242	-9.7	242	-11.4	243	-12.5
	P Values‡	Among Treatments	0.6356		0.0336*		0.0131*		0.0979		0.2265	
		RBX vs. PBO	--		0.3056		0.6300		--		--	
		PAR vs. PBO	--		0.1150		0.0218*		--		--	
Observed Cases	Mean Change From Baseline	RBX	264	23.0	251	-5.8	229	-8.1	210	-10.9	205	-12.7
		PBO	254	23.0	241	-6.4	234	-8.6	224	-11.0	221	-12.4
		PAR	262	22.8	238	-7.2	224	-10.2	210	-12.4	210	-13.7
	P Values‡	Among Treatments	0.6356		0.0336*		0.0074*		0.0847		0.1754	
		RBX vs. PBO	--		0.3056		0.9387		--		--	
		PAR vs. PBO	--		0.1150		0.0049*		--		--	

* $p \leq 0.05$

† Mean change from baseline value

‡ P values are based on a 2-way ANOVA.

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.6A, 4.6B, and 4.6C

9.3.2.2 HAM-D Item-1 Score

Significant differences were observed among the 3 treatment groups in the mean change from baseline in the HAM-D Item 1 score at days 14, 28, and 56 in both the LOCF and OC analyses. In the pairwise comparison, the mean change from baseline in the HAM-D Item 1 score was significantly greater in the paroxetine group than in the placebo group at days 14, 28, and 56 in both the LOCF and OC analyses. However, no significant differences were observed between the reboxetine and placebo groups in either the LOCF or OC analyses (Table 17).

Table 17. Mean Change From Baseline in the HAM-D Item 1 Score

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	264	2.6	251	-0.6	252	-0.9	252	-1.2	252	-1.4
		PBO	254	2.6	241	-0.7	246	-1.0	246	-1.2	247	-1.4
		PAR	262	2.6	240	-0.9	243	-1.2	243	-1.4	244	-1.6
	P Values‡	Among Treatments	0.7215		0.0004*		0.0051*		0.1952		0.0128*	
		RBX vs. PBO	--		0.8670		0.7357		--		0.8390	
		PAR vs. PBO	--		0.0009*		0.0029*		--		0.0077*	
Observed Cases	Mean Change From Baseline	RBX	264	2.6	251	-0.6	230	-1.0	211	-1.3	206	-1.5
		PBO	254	2.6	241	-0.7	236	-1.0	224	-1.3	222	-1.5
		PAR	262	2.6	240	-0.9	225	-1.3	211	-1.5	211	-1.8
	P Values‡	Among Treatments	0.7215		0.0004*		0.0076*		0.1854		0.0212*	
		RBX vs. PBO	--		0.8670		0.4943		--		0.3975	
		PAR vs. PBO	--		0.0009*		0.0026*		--		0.0062*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine
Source: Section 13, Tables 4.10A, 4.10B, and 4.10C

9.3.2.3 HAM-D Retardation Cluster Score

No statistically significant differences were observed among the 3 treatment groups on the mean change from baseline in the HAM-D Retardation Cluster (Items 1, 7, 8, and 14 [30, 31]) score in either the LOCF or OC analyses (Table 18).

Table 18. Mean Change From Baseline in the HAM-D Retardation Cluster Score

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	264	7.4	251	-1.9	252	-2.6	252	-3.4	252	-3.7
		PBO	254	7.3	241	-1.8	246	-2.5	246	-3.2	247	-3.6
		PAR	262	7.3	240	-2.1	243	-2.9	243	-3.6	244	-4.1
	P Values‡	Among Treatments	0.9961		0.2530		0.1678		0.3127		0.1214	
		RBX vs. PBO	--		--		--		--		--	
		PAR vs. PBO	--		--		--		--		--	
Observed Cases	Mean Change From Baseline	RBX	264	7.4	251	-1.9	230	-2.8	211	-3.7	206	-4.2
		PBO	254	7.3	241	-1.8	235	-2.6	224	-3.5	222	-3.9
		PAR	262	7.3	240	-2.1	225	-3.1	211	-3.9	211	-4.5
	P Values‡	Among Treatments	0.9961		0.2530		0.1189		0.2081		0.0679	
		RBX vs. PBO	--		--		--		--		--	
		PAR vs. PBO	--		--		--		--		--	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine
Source: Section 13, Tables 4.11A, 4.11B, and 4.11C

9.3.2.4 CGI Severity of Illness

Significant differences were observed among the 3 treatment groups in the mean change from baseline in the CGI Severity of Illness score at each postbaseline evaluation (days 14, 28, 42, and 56) in both the LOCF and OC analyses. In the pairwise comparison, the mean change from baseline in the CGI Severity of Illness score was significantly greater in the paroxetine group than in the placebo group at each postbaseline evaluation in both the LOCF and OC analyses. However, no significant differences were observed between the reboxetine and placebo groups in either the LOCF or OC analyses (Table 19).

Table 19. Mean Change From Baseline in the CGI Severity of Illness Score

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	264	4.3	252	-0.6	252	-0.9	252	-1.2	252	-1.5
		PBO	253	4.3	241	-0.6	245	-0.9	245	-1.2	246	-1.5
		PAR	262	4.3	238	-0.7	242	-1.2	242	-1.5	243	-1.8
	P Values‡	Among Treatments	0.8172		0.0305*		0.0011*		0.0303*		0.0177*	
		RBX vs. PBO	--		0.6398		0.6463		0.6810		0.8352	
		PAR vs. PBO	--		0.0128*		0.0007*		0.0134*		0.0103*	
Observed Cases	Mean Change From Baseline	RBX	264	4.3	252	-0.6	229	-0.9	212	-1.4	204	-1.7
		PBO	253	4.3	241	-0.6	235	-0.9	224	-1.3	220	-1.6
		PAR	262	4.3	238	-0.7	225	-1.2	210	-1.6	210	-2.0
	P Values‡	Among Treatments	0.8172		0.0305*		0.0008*		0.0109*		0.0123*	
		RBX vs. PBO	--		0.6398		0.6087		0.5376		0.3489	
		PAR vs. PBO	--		0.0128*		0.0004*		0.0038*		0.0034*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, CGI = Clinical Global Impression, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine
Source: Section 13, Tables 4.14A, 4.14B, and 4.14C

The distribution of patients by CGI Severity of Illness score at baseline and at endpoint is presented in a cross-tabulation in Section 13, Table 4.15.

9.3.3 Categorical Secondary Measures of Antidepressant Efficacy

9.3.3.1 HAM-D Response Rate

Significant differences were observed among the 3 treatment groups in the HAM-D response rate at days 14 and 28 in the LOCF analysis and at each postbaseline evaluation (days 14, 28,

42, and 56) in the OC analyses. In the pairwise comparison, the HAM-D response rate was significantly greater in the paroxetine group than in the placebo group at day 28 in the LOCF analysis and at days 28, 42, and 56 in the OC analyses. However, no significant differences were observed between the reboxetine and placebo groups in either the LOCF or OC analyses (Table 20).

Table 20. HAM-D Response Rate

Type of Analysis	Statistic	Group or Comparison	Visit							
			Day 14		Day 28		Day 42		Day 56	
			n	%	n	%	n	%	n	%
LOCF	Response rate†	RBX	44	17.5	87	34.5	125	49.6	144	57.1
		PBO	60	24.9	88	35.8	115	46.7	136	55.1
		PAR	64	26.9	111	45.9	138	57.0	156	64.2
	P Values‡	Among Treatments	0.0366*		0.0113*		0.0511		0.0739	
		RBX vs. PBO	0.0539		0.9275		--		--	
		PAR vs. PBO	0.6215		0.0147*		--		--	
Observed Cases	Response rate†	RBX	44	17.5	83	36.2	113	53.8	129	62.9
		PBO	60	24.9	85	36.3	112	50.0	131	59.3
		PAR	64	26.9	109	48.7	131	62.4	152	72.4
	P Values‡	Among Treatments	0.0366*		0.0050*		0.0225*		0.0124*	
		RBX vs. PBO	0.0539		0.9138		0.3693		0.3661	
		PAR vs. PBO	0.6215		0.0048*		0.0057*		0.0038*	

* $p \leq 0.05$

† Response was defined as a decrease of ≥50% in the 21-Item HAM-D total score versus baseline.

‡ P values are based on a Cochran-Mantel-Haenszel test.

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.7A, 4.7B, and 4.7C

9.3.3.2 HAM-D Remission Rate

Significant differences were observed among the 3 treatment groups in the HAM-D remission rate at days 28, 42, and 56 in both the LOCF and OC analyses. In the pairwise comparison, the HAM-D remission rate was significantly greater in the paroxetine group than in the placebo group at days 28, 42, and 56 in both the LOCF and OC analyses. However, no significant differences were observed between the reboxetine and placebo groups in either the LOCF or OC analyses (Table 21).

Table 21. HAM-D Remission Rate

Type of Analysis	Statistic	Group or Comparison	Visit							
			Day 14		Day 28		Day 42		Day 56	
			n	%	n	%	n	%	n	%
LOCF	Remission rate†	RBX	46	18.3	74	29.4	106	42.1	132	52.4
		PBO	53	22.0	83	33.7	110	44.7	124	50.2
		PAR	57	23.9	105	43.4	130	53.7	152	62.6
	P Values‡	Among Treatments	0.3579		0.0020*		0.0204*		0.0079*	
		RBX vs. PBO	--		0.3796		0.6034		0.6027	
		PAR vs. PBO	--		0.0159*		0.0331*		0.0041*	
Observed Cases	Remission rate†	RBX	46	18.3	71	31.0	96	45.7	119	58.0
		PBO	53	22.0	80	34.2	107	47.8	119	53.8
		PAR	57	23.9	103	46.0	124	59.0	147	70.0
	P Values‡	Among Treatments	0.3579		0.0010*		0.0079*		0.0013*	
		RBX vs. PBO	--		0.4962		0.6617		0.3426	
		PAR vs. PBO	--		0.0063*		0.0099*		0.0004*	

* $p \leq 0.05$

† Remission was defined as a total score of ≤10 on the 21-Item HAM-D.

‡ P values are based on a Cochran-Mantel-Haenszel test.

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.8A, 4.8B, and 4.8C

9.3.3.3 MADRS Response Rate

Significant differences were observed among the 3 treatment groups in the MADRS response rate at each postbaseline evaluation (days 14, 28, 42, and 56) in both the LOCF and OC analyses. In the pairwise comparison, the MADRS response rate was significantly greater in the paroxetine group than in the placebo group at days 28, 42, and 56 in both the LOCF and OC analyses. However, no significant differences were observed between the reboxetine and placebo groups in either the LOCF or OC analyses (Table 22).

Table 22. MADRS Response Rate

Type of Analysis	Statistic	Group or Comparison	Visit							
			Day 14		Day 28		Day 42		Day 56	
			n	%	n	%	n	%	n	%
LOCF	Response rate†	RBX	48	19.2	81	32.3	119	47.4	140	55.8
		PBO	55	22.8	94	38.2	111	45.1	132	53.4
		PAR	68	28.3	116	47.7	141	58.0	158	64.8
	P Values‡	Among Treatments	0.0402*		0.0009*		0.0051*		0.0178*	
		RBX vs. PBO	0.3620		0.1737		0.5472		0.6038	
		PAR vs. PBO	0.1038		0.0198*		0.0022*		0.0088*	
Observed Cases	Response rate†	RBX	48	19.2	79	34.5	111	52.9	130	63.4
		PBO	55	22.8	92	39.0	108	48.0	127	57.2
		PAR	68	28.3	115	51.1	135	64.6	154	73.0
	P Values‡	Among Treatments	0.0402*		0.0004*		0.0009*		0.0017*	
		RBX vs. PBO	0.3620		0.2725		0.2387		0.1789	
		PAR vs. PBO	0.1038		0.0044*		0.0002*		0.0004*	

* $p \leq 0.05$

† Response was defined as a decrease of ≥50% in the MADRS total score versus baseline.

‡ P values are based on a Cochran-Mantel-Haenszel test.

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.2A, 4.2B, and 4.2C

9.3.3.4 MADRS Remission Rate

Significant differences were observed among the 3 treatment groups in the MADRS remission rate at days 28, 42, and 56 in both the LOCF and OC analyses. In the pairwise comparison, the MADRS remission rate was significantly greater in the paroxetine group than in the placebo group at days 28, 42, and 56 in both the LOCF and OC analyses. However, no significant differences were observed between the reboxetine and placebo groups in either the LOCF or OC analyses (Table 23).

Table 23. MADRS Remission Rate

Type of Analysis	Statistic	Group or Comparison	Visit							
			Day 14		Day 28		Day 42		Day 56	
			n	%	n	%	n	%	n	%
LOCF	Remission rate†	RBX	40	15.9	70	27.8	113	44.8	128	50.8
		PBO	50	20.7	80	32.5	104	42.3	121	49.0
		PAR	52	21.7	100	41.2	129	53.1	147	60.2
	P Values‡	Among Treatments	0.2468		0.0034*		0.0261*		0.0189*	
		RBX vs. PBO	--		0.3022		0.5114		0.7075	
		PAR vs. PBO	--		0.0306*		0.0113*		0.0105*	
Observed Cases	Remission rate†	RBX	40	15.9	67	29.1	105	49.8	118	57.3
		PBO	50	20.7	78	33.1	102	45.3	117	52.7
		PAR	52	21.7	99	44.0	123	58.9	143	67.8
	P Values‡	Among Treatments	0.2468		0.0010*		0.0097*		0.0036*	
		RBX vs. PBO	--		0.3754		0.3266		0.3615	
		PAR vs. PBO	--		0.0072*		0.0026*		0.0010*	

* $p \leq 0.05$

† Remission was defined as a MADRS total score of ≤12.

‡ P values are based on a Cochran-Mantel-Haenszel test.

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.3A, 4.3B, and 4.3C

9.3.3.5 CGI Global Improvement Response Rate

Significant differences were observed among the 3 treatment groups in the CGI Global Improvement response rate at days 42 and 56 in both the LOCF and OC analyses. In the pairwise comparison, the CGI Global Improvement response rate was significantly greater in the paroxetine group than in the placebo group at days 42 and 56 in both the LOCF and OC analyses. However, no significant differences were observed between the reboxetine and placebo groups in either the LOCF or OC analyses (Table 24).

Table 24. CGI Global Improvement Response Rate

Type of Analysis	Statistic	Group or Comparison	Visit							
			Day 14		Day 28		Day 42		Day 56	
			n	%	n	%	n	%	n	%
LOCF	Response rate†	RBX	54	21.5	91	36.3	124	49.4	138	55.0
		PBO	54	22.3	93	37.8	110	44.7	125	50.6
		PAR	62	26.1	108	44.6	135	55.8	161	66.3
	P Values‡	Among Treatments	0.4251		0.0936		0.0404*		0.0007*	
		RBX vs. PBO	--		--		0.2676		0.3282	
		PAR vs. PBO	--		--		0.0130*		0.0003*	
Observed Cases	Response rate†	RBX	54	21.5	88	38.6	115	54.5	127	62.6
		PBO	54	22.3	92	39.0	107	47.8	120	54.3
		PAR	62	26.1	106	47.1	129	61.4	155	73.8
	P Values‡	Among Treatments	0.4251		0.0961		0.0155*		0.0001*	
		RBX vs. PBO	--		--		0.1665		0.0743	
		PAR vs. PBO	--		--		0.0031*		<.0001*	

* $p \leq 0.05$

† Response was defined as a score of ≤2 (corresponding to “very much improved” or “much improved”) on the CGI Global Improvement scale.

‡ P values are based on a Cochran-Mantel-Haenszel test.

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: CGI = Clinical Global Impression, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.13A, 4.13B, and 4.13C

The distribution of patients by category of CGI Global Improvement score at each visit is presented in Section 13, Tables 4.12A (LOCF analysis) and 4.12B (OC analysis).

9.3.4 Secondary Measures of Energy and Social Function

9.3.4.1 Social Adaptation Self-evaluation Scale

The mean increase from baseline in the SASS total score was significantly greater in the reboxetine group (+6.3) than in the placebo group (+4.9) at day 56 in the LOCF analysis (p=0.048) (Table 25). The mean increase from baseline in the SASS total score was also significantly greater in the paroxetine group (+7.2) than in the placebo group (+4.9) at day 56 in the LOCF analysis (p=0.015).

Table 25. Mean Change From Baseline in the SASS Total Score

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	264	29.2	251	1.9	251	3.6	251	5.3	251	6.3
		PBO	252	28.8	240	1.7	245	2.8	245	4.1	246	4.9
		PAR	261	28.4	239	3.0	241	4.8	241	6.2	242	7.2
	P Values‡	Among Treatments	0.5366		0.1258		0.0142*		0.0133*		0.0340*	
		RBX vs. PBO	--		--		0.2407		0.0438*		0.0478*	
		PAR vs. PBO	--		--		0.0037*		0.0043*		0.0146*	
Observed Cases	Mean Change From Baseline	RBX	264	29.2	251	1.9	231	3.7	212	5.5	205	6.9
		PBO	252	28.8	240	1.7	235	2.9	223	4.3	217	5.1
		PAR	261	28.4	239	3.0	223	5.0	209	6.8	209	8.0
	P Values‡	Among Treatments	0.5366		0.1258		0.0259*		0.0068*		0.0209*	
		RBX vs. PBO	--		--		0.3897		0.0578		0.0400*	
		PAR vs. PBO	--		--		0.0076*		0.0018*		0.0088*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine, SASS = Social Adaption Self-evaluation Scale
Source: Section 13, Tables 4.16A, 4.16B, and 4.16C

In both the LOCF and OC analyses, statistically significant differences were observed among the treatment groups on days 28, 42, and 56, with reboxetine producing a significantly greater increase in the SASS total score than placebo on days 42 (LOCF analysis) and 56 (LOCF and OC analyses) and paroxetine producing a significantly greater increase in the SASS total score than placebo on days 28, 42, and 56 (LOCF and OC analyses).

9.3.4.2 MFI General Fatigue Subscale

No significant differences were observed among the 3 treatment groups in the mean change from baseline in the MFI General Fatigue subscale score at day 56 in either the LOCF (p=0.089) or OC analyses (p=0.081) (Table 26). Both of the active treatment groups demonstrated a mean change from baseline in the MFI General Fatigue subscale score that was numerically superior to the mean change that was observed in the placebo group (decreasing scores indicate improvement).

Table 26. Mean Change From Baseline in the MFI General Fatigue Subscale Score

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	263	17.00	248	-1.95	249	-2.61	249	-3.54	249	-3.93
		PBO	250	16.66	234	-1.60	243	-2.21	243	-2.77	244	-3.14
		PAR	259	16.81	237	-1.75	239	-2.91	239	-3.30	240	-4.00
	P Values‡	Among Treatments	0.5721		0.5272		0.1311		0.1665		0.0894	
		RBX vs. PBO	--		--		--		--		--	
		PAR vs. PBO	--		--		--		--		--	
Observed Cases	Mean Change From Baseline	RBX	263	17.00	248	-1.95	228	-2.72	207	-3.80	204	-4.34
		PBO	250	16.66	234	-1.60	233	-2.24	220	-2.95	214	-3.38
		PAR	259	16.81	237	-1.75	221	-3.07	206	-3.55	208	-4.40
	P Values‡	Among Treatments	0.5721		0.5272		0.0981		0.1983		0.0806	
		RBX vs. PBO	--		--		--		--		--	
		PAR vs. PBO	--		--		--		--		--	

* $p \leq 0.05$

† Mean change from baseline value

‡ P values are based on a 2-way ANOVA.

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, LOCF = last observation carried forward, MFI = Multidimensional Fatigue Inventory, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.17A, 4.17B, and 4.17C

9.3.4.3 Medical Outcomes Study Short-Form Health Survey (36-item)

9.3.4.3.1 Social Functioning Scale

No statistically significant differences were observed among the 3 treatment groups in the mean change from baseline in the total score of the MOS SF-36 Social Functioning scale at day 56 in either the LOCF (p=0.056) or OC analyses (p=0.053) (Table 27). However, statistically significant differences in favor of paroxetine over placebo were observed at day 28 in the LOCF analysis and at days 28 and 42 in the OC analysis, whereas a statistically significant difference in favor of reboxetine over placebo was observed at day 42 in the OC analysis.

Table 27. Mean Change From Baseline in the Total Score of the MOS SF-36 Social Functioning Scale

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	264	37.55	248	12.85	250	17.75	250	24.65	250	24.15
		PBO	252	34.47	237	16.03	245	18.57	245	22.40	246	24.95
		PAR	259	33.54	238	18.64	240	25.31	240	27.92	241	30.39
	P Values‡	Among Treatments	0.1191		0.0592		0.0069*		0.0699		0.0560	
		RBX vs. PBO	--		--		0.8598		--		--	
		PAR vs. PBO	--		--		0.0046*		--		--	
Observed Cases	Mean Change From Baseline	RBX	264	37.55	248	12.85	231	18.02	209	26.32	201	26.00
		PBO	252	34.47	237	16.03	234	19.12	220	23.01	214	25.06
		PAR	259	33.54	238	18.64	220	27.22	209	30.14	208	32.39
	P Values‡	Among Treatments	0.1191		0.0592		0.0010*		0.0161*		0.0534	
		RBX vs. PBO	--		--		0.8906		0.0445*		--	
		PAR vs. PBO	--		--		0.0012*		0.0060*		--	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, LOCF = last observation carried forward, MOS SF-36 = Medical Outcomes Study Short-Form Health Survey (36-item), PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.19A, 4.19B, and 4.19C

9.3.4.3.2 Vitality Scale

No statistically significant differences were observed among the 3 treatment groups in the mean change from baseline in the total score of the MOS SF-36 Vitality scale at day 56 in either the LOCF (p=0.382) or OC analyses (p=0.128) (Table 28). Both of the active treatment groups demonstrated a mean change from baseline at day 56 that was numerically superior to the mean change that was observed in the placebo group (increasing scores indicate improvement). A statistically significant difference in favor of paroxetine over placebo was observed at day 28 in the OC analysis.

Table 28. Mean Change From Baseline in the Total Score of the MOS SF-36 Vitality Scale

Type of Analysis	Statistic	Group or Comparison	Visit									
			Baseline		Day 14		Day 28		Day 42		Day 56	
			n	Mean	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	264	21.44	248	12.04	250	17.97	250	24.54	250	26.14
		PBO	252	21.19	237	12.57	245	16.12	245	20.39	246	23.25
		PAR	258	20.54	237	13.59	239	20.98	239	24.69	240	26.85
	P Values‡	Among Treatments	0.7037		0.6257		0.0914		0.1267		0.3818	
		RBX vs. PBO	--		--		--		--		--	
		PAR vs. PBO	--		--		--		--		--	
Observed Cases	Mean Change From Baseline	RBX	264	21.44	248	12.04	231	18.46	210	26.24	202	29.28
		PBO	252	21.19	237	12.57	234	16.35	219	21.39	215	24.70
		PAR	258	20.54	237	13.59	217	22.76	208	26.68	207	29.81
	P Values‡	Among Treatments	0.7037		0.6257		0.0315*		0.0576		0.1280	
		RBX vs. PBO	--		--		0.4203		--		--	
		PAR vs. PBO	--		--		0.0096*		--		--	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference ($p \leq 0.05$) was observed among the 3 treatment groups.

Abbreviations: ANOVA = analysis of variance, LOCF = last observation carried forward, MOS SF-36 = Medical Outcomes Study Short-Form Health Survey (36-item), PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.18A, 4.18B, and 4.18C

9.3.5 Efficacy Discussion and Conclusions

This study failed to meet the protocol-specified primary objective, which was to demonstrate that the antidepressant efficacy of reboxetine, administered at a dose of 4 mg/day during the first week and at a dose of 8 to 10 mg/day during the following 7 weeks, is superior to that of placebo, as determined by a 2-way ANOVA of the mean change from baseline in the MADRS total score at day 56 in the ITT patient population.

As shown in Table 29, statistically significant differences, favoring paroxetine over placebo, were observed on the primary efficacy endpoint and on a number of secondary efficacy endpoints. No significant differences were observed between the reboxetine and placebo groups on any of the antidepressant efficacy endpoints, although the response in the reboxetine group was always at least equal to, or numerically better than, the response in the placebo group.

Table 29. Summary of Antidepressant Efficacy Measures at Day 56 (LOCF Analysis)

	Results by Treatment Group			P Values		
	RBX N=264	PBO N=254	PAR N=262	Overall	RBX vs PBO	PAR vs PBO
Primary Endpoint						
MADRS total score, mean change from baseline	-14.7	-14.4	-16.8	0.0422*	0.5512	0.0155*
Secondary Endpoints						
Mean Change From Baseline						
HAM-D Item 1	-1.4	-1.4	-1.6	0.0128*	0.8390	0.0077*
HAM-D Retardation Cluster	-3.7	-3.6	-4.1	0.1214	--	--
CGI Severity of Illness	-1.5	-1.5	-1.8	0.0177*	0.8352	0.0103*
HAM-D Total Score	-11.5	-11.5	-12.5	0.2265	--	--
% Responders or Remitters						
MADRS Response	55.8	53.4	64.8	0.0178*	0.6038	0.0088*
MADRS Remission	50.8	49.0	60.2	0.0189*	0.7075	0.0105*
HAM-D Response	57.1	55.1	64.2	0.0739	--	--
HAM-D Remission	52.4	50.2	62.6	0.0079*	0.6027	0.0041*
CGI Global Improvement Response	55.0	50.6	66.3	0.0007*	0.3282	0.0003*

* $p \leq 0.05$

-- P values for pairwise comparisons between reboxetine and placebo or paroxetine and placebo are shown for only those endpoints on which a significant difference was observed among the 3 treatment groups ($p \leq 0.05$ for overall comparison).

Abbreviations: LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Tables 4.1C-4.3C, 4.6C-4.8C, 4.10C, 4.11C, 4.13C, 4.14C

Despite the fact that this study (study 046) and a previously conducted study (study M/2020/0047, study 047 [36]) were conducted according to the same study design, the results of the 2 studies differed markedly. Study 047 demonstrated that reboxetine was significantly superior to placebo on the primary efficacy endpoint and on a number of secondary efficacy endpoints, whereas this study showed no statistically significant differences between reboxetine and placebo on any of the antidepressant efficacy endpoints. This difference in overall study results can be attributed largely to a difference in the placebo response, which was much higher in this study (mean change from baseline in the MADRS total score, –14.4) than in study 047 (mean change from baseline in the MADRS total score, –12.3). In contrast, the response in the reboxetine group in this study (mean change from baseline in the MADRS total score, –14.7) was very consistent with the results in study 047

(mean change from baseline in the MADRS total score, –14.5). Therefore, the failure to demonstrate a statistically significant difference between the reboxetine and placebo groups in this study can be attributed to an increased placebo response, not a decreased reboxetine response. In the paroxetine group, the response in this study (mean change from baseline in the MADRS total score, –16.8) was slightly higher than the response in study 047 (mean change from baseline in the MADRS total score, –15.3). This slight increase enabled the paroxetine group to overcome the increased placebo response in this study, resulting in a statistically significant difference between paroxetine and placebo.

The failure to distinguish an active drug from placebo in antidepressant studies is not uncommon, as demonstrated by the negative studies that were reported as part of the development programs of many approved antidepressant drugs [10]. In general, placebo response rates of 28% to 40% have been reported in patients with MDD [37]. In contrast, the placebo response rate in this study was 55.1% (based on the HAM-D response rate).

To identify the factors that might have contributed to the high placebo response in this study, retrospective exploratory analyses were conducted using visual tools, such as Spotfire.net™, to explore possible patterns or trends in the data, with the intention that more formal statistical analyses would be performed if any trends were observed. Subset analyses were conducted for the following variables to identify possible trends in placebo response: demographics (sex, race), social situation (marital status, living situation, highest educational level, occupation, current employment status), previous history of depression (age at onset of major depression, number of previous episodes, duration of last episode, previous hospitalization for depression), characteristics of present depressive episode (single/recurrent episode, duration, presence of precipitating stress), severity of depression at baseline (baseline scores for HAM-D total, HAM-D Retardation Cluster, HAM-D Item 1 [depressed mood], HAM-D Item 7 [work and activities], HAM-D Item 8 [retardation], and CGI Severity of Illness), and discontinuations due to TESS. Because the placebo response rates were similar in the subsets described above, no formal statistical analyses were undertaken.

The results from the secondary measures of energy and social function indicate that quality of life improved in all treatment groups during the study. Statistically significant differences were observed among the 3 treatment groups on the mean change from baseline in the SASS total score on days 28, 42, and 56 in both the LOCF and OC analyses, with reboxetine producing a significantly greater increase in the SASS total score than placebo on days 42 (LOCF analysis) and 56 (LOCF and OC analyses) and paroxetine producing a significantly greater increase in the SASS total score than placebo on days 28, 42, and 56 (LOCF and OC analyses).

On the other secondary measures of energy and social function, including the MOS SF-36 Social Functioning and Vitality scales and the MFI General Fatigue subscale, no statistically significant differences were observed among the 3 treatment groups at endpoint (day 56). However, on the MOS SF-36 Social Functioning scale, reboxetine produced a significantly greater increase than placebo on day 42 (OC analysis) and paroxetine produced a significantly greater increase than placebo on days 28 (LOCF and OC analyses) and 42 (OC analysis).

9.4 Safety Results

9.4.1 Treatment-Emergent Signs and Symptoms

9.4.1.1 Brief Summary

Treatment-emergent signs and symptoms were reported in a similar percentage of patients in each of the treatment groups (90.5% in the reboxetine group, 81.9% in the placebo group, and 88.2% in the paroxetine group). The percentage of patients who discontinued due to TESS was higher in the active treatment groups (9.8% in the reboxetine group and 8.4% in the paroxetine group) than in the placebo group (3.5%). Table 30 presents an overview of the percentage of patients in each treatment group who had at least one TESS (overall, drug-related, or serious) or who discontinued due to a TESS.

Table 30. Overall Summary of Treatment-Emergent Signs and Symptoms

	RBX N=264		PBO N=254		PAR N=262	
	n	%	n	%	n	%
Patients with at least one TESS	239	90.5	208	81.9	231	88.2
Drug-related*	214	81.1	152	59.8	200	76.3
Serious	4	1.5	1	0.4	4	1.5
Patients who discontinued due to TESS	26	9.8	9	3.5	22	8.4

* TESS were considered to be drug-related if, in the opinion of the investigator, there was a reasonable possibility that the event was caused by the investigational medication.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Tables 5.1, 5.4, 5.5, and 5.7

9.4.1.2 TESS by COSTART Body System

The frequency of TESS is summarized by body system in Table 31. In each of the 3 treatment groups, the most frequently reported TESS were events that were related to the digestive and nervous systems and to the body as a whole.

Table 31. Frequency of TESS by Body System

COSTART Body System*	RBX N=264		PBO N=254		PAR N=262	
	n	%	n	%	n	%
Patients with at least one TESS	**239**	**90.5**	**208**	**81.9**	**231**	**88.2**
Digestive	179	67.8	111	43.7	169	64.5
Nervous	164	62.1	109	42.9	142	54.2
Body	126	47.7	121	47.6	145	55.3
Skin	62	23.5	16	6.3	32	12.2
Cardiovascular	50	18.9	19	7.5	27	10.3
Urogenital	46	17.4	21	8.3	52	19.8
Special Senses	22	8.3	15	5.9	23	8.8
Respiratory	20	7.6	22	8.7	35	13.4
Metabolic and nutritional	12	4.5	8	3.1	12	4.6
Musculo-skeletal	5	1.9	5	2.0	7	2.7
Hemic and lymphatic	0	0	4	1.6	2	0.8

* Arranged in decreasing order of frequency based on the reboxetine group.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Table 5.1

Section 13, Table 5.1, summarizes the TESS by body system and treatment group. The patients who reported TESS are listed in Appendix 16, Table 12.1A (by patient) and Table 12.1B (by body system and COSTART term).

9.4.1.3 TESS by COSTART Preferred Term

The TESS that were reported in at least 1% of the patients in any treatment group are summarized in Table 32.

Table 32. TESS Reported in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=264		PBO N=254		PAR N=262	
	n	%	n	%	n	%
DIGESTIVE						
Dry mouth	120	45.5	40	15.7	62	23.7
Constipation	66	25.0	17	6.7	38	14.5
Nausea	38	14.4	31	12.2	73	27.9
Anorexia	26	9.8	6	2.4	20	7.6
Diarrhea	18	6.8	26	10.2	53	20.2
Dyspepsia	11	4.2	14	5.5	16	6.1
Vomiting	10	3.8	12	4.7	11	4.2
Flatulence	6	2.3	5	2.0	12	4.6
Gastroenteritis	5	1.9	2	0.8	7	2.7
Gastrointestinal disorder	3	1.1	1	0.4	1	0.4
Thirst	2	0.8	2	0.8	4	1.5
Tooth disorder	1	0.4	6	2.4	1	0.4
Increased appetite	0	0	3	1.2	2	0.8
NERVOUS						
Insomnia	103	39.0	36	14.2	47	17.9
Dizziness	41	15.5	24	9.4	28	10.7
Anxiety	19	7.2	18	7.1	9	3.4
Somnolence	18	6.8	16	6.3	46	17.6
Nervousness	17	6.4	14	5.5	10	3.8
Paresthesia	11	4.2	6	2.4	4	1.5
Abnormal dreams	7	2.7	6	2.4	4	1.5
Depression	5	1.9	1	0.4	2	0.8
Hypesthesia	5	1.9	4	1.6	1	0.4
Libido decreased	5	1.9	3	1.2	12	4.6
Akathisia	4	1.5	3	1.2	4	1.5
Hypertonia	4	1.5	1	0.4	6	2.3
Tremor	4	1.5	1	0.4	10	3.8
Hyperkinesia	2	0.8	1	0.4	3	1.1
Amnesia	1	0.4	7	2.8	4	1.5
Emotional lability	1	0.4	3	1.2	1	0.4
Incoordination	1	0.4	0	0	3	1.1
Sleep disorder	1	0.4	3	1.2	7	2.7
Thinking abnormal	1	0.4	1	0.4	6	2.3
Confusion	0	0	0	0	3	1.1

continued

Table 32. TESS Reported in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=264		PBO N=254		PAR N=262	
	n	%	n	%	n	%
BODY						
Headache	73	27.7	73	28.7	71	27.1
Asthenia	21	8.0	9	3.5	46	17.6
Infection	18	6.8	17	6.7	13	5.0
Chills	14	5.3	1	0.4	2	0.8
Pain	11	4.2	7	2.8	4	1.5
Abdominal pain	8	3.0	13	5.1	10	3.8
Back pain	5	1.9	8	3.1	7	2.7
Reaction unevaluable	5	1.9	2	0.8	13	5.0
Allergic reaction	4	1.5	2	0.8	4	1.5
Accidental injury	2	0.8	5	2.0	13	5.0
Chest pain	2	0.8	3	1.2	2	0.8
Fever	2	0.8	0	0	3	1.1
Flu syndrome	2	0.8	8	3.1	8	3.1
Generalized edema	0	0	4	1.6	1	0.4
SKIN						
Sweating	40	15.2	7	2.8	17	6.5
Rash	12	4.5	3	1.2	6	2.3
Pruritus	5	1.9	1	0.4	0	0
Acne	4	1.5	2	0.8	2	0.8
Skin disorder	3	1.1	1	0.4	1	0.4
CARDIOVASCULAR						
Vasodilatation	19	7.2	3	1.2	6	2.3
Palpitation	14	5.3	7	2.8	12	4.6
Hypertension	6	2.3	3	1.2	2	0.8
Migraine	6	2.3	5	2.0	3	1.1
Tachycardia	6	2.3	0	0	2	0.8
Postural hypotension	4	1.5	0	0	1	0.4
Peripheral vascular disorder	3	1.1	0	0	1	0.4
UROGENITAL						
Impotence	11	4.2	0	0	8	3.1
Abnormal ejaculation	9	3.4	0	0	5	1.9
Urination impaired	8	3.0	0	0	6	2.3
Urinary frequency	5	1.9	6	2.4	7	2.7
Urinary retention	5	1.9	1	0.4	0	0
Dysuria	4	1.5	1	0.4	1	0.4
Urinary tract infection	4	1.5	2	0.8	3	1.1
Penis disorder	3	1.1	0	0	0	0
Vaginal moniliasis	3	1.1	0	0	3	1.1
Dysmenorrhea	2	0.8	3	1.2	2	0.8
Sexual function abnormal	1	0.4	2	0.8	3	1.1

continued

Table 32. TESS Reported in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=264		PBO N=254		PAR N=262	
	n	%	n	%	n	%
Anorgasmia	0	0	0	0	8	3.1
SPECIAL SENSES						
Abnormality of accommodation	9	3.4	3	1.2	7	2.7
Taste perversion	4	1.5	3	1.2	5	1.9
Otitis media	3	1.1	1	0.4	1	0.4
Dry eyes	0	0	2	0.8	3	1.1
RESPIRATORY						
Pharyngitis	9	3.4	6	2.4	9	3.4
Sinusitis	5	1.9	10	3.9	7	2.7
Cough increased	4	1.5	1	0.4	4	1.5
Rhinitis	1	0.4	3	1.2	7	2.7
Yawn	0	0	0	0	6	2.3
METABOLIC AND NUTRITIONAL						
Weight loss	8	3.0	3	1.2	5	1.9
Weight gain	2	0.8	1	0.4	7	2.7
Peripheral edema	0	0	4	1.6	0	0
MUSCULO-SKELETAL						
Myalgia	2	0.8	1	0.4	3	1.1
Arthralgia	0	0	3	1.2	1	0.4

* Arranged in decreasing order of frequency based on the reboxetine group.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Table 5.1

In the reboxetine group, the most frequently reported TESS (reported in at least 5% of reboxetine-treated patients and at least 2 times more frequently in the reboxetine-treated patients than in the placebo-treated patients) were dry mouth, constipation, anorexia, insomnia, asthenia, chills, sweating, and vasodilatation.

In the paroxetine group, the most frequently reported TESS (reported in at least 5% of paroxetine-treated patients and at least 2 times more frequently in the paroxetine-treated patients than in the placebo-treated patients) were constipation, nausea, anorexia, somnolence, asthenia, reaction unevaluable, accidental injury, and sweating.

9.4.1.4 TESS by Maximum Intensity

The majority of TESS reported by patients in each treatment group were mild to moderate in intensity. Severe TESS were reported in 19.3% (51/264) of the patients in the reboxetine group, in 11.4% (29/254) of the patients in the placebo group, and in 18.3% (48/262) of the patients in the paroxetine group (Section 13, Table 5.2). The TESS that were reported in at least 5% of the patients in any treatment group are summarized by maximum intensity in Table 33.

Table 33. TESS Reported in ≥5% of Patients in Any Treatment Group, by Maximum Intensity

COSTART Body System/Preferred Term*	RBX N=264		PBO N=254		PAR N=262	
	n (%)		n (%)		n (%)	
	Mild/Mod	Severe	Mild/Mod	Severe	Mild/Mod	Severe
Patients with at least one TESS	**188 (71.2)**	**51 (19.3)**	**179 (70.5)**	**29 (11.4)**	**183 (69.8)**	**48 (18.3)**
DIGESTIVE						
Dry mouth	117 (44.3)	3 (1.1)	39 (15.4)	1 (0.4)	60 (22.9)	2 (0.8)
Constipation	63 (23.9)	3 (1.1)	15 (5.9)	2 (0.8)	36 (13.7)	2 (0.8)
Nausea	35 (13.3)	3 (1.1)	30 (11.8)	1 (0.4)	70 (26.7)	3 (1.1)
Anorexia	24 (9.1)	2 (0.8)	6 (2.4)	0	20 (7.6)	0
Diarrhea	18 (6.8)	0	25 (9.8)	1 (0.4)	49 (18.7)	4 (1.5)
Dyspepsia	11 (4.2)	0	11 (4.3)	3 (1.2)	14 (5.3)	2 (0.8)
NERVOUS						
Insomnia	89 (33.7)	14 (5.3)	33 (13.0)	3 (1.2)	43 (16.4)	4 (1.5)
Dizziness	40 (15.2)	1 (0.4)	22 (8.7)	2 (0.8)	25 (9.5)	3 (1.1)
Anxiety	18 (6.8)	1 (0.4)	15 (5.9)	3 (1.2)	8 (3.1)	1 (0.4)
Somnolence	15 (5.7)	3 (1.1)	16 (6.3)	0	41 (15.6)	5 (1.9)
Nervousness	16 (6.1)	1 (0.4)	13 (5.1)	1 (0.4)	10 (3.8)	0
BODY						
Headache	69 (26.1)	4 (1.5)	68 (26.8)	5 (2.0)	63 (24.0)	8 (3.1)
Asthenia	20 (7.6)	1 (0.4)	9 (3.5)	0	42 (16.0)	3 (1.1)
Infection	18 (6.8)	0	17 (6.7)	0	12 (4.6)	1 (0.4)
Chills	14 (5.3)	0	1 (0.4)	0	2 (0.8)	0
Abdominal pain	7 (2.7)	1 (0.4)	12 (4.7)	1 (0.4)	9 (3.4)	1 (0.4)
Reaction unevaluable	5 (1.9)	0	1 (0.4)	1 (0.4)	12 (4.6)	1 (0.4)
Accidental injury	2 (0.8)	0	5 (2.0)	0	10 (3.8)	3 (1.1)
SKIN						
Sweating	36 (13.6)	4 (1.5)	7 (2.8)	0	16 (6.1)	1 (0.4)
CARDIOVASCULAR						
Vasodilatation	18 (6.8)	1 (0.4)	3 (1.2)	0	6 (2.3)	0
Palpitation	14 (5.3)	0	5 (2.0)	2 (0.8)	11 (4.2)	1 (0.4)

* Arranged in decreasing order of frequency based on the reboxetine group.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Table 5.2

All TESS are summarized by maximum intensity in Section 13, Table 5.2.

9.4.1.5 TESS by Week of Onset and by Maximum Intensity

The total number of TESS and the percentage of patients who reported at least one TESS are summarized by week of onset and by maximum intensity in Table 34.

Table 34. TESS by Week of Onset and by Maximum Intensity

	Week 1*			Weeks 2-8*		
	RBX N=264	PBO N=254	PAR N=262	RBX N=264	PBO N=254	PAR N=262
Total number of TESS; n (%)†						
Mild	251 (51.2)	115 (61.8)	260 (58.8)	323 (53.7)	246 (52.7)	299 (53.0)
Moderate	212 (43.3)	60 (32.3)	157 (35.5)	236 (39.3)	190 (40.7)	211 (37.4)
Severe	27 (5.5)	11 (5.9)	25 (5.7)	42 (7.0)	31 (6.6)	53 (9.4)
Not reported	0	0	0	0	0	1 (0.2)
Total	490 (100)	186 (100)	442 (100)	601 (100)	467 (100)	564 (100)
Percentage of patients with at least one TESS; n (%)‡						
Mild	75 (28.4)	59 (23.2)	68 (26.0)	55 (20.8)	74 (29.1)	62 (23.7)
Moderate	101 (38.3)	44 (17.3)	84 (32.1)	104 (39.4)	92 (36.2)	97 (37.0)
Severe	21 (8.0)	9 (3.5)	19 (7.3)	33 (12.5)	21 (8.3)	36 (13.7)
Total	197 (74.6)	112 (44.1)	171 (65.3)	192 (72.7)	187 (73.6)	195 (74.4)

* During week 1, reboxetine was administered at a dose of 4 mg/day and paroxetine was administered at a dose of 20 mg/day. During weeks 2 through 8, reboxetine was administered at a dose of 8 to 10 mg/day and paroxetine was administered at a dose of 20 to 40 mg/day.

† Percentages are based on the total number of events that started during the specified time period for each treatment group.

‡ Percentages are based on the number of intent-to-treat patients in each treatment group.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Tables 5.12A and 5.12B

The total number of TESS that were reported during the first week of treatment, when reboxetine was administered at a dose of 4 mg/day and paroxetine was administered at a dose of 20 mg/day, was higher in the reboxetine (490) and paroxetine (442) groups than in the placebo group (186). However, the percentage of events that were severe in intensity was similar among the 3 treatment groups (5.5% [27/490] in the reboxetine group, 5.9% [11/186] in the placebo group, and 5.7% [25/442] in the paroxetine group) during the first week of treatment.

The percentage of patients who experienced at least one TESS during the first week of treatment was higher in the reboxetine (74.6%; 197/264) and paroxetine (65.3%; 171/262) groups than in the placebo group (44.1%; 112/254). Likewise, the percentage of patients who experienced at least one TESS that was severe in intensity during the first week of treatment was higher in the reboxetine (8.0%; 21/264) and paroxetine (7.3%; 19/262) groups than in the placebo group (3.5%; 9/254).

Among the TESS that started during weeks 2 through 8, the percentage of patients who experienced at least one TESS was similar among the 3 treatment groups (72.7% in the

reboxetine group, 73.6% in the placebo group, and 74.4% in the paroxetine group) (Table 34).

TESS that occurred during the first week of treatment (onset day ≤7) are summarized by maximum intensity in Section 13, Table 5.12A. TESS that occurred after the first week of treatment (onset day >7) are summarized by maximum intensity in Section 13, Table 5.12B.

9.4.1.6 TESS by Gender

The TESS that were reported in ≥5% of the male or female patients in any treatment group are summarized by gender in Table 35.

Table 35. TESS Reported in ≥5% of Male or Female Patients in Any Treatment Group, by Gender

COSTART Body System/Preferred Term*	RBX		PBO		PAR	
	Female N=186	Male N=78	Female N=177	Male N=77	Female N=181	Male N=81
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one TESS	**166 (89.2)**	**73 (93.6)**	**144 (81.4)**	**64 (83.1)**	**164 (90.6)**	**67 (82.7)**
DIGESTIVE						
Dry mouth	81 (43.5)	39 (50.0)	30 (16.9)	10 (13.0)	43 (23.8)	19 (23.5)
Constipation	44 (23.7)	22 (28.2)	12 (6.8)	5 (6.5)	31 (17.1)	7 (8.6)
Nausea	33 (17.7)	5 (6.4)	26 (14.7)	5 (6.5)	60 (33.1)	13 (16.0)
Anorexia	22 (11.8)	4 (5.1)	5 (2.8)	1 (1.3)	15 (8.3)	5 (6.2)
Diarrhea	16 (8.6)	2 (2.6)	19 (10.7)	7 (9.1)	32 (17.7)	21 (25.9)
Dyspepsia	8 (4.3)	3 (3.8)	11 (6.2)	3 (3.9)	13 (7.2)	3 (3.7)
Vomiting	8 (4.3)	2 (2.6)	12 (6.8)	0	7 (3.9)	4 (4.9)
NERVOUS						
Insomnia	75 (40.3)	28 (35.9)	24 (13.6)	12 (15.6)	35 (19.3)	12 (14.8)
Dizziness	32 (17.2)	9 (11.5)	17 (9.6)	7 (9.1)	21 (11.6)	7 (8.6)
Anxiety	15 (8.1)	4 (5.1)	12 (6.8)	6 (7.8)	8 (4.4)	1 (1.2)
Somnolence	12 (6.5)	6 (7.7)	15 (8.5)	1 (1.3)	31 (17.1)	15 (18.5)
Nervousness	13 (7.0)	4 (5.1)	9 (5.1)	5 (6.5)	7 (3.9)	3 (3.7)
Libido decreased	1 (0.5)	4 (5.1)	1 (0.6)	2 (2.6)	6 (3.3)	6 (7.4)
BODY						
Headache	52 (28.0)	21 (26.9)	47 (26.6)	26 (33.8)	52 (28.7)	19 (23.5)
Asthenia	17 (9.1)	4 (5.1)	6 (3.4)	3 (3.9)	36 (19.9)	10 (12.3)
Infection	12 (6.5)	6 (7.7)	13 (7.3)	4 (5.2)	12 (6.6)	1 (1.2)
Chills	10 (5.4)	4 (5.1)	1 (0.6)	0	1 (0.6)	1 (1.2)
Abdominal pain	5 (2.7)	3 (3.8)	9 (5.1)	4 (5.2)	6 (3.3)	4 (4.9)
Back pain	4 (2.2)	1 (1.3)	7 (4.0)	1 (1.3)	1 (0.6)	6 (7.4)
Reaction unevaluable	5 (2.7)	0	2 (1.1)	0	10 (5.5)	3 (3.7)
Accidental injury	1 (0.5)	1 (1.3)	3 (1.7)	2 (2.6)	8 (4.4)	5 (6.2)
SKIN						
Sweating	29 (15.6)	11 (14.1)	3 (1.7)	4 (5.2)	11 (6.1)	6 (7.4)
Rash	11 (5.9)	1 (1.3)	2 (1.1)	1 (1.3)	4 (2.2)	2 (2.5)
CARDIOVASCULAR						
Vasodilatation	16 (8.6)	3 (3.8)	3 (1.7)	0	6 (3.3)	0
Palpitation	10 (5.4)	4 (5.1)	6 (3.4)	1 (1.3)	8 (4.4)	4 (4.9)

continued

Table 35. TESS Reported in ≥5% of Male or Female Patients in Any Treatment Group, by Gender

COSTART Body System/Preferred Term*	RBX		PBO		PAR	
	Female N=186	Male N=78	Female N=177	Male N=77	Female N=181	Male N=81
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
UROGENITAL						
Impotence	0	11 (14.1)	0	0	0	8 (9.9)
Abnormal ejaculation	0	9 (11.5)	0	0	1 (0.6)	4 (4.9)
Urination impaired	1 (0.5)	7 (9.0)	0	0	5 (2.8)	1 (1.2)
Urinary retention	1 (0.5)	4 (5.1)	1 (0.6)	0	0	0
Dysuria	0	4 (5.1)	1 (0.6)	0	1 (0.6)	0
SPECIAL SENSES						
Abnormality of accommodation	5 (2.7)	4 (5.1)	2 (1.1)	1 (1.3)	7 (3.9)	0
METABOLIC AND NUTRITIONAL						
Weight loss	4 (2.2)	4 (5.1)	3 (1.7)	0	4 (2.2)	1 (1.2)

* Arranged in decreasing order of frequency based on the reboxetine group.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Table 5.3

Of the TESS that were reported in ≥5% of male or female reboxetine-treated patients, nausea, anorexia, diarrhea, rash, and vasodilatation were reported at least 2 times more frequently in the reboxetine-treated female patients than in the reboxetine-treated male patients, whereas decreased libido, impotence, abnormal ejaculation, urination impaired, urinary retention, dysuria, and weight loss were reported at least 2 times more frequently in the reboxetine-treated male patients than in the reboxetine-treated female patients.

Of the male reboxetine-treated patients who reported at least one symptom of restricted urine flow (ie, urinary retention [5.1%; 4/78], urination impaired [9.0%; 7/78], or urinary frequency [3.8%; 3/78]), only one patient reported more than one of these individual symptoms (patient no. 2197, who reported both urinary frequency and urinary retention). Therefore, the frequency of male reboxetine-treated patients who reported at least one symptom of restricted urine flow was 16.7% (13/78) in this study. All reports of urinary retention, urination impaired, or urinary frequency were mild to moderate in intensity, and only 2 patients in the reboxetine group discontinued treatment due to one of these events (patient no. 1392 discontinued due to urinary retention and patient no. 1131 discontinued due to urination impaired). In addition, the concomitant medication records indicate that none of these reboxetine-treated patients received medication (ie, Flomax [tamsulosin hydrochloride], Cardura [doxazosin mesylate], or Hytrin [terazosin hydrochloride]) for the urinary symptoms. None of the reboxetine-treated male patients were known to have required urinary catheterization for treatment of symptoms of restricted urine flow.

Of the TESS that were reported in ≥5% of male or female paroxetine-treated patients, nausea and infection were reported at least 2 times more frequently in the paroxetine-treated female patients than in the paroxetine-treated male patients, whereas decreased libido, back pain, and impotence were reported at least 2 times more frequently in the paroxetine-treated male patients than in the paroxetine-treated female patients.

All TESS are summarized by gender in Section 13, Table 5.3.

9.4.1.7 Drug-Related TESS

TESS that were judged by the investigators to have been caused by the study medication were reported in 81.1% (214/264) of reboxetine-treated patients, 59.8% (152/254) of placebo-treated patients, and 76.3% (200/262) of paroxetine-treated patients. The drug-related TESS that were reported in at least 5% of patients in any treatment group are summarized in Table 36.

Table 36. Drug-Related* TESS Reported in ≥5% of Patients in Any Treatment Group

COSTART Body System/ Preferred Term†	RBX N=264		PBO N=254		PAR N=262	
	n	%	n	%	n	%
Patients with at least one drug-related TESS	**214**	**81.1**	**152**	**59.8**	**200**	**76.3**
DIGESTIVE						
Dry mouth	118	44.7	35	13.8	60	22.9
Constipation	56	21.2	11	4.3	34	13.0
Nausea	32	12.1	26	10.2	65	24.8
Anorexia	23	8.7	5	2.0	17	6.5
Diarrhea	14	5.3	13	5.1	35	13.4
NERVOUS						
Insomnia	94	35.6	30	11.8	42	16.0
Dizziness	33	12.5	20	7.9	26	9.9
Anxiety	17	6.4	11	4.3	8	3.1
Somnolence	16	6.1	14	5.5	38	14.5
BODY						
Headache	51	19.3	48	18.9	48	18.3
Asthenia	19	7.2	7	2.8	40	15.3
SKIN						
Sweating	37	14.0	7	2.8	16	6.1
CARDIOVASCULAR						
Vasodilatation	14	5.3	3	1.2	1	0.4

* TESS were considered to be drug-related if, in the opinion of the investigator, there was a reasonable possibility that the event was caused by the investigational medication.

† Arranged in decreasing order of frequency based on the reboxetine group.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Table 5.4

Of the drug-related TESS that were reported in ≥5% of patients in the reboxetine treatment group, the following events were reported at least 2 times more frequently in the reboxetine-treated patients than in the placebo-treated patients: dry mouth, constipation, anorexia, insomnia, asthenia, sweating, and vasodilatation.

Of the drug-related TESS that were reported in at least 5% of patients in the paroxetine treatment group, the following events were reported at least 2 times more frequently in the paroxetine-treated patients than in the placebo-treated patients: constipation, nausea, anorexia, diarrhea, somnolence, asthenia, and sweating.

All drug-related TESS are summarized by COSTART body system and preferred term in Section 13, Table 5.4.

9.4.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

9.4.2.1 Deaths

No deaths were reported during this study (Section 13, Table 5.11).

9.4.2.2 Serious Adverse Events

Serious TESS were reported in a similar percentage of patients in each of the 3 treatment groups: 1.5% (4/264) of reboxetine-treated patients, 0.4% (1/254) of placebo-treated patients, and 1.5% (4/262) of paroxetine-treated patients. The frequency of patients who experienced serious TESS is summarized in Table 37. Narrative summaries for patients who experienced serious TESS are provided Section 9.4.2.4.

Table 37. Frequency of Serious TESS

COSTART Body System/Preferred Term*	RBX N=264		PBO N=254		PAR N=262	
	n	%	n	%	n	%
At least one serious TESS	**4**	**1.5**	**1**	**0.4**	**4**	**1.5**
BODY						
Overdose	1	0.4	0	0	0	0
Suicide attempt	1	0.4	0	0	0	0
Abdominal pain	0	0	0	0	1	0.4
Chest pain	0	0	0	0	1	0.4
CARDIOVASCULAR						
Palpitation	1	0.4	0	0	0	0
NERVOUS						
Depression	1	0.4	1	0.4	1	0.4
UROGENITAL						
Kidney calculus	0	0	0	0	1	0.4

* Arranged in decreasing order of frequency based on the reboxetine group.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Table 5.7

Among the serious TESS that occurred during the study, 4 events were judged by the investigators to have been caused by the study medication. These drug-related serious TESS included 3 cases of depression (patient no. 1656 in the reboxetine group, patient no. 1193 in the placebo group, and patient no. 1028 in the paroxetine group) and 1 case of palpitation (patient no. 1184 in the reboxetine group). Narrative summaries for all patients who experienced serious TESS are provided in Section 9.4.2.4.

All serious TESS are summarized by COSTART body system and preferred term in Section 13, Table 5.7. Patients who experienced serious TESS are listed in Section 13, Tables 5.8A (by patient) and 5.8B (by COSTART body system and preferred term).

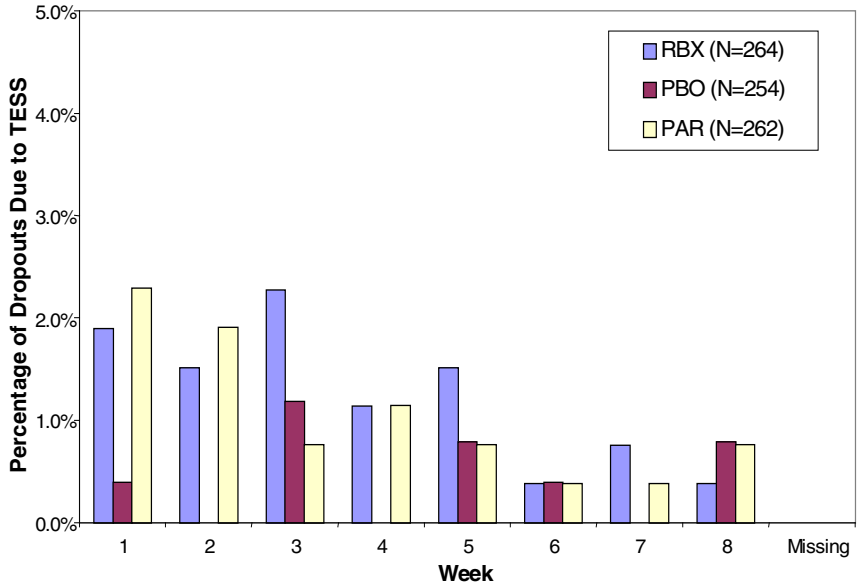
9.4.2.3 Discontinuations Due to Treatment-Emergent Signs and Symptoms

The percentage of patients who discontinued treatment due to TESS at any time during the treatment period was higher in the reboxetine (9.8%; 26/264) and paroxetine (8.4%; 22/262) groups than in the placebo (3.5%; 9/254) group (Section 13, Table 5.5).

During the first week of treatment, when reboxetine was administered at a dose of 4 mg/day and paroxetine was administered at a dose of 20 mg/day, the rate of discontinuations due to TESS was similar in the reboxetine (1.9%; 5/264) and paroxetine (2.3%; 6/262) groups (Figure 3). During the second week of treatment, when the reboxetine dose was increased from 4 mg/day to 8 mg/day, the rate of discontinuations due to TESS decreased slightly in both the reboxetine (1.5%; 4/264) and paroxetine (1.9%; 5/262) groups. During the third week of treatment, the rate of discontinuations due to TESS continued to decrease in the paroxetine group (0.8%; 2/262) but increased slightly in the reboxetine group (2.3%; 6/264).

After the third week of treatment, the rate of discontinuations due to TESS was ≤1.5% in all treatment groups.

Figure 3. Percentage of Patients Who Discontinued Due to TESS, by Week of Discontinuation



Source: Section 13, Table 5.6A

Most TESS that led to discontinuation of treatment were reported for only 1 or 2 patients in any treatment group. The TESS that led to discontinuation of treatment in ≥1% of patients in any treatment group are summarized in Table 38.

Table 38. TESS That Led to Discontinuation of Treatment in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=264		PBO N=254		PAR N=262	
	n	%	n	%	n	%
At least one TESS that led to discontinuation	**26**	**9.8**	**9**	**3.5**	**22**	**8.4**
NERVOUS						
Insomnia	6	2.3	0	0	2	0.8
Dizziness	2	0.8	0	0	3	1.1
Somnolence	1	0.4	1	0.4	3	1.1
BODY						
Headache	5	1.9	2	0.8	4	1.5
Asthenia	1	0.4	0	0	3	1.1
DIGESTIVE						
Anorexia	3	1.1	0	0	0	0
Dry mouth	3	1.1	0	0	1	0.4
Nausea	3	1.1	1	0.4	3	1.1
CARDIOVASCULAR						
Palpitation	5	1.9	0	0	1	0.4

* Arranged in decreasing order of frequency based on the reboxetine group.

Abbreviations: PAR = paroxetine, PBO = placebo, RBX = reboxetine, TESS = treatment-emergent signs and symptoms

Source: Section 13, Table 5.5

The most frequently reported TESS that led to discontinuation of reboxetine treatment was insomnia, which led to discontinuation of treatment in 2.3% of reboxetine-treated patients. The most frequently reported TESS that led to discontinuation of paroxetine treatment was headache, which led to discontinuation of treatment in 1.5% of paroxetine-treated patients.

Most of the TESS that led to discontinuation of treatment were nonserious in nature. Serious TESS led to discontinuation of treatment in 0.8% (2/264) of reboxetine-treated patients (overdose of Ativan in patient no. 1387 and palpitation in patient no. 1184), in 0.4% (1/254) of placebo-treated patients (depression in patient no. 1193) and in 1.5% (4/262) of paroxetine-treated patients (abdominal pain in patient no. 1418, depression in patient no. 1028, chest pain in patient no. 1580, and kidney calculus in patient no. 1409) (Section 13, Table 5.9). Narrative summaries for all patients who experienced serious TESS are provided in Section 9.4.2.4.

Patients who discontinued treatment due to TESS are listed in Section 13, Tables 5.6A (by patient) and 5.6B (by body system and preferred term). Patients who discontinued treatment due to serious TESS are listed in Section 13, Tables 5.10A (by patient) and 5.10B (by body system and preferred term). CRFs for patients who discontinued treatment due to TESS are in Appendix 18.

9.4.2.4 Narratives

Narrative summaries for the patients who experienced serious TESS are presented below. Both the verbatim and the COSTART terms for each event are presented (COSTART terms are shown in parentheses). CRFs for these patients are in Appendix 18.

9.4.2.4.1 Reboxetine

Patient No.: 1184
Investigator: Pomara (No. 46193)
Treatment: Reboxetine
Event: Palpitation (Palpitation)

This 44-year-old female patient was randomized to reboxetine on 19 July 2000. She had a history of a heart murmur during childhood. Prior to the start of the study, she had taken Claritin D (loratadine and pseudoephedrine sulfate) for seasonal allergies (from 1997 through June 2000) and ibuprofen for headache and muscle pains (from 1999 through June 2000). Her pulse rate was 86 beats/min at screen and 80 beats/min at baseline (see table, below). On 19 July 2000 (the first day of study medication), the patient experienced palpitations and increased anxiety. Both events resolved on 23 July 2000. On 23 July 2000, the patient experienced nausea and dizziness, which resolved on 5 August 2000. On 26 July 2000, the patient again reported palpitations. The patient was advised by the investigator to monitor her pulse and to discontinue study medication if her pulse exceeded 100 beats/min. On 2 August 2000, the patient reported that her pulse rate ranged from 105 to 108 beats/min. She was advised to stop taking the study medication (date of last dose of study medication was 1 August 2000). On 4 August 2000, an ECG showed normal sinus rhythm and a heart rate of 87 beats/min. The patient was referred to her personal physician for further treatment of depression. The patient recovered from the palpitations on 11 August 2000. The investigator considered this event to be related to the study medication. The classification of the event as a serious adverse event was based on the investigator's judgment.

The patient's pulse rate and blood pressure values during the study are shown below:

Date	Pulse Rate (beats/min)	Systolic/Diastolic Blood Pressure (mmHg)
12 July 2000 (screen)	86	120/68
19 July 2000	80	110/80
26 July 2000	88	112/65
1 August 2000	102	117/83
4 August 2000	87	120/83

Patient No.: 1387
Investigator: Hassman (No. 46121)
Treatment: Reboxetine
Event: Overdose of Ativan (Overdose)

This 30-year-old female patient was randomized to reboxetine on 22 June 2000. She had a history of MDD and a history of increased mood swings and irritability during menstrual

cycles. On 7 August 2000, the patient experienced irritability, racing thoughts, decreased concentration, and volatile behavior due to an exaggerated premenstrual syndrome response. On 9 August 2000, she began to take Ativan (lorazepam) for insomnia. The patient stated that she misunderstood the directions for taking the Ativan. On 10 August 2000, she ingested a total of twenty-nine 1-mg tablets of Ativan during a 15-hour period. She became sick, and she was transported to the hospital. She did not lose consciousness. She was treated with charcoal, was stabilized in the emergency room, and then was admitted to the psychiatric hospital. The patient denied suicide ideation. The study drug was permanently discontinued (date of last dose, 9 August 2000). While the patient was hospitalized, she was treated with Klonopin (clonazepam) (0.5 mg, 3 times per day) and Zoloft (sertraline hydrochloride) (50 mg per day). The patient was discharged from the hospital on 15 August 2000. She continued treatment with Zoloft and Klonopin, and she was advised to follow up with outpatient psychiatric care. She recovered from this event on 16 August 2000. The investigator considered the event to be unrelated to the study medication.

Patient No.: *1656*
Investigator: *Downs (No. 33915)*
Treatment: *Reboxetine*
Event: *Worsening of suicidal ideation (Depression)*

This 30-year-old female patient was randomized to reboxetine on 25 August 2000. Her first episode of depression occurred 5 months prior to the start of the study. However, she had no prior hospitalizations or treatment for depression before the start of the study. In July 2000, she had an abortion. During the study, she was treated with Depo-Provera (medroxyprogesterone acetate) for birth control and Benadryl Cream (diphenhydramine hydrochloride and zinc acetate) for poison ivy. The patient's mood and affect (based on the CGI Severity of Illness score) was "severe" at baseline, "moderate" on day 14, and "severe" on day 28. On day 28, her dose was increased from 8 to 10 mg/day. Her mood and affect improved to "moderate" on day 42 and remained at the "moderate" level at the end of the study (date of last dose, 18 October 2000).

On 23 October 2000, the patient completed a baseline visit for enrollment in an open-label follow-up study of reboxetine (protocol 950E-CNS-0005-0087; Study 087). During this visit she acknowledged some worsening of the depression, with "wishes to die," but she denied suicidal ideation. She was enrolled in Study 087, and she took her first dose of study medication for Study 087 during the evening of 23 October 2000. During the early morning of 24 October 2000, she telephoned the clinic and stated that she had not admitted all of the suicidal thoughts that she was experiencing. She admitted that she had cut her wrist twice with a box cutter on 21 October 2000 (3 days after she completed Study 046). Her symptoms included worsening of wishes to die, suicidal ideation with plan, and intermittent suicidal intention. She was admitted to an in-patient psychiatric unit on 24 October 2000. Study medication for Study 087 was discontinued on 24 October 2000. On 6 November 2000, she

was discharged from the hospital in stable condition. The investigator considered the event to be related to study medication.

Patient No.: *2130*
Investigator: *Sagman (No. 46150)*
Treatment: *Reboxetine*
Event: *Suicide attempt (Suicide attempt)*

This 21-year-old female patient was randomized to reboxetine on 29 June 2000. She had a history of 2 previous episodes of depression; the first episode started when she was 13 years old. At the time of admission to the study, the duration of the current episode was 1 year. The patient had no history of prior hospitalization for depression. The patient's concomitant medications included acetaminophen for headaches and ibuprofen for cramps. On 22 August 2000, the patient took an overdose of ibuprofen (ten 400-mg tablets), Extra-Strength Tylenol (acetaminophen) (five 500-mg tablets), and clonazepam (five 0.5-mg tablets). The patient did not overdose on study medication. She was taken to the emergency room by her mother, where she was treated with an IV and 5 g of oral charcoal. Lab results showed that acetaminophen levels decreased from 318 to 222 within the first 12 hours (toxic range, >300 for more than 12 hours). Lab results for electrolytes, complete blood cell count (CBC), prothrombin time/partial thromboplastin time (PT/PTT), creatine phosphokinase (CPK-MB), creatinine (CR), and liver function tests (LFTs) were all within normal limits, and salicylate and ethanol tests were negative. An ECG showed normal sinus rhythm. At the time of the event, the patient had completed the study (date of last dose, 22 August 2000). The patient totally recovered from this event on 23 August 2000. The investigator considered the event to be unrelated to the study medication.

9.4.2.4.2 Placebo

Patient No.: *1193*
Investigator: *Salzman (No. 46170)*
Treatment: *Placebo*
Event: *Suicidal ideation (Depression)*

This 25-year-old female patient was randomized to placebo on 24 August 2000. Her medical history indicated that she had donated her left kidney in June 1999 and that she had frequent tension headaches. The patient had been taking naproxen sodium for headaches. Prior to the event, the patient had been in distress, particularly with regard to a work situation. According to the patient, while she was driving to work on the afternoon of 10 September 2000, she "found herself veering into an oncoming car," but she had no memory of how this happened. She was significantly distressed about the near accident. She left her car on the side of the road, and she walked home. On the morning of 11 September 2000, she called a help-line, and she was advised to go to the emergency room. She went to a local hospital emergency room that afternoon, and she was admitted to the

psychiatric unit for treatment of depression and suicidal ideation. The attending psychiatrist advised her to discontinue the study medication (her last dose was on the morning of 11 September 2000). The patient reported that she was given temazepam on the evening of 11 September 2000 to help her sleep. She was also given a dose of paroxetine on the morning of 12 September 2000. The results of a physical examination and blood tests (chemistry panel, complete blood cell count with differential, and urinalysis) were all normal. On the afternoon of 12 September 2000, the patient stated that she was not suicidal and requested that she be discharged. She was discharged shortly thereafter. On 21 September 2000, the patient returned to the study site for the termination visit. At the follow-up visit, the patient was considered to be not recovered, but the event was considered to be chronic or stable. The investigator considered this event to be related to the study medication.

9.4.2.4.3 Paroxetine

Patient No.: *1028*
Investigator: *Kwentus (No. 45641) / Roberson (No. 47536)*
Treatment: *Paroxetine*
Event: *Suicidal ideation (Depression)*

This 49-year-old female patient was randomized to paroxetine on 30 June 2000. She had a history of environmental allergies, hypoglycemia, and childhood arrhythmia. She was treated with Ativan (lorazepam) as a sleep aid (date of last dose, 19 July 2000). Other concomitant medications that were taken near the time of the event included Mircette (desogestrel/ethinyl estradiol and ethinyl estradiol) for birth control, erythromycin for infected bug bites, and Tylenol (acetaminophen) for headache (date of last dose, 10 July 2000). On 20 July 2000, the patient exhibited signs of increased depressive symptoms. On the same day, she made a threat of self-harm (not suicide), and she was examined in the emergency room. On 21 July 2000, the patient showed improvement, and there was no sign of suicidal ideation. On 24 July 2000, marital discord resurfaced, and the patient threatened self-harm again. The event was considered to be serious on 24 July 2000. The patient was discontinued from the study (date of last dose, 24 July 2000). The patient was started on Effexor (venlafaxine hydrochloride), 75 mg twice daily. She was referred to a mental health center for continued therapy, and marital therapy was also recommended. At the follow-up visit on 25 July 2000, the patient was considered to be recovered from this event. The absence of suicidal ideation was noted by the physician. The investigator considered this event to be related to the study medication.

Patient No.: *1409*
Investigator: *Swarner (No. 46255)*
Treatment: *Paroxetine*
Event: *Bilateral kidney stones (Kidney calculus)*

This 53-year-old male patient was randomized to paroxetine on 26 July 2000. The patient had a history of kidney stones, hypertension, and diabetes. He was taking Glucophage (metformin hydrochloride) for non-insulin dependent diabetes and atenolol for hypertension. On 9 August 2000, a computed tomography (CT) scan revealed 2 renal calculi in the right kidney and 1 calculus in the left kidney. On 15 August 2000, the patient was evaluated for intermittent gross hematuria, which had been occurring during the previous 3 weeks. The patient also reported flank pain that was occurring more on the right side than on the left. Study drug was permanently discontinued (date of last dose, 31 August 2000). On 1 September 2000, surgery was performed to remove the stone from the left kidney and to place stents in the right and left ureters. On 14 September 2000, a follow-up procedure was performed to remove stones from the right kidney and to remove the stents from the right and left ureters. The patient recovered from this event on 14 September 2000. The investigator considered the event to be unrelated to the study medication.

Patient No.: *1418*
Investigator: *Helfing (No. 42984)*
Treatment: *Paroxetine*
Event: *Abdominal pain (Abdominal pain)*

This 22-year-old female patient was randomized to paroxetine on 3 August 2000. No pertinent medical history was noted. The only concomitant medication that was noted was Advil for headaches. On 16 September 2000, the patient started to have abdominal pain. On 17 September 2000, she was hospitalized with a diagnosis of gall stones. Study medication was discontinued (date of last dose, 16 September 2000). On 18 September 2000, the patient underwent surgery for removal of the gall bladder. She was released from the hospital 2 days later. She recovered from this event on 3 October 2000. The investigator considered the event to be unrelated to treatment with study medication.

Patient No.: *1580*
Investigator: *Jain (No. 46274)*
Treatment: *Paroxetine*
Event: *Chest pain (Chest pain)*

This 25-year-old female patient was randomized to paroxetine on 11 August 2000. No pertinent medical history was noted, and no relevant concomitant medications were noted. On 3 October 2000, the patient was hospitalized for chest pains. An ECG showed no changes, compared with the baseline ECG that was performed in August, at the beginning of the study. Study drug was discontinued (date of last dose was 2 October 2000). While the patient was hospitalized, she was found to have gall stones. On 9 October 2000, a

cholecystectomy was performed. The patient recovered from this event on 9 October 2000. The investigator considered the event to be unrelated to study medication.

9.4.3 Clinical Laboratory Evaluation

9.4.3.1 Hematology

9.4.3.1.1 Mean Change from Baseline

No statistically significant differences were noted among the treatment groups in the mean change from baseline values for hematocrit, leukocyte count, or leukocyte differential (neutrophils, lymphocytes, monocytes, eosinophils, or basophils) at days 28 or 56 (Section 13, Table 7.1).

Statistically significant differences were noted among the treatment groups in the mean change from baseline values for hemoglobin, erythrocytes, and platelets at day 56. For hemoglobin and erythrocytes, slightly greater mean decreases were observed in the paroxetine group (changes of $–0.16x10^6$/µL for erythrocytes and –0.31 g/dL for hemoglobin) than in the placebo (changes of $–0.11x10^6$/µL for erythrocytes and –0.20 g/dL for hemoglobin) or reboxetine (changes of $–0.07x10^6$/µL for erythrocytes and –0.10 g/dL for hemoglobin) groups between baseline and day 56. For platelet count, a slight mean increase was observed in the reboxetine group (change of $6.7x10^3$/µL) and slight mean decreases were observed in the placebo (change of $-8.1x10^3$/µL) and paroxetine (change of $–5.8x10^3$/µL) groups between baseline and day 56. However, the mean values remained within normal ranges, and none of these differences was considered to be clinically meaningful.

Section 13, Table 7.1, provides summary statistics for each hematologic assay.

9.4.3.1.2 Values Outside of Predefined Normal Ranges

The majority of patients in each treatment group had postbaseline hematology values that were within the predefined normal ranges (Section 13, Table 7.3). For any assay, fewer than 13% of patients had values outside of normal ranges. No evidence of a treatment-related effect was noted on any hematologic assay.

The frequency of patients who had hematology assay values outside of the predefined normal ranges is summarized in Section 13, Table 7.3. Patients with postbaseline hematology assay values outside of the predefined normal ranges are listed in Appendix 17, Table 13.2.

9.4.3.2 Chemistries

9.4.3.2.1 Mean Change from Baseline

No statistically significant differences were noted among the treatment groups in the mean change from baseline values for the majority of the serum chemistry assays, including ALT, bilirubin, blood urea nitrogen, creatinine, glucose, potassium, sodium, or carbon dioxide content (Section 13, Table 7.2).

Statistically significant differences were noted among the treatment groups in the mean change from baseline values for alkaline phosphatase, AST, and uric acid at day 28 and for alkaline phosphatase and serum chloride at day 56. However, for each of these assays, the mean values remained within normal ranges, and none of the changes was considered to be clinically meaningful.

Section 13, Table 7.2, provides summary statistics for each chemistry assay.

9.4.3.2.2 Values Outside of Predefined Normal Ranges

The majority of patients in each treatment group had postbaseline chemistry values that were within the predefined normal ranges (Section 13, Table 7.4). With the exception of glucose values, fewer than 10% of patients in any treatment group had postbaseline chemistry values that were outside of normal ranges.

Glucose values that exceeded the predefined limit (>115 mg/dL for patients ≤49 years of age or >125 mg/dL for patients >50 years of age) were reported in comparable proportions of patients in each treatment group: 15.5% (25/161) of the patients in the reboxetine group, 12.8% (22/172) of the patients in the placebo group, and 18.0% (29/161) of the patients in the paroxetine group had glucose values that exceeded the predefined limit.

The percentage of patients who had renal or liver function tests that were normal at baseline but were above the predefined limits postbaseline are summarized in Table 39.

Table 39. Frequency of Patients With at Least One Postbaseline Value Above the Predefined Normal Limits* for Liver or Renal Function Tests

Test	RBX		PBO		PAR	
	N†	n (%)‡	N†	n (%)‡	N†	n (%)‡
Alkaline Phosphatase	177	3 (1.7)	180	1 (0.6)	174	4 (2.3)
Total Bilirubin	179	2 (1.1)	184	4 (2.2)	177	2 (1.1)
ALT	171	4 (2.3)	174	2 (1.1)	171	9 (5.3)
AST	174	3 (1.7)	176	6 (3.4)	176	8 (4.5)
Creatinine	175	1 (0.6)	182	0	178	0
BUN	174	3 (1.7)	181	0	176	0

* Predefined normal limits: alkaline phosphatase 20-225 U/L, depending on sex and age of patient; total bilirubin 0.0-1.3 mg/dL; ALT 0-48 U/L; AST 0-55 U/L, depending on age of patient; creatinine 0.5-1.4 mg/dL; BUN 7-30 mg/dL, depending on age of patient.

† No. of patients with a normal baseline value and at least one postbaseline measurement.

‡ No. (%) of patients with a normal baseline value and at least one postbaseline value exceeding the predefined normal limits.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Table 7.4

The abnormal values for renal or liver function tests that were observed in the reboxetine group represented minor elevations in assay values. No clinically significant abnormal

values (defined as values at least 3 times the upper limit of normal for ALT, AST, alkaline phosphatase, and bilirubin and creatinine values of at least 3.0 mg/dL) were observed.

The frequency of patients who had chemistry assay values that were outside of the predefined normal ranges is summarized in Section 13, Table 7.4. Patients with postbaseline chemistry assay values outside of the predefined normal ranges are listed in Appendix 17, Table 13.3.

9.4.4 Vital Signs

9.4.4.1 Mean Change From Baseline

Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline values for sitting systolic blood pressure at days 7 and 21. In the pairwise comparison, the mean change from baseline values for sitting systolic blood pressure were significantly greater in the paroxetine group than in the placebo group at days 7 and 21; no significant differences were observed in the pairwise comparisons between the reboxetine and placebo groups (Section 13, Table 6.1).

Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline values for sitting diastolic blood pressure at each visit. In the pairwise comparison, the mean change from the baseline diastolic blood pressure was significantly greater in the reboxetine group than in the placebo group at each visit. At the end of the study (day 56), the mean change from baseline diastolic blood pressure was +1.8 mmHg in the reboxetine group, -1.1 mmHg in the placebo group, and +0.2 mmHg in the paroxetine group (Section 13, Table 6.2).

Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline pulse rate at each visit. In the pairwise comparison, the mean change from the baseline pulse rate was significantly greater in the reboxetine group than in the placebo group at each visit. At the end of the study (day 56), the mean change from baseline pulse rate was +8.0 beats per minute in the reboxetine group, +0.5 beats per minute in the placebo group, and -2.3 beats per minute in the paroxetine group (Section 13, Table 6.3).

Statistically significant differences were also observed among the 3 treatment groups in the mean change from baseline body weight at days 14, 21, 28, and 56. In the pairwise comparison, the mean change from baseline body weight was significantly greater in the reboxetine group than in the placebo group at days 14, 21, 28, and 56. At the end of the study (day 56), the mean change from baseline body weight was -4.2 lb in the reboxetine group, +0.3 lb in the placebo group, and -1.0 lb in the paroxetine group (Section 13, Table 6.4).

9.4.4.2 Values Outside of Predefined Normal Limits

As shown in Table 40, fewer than 3% of the patients in any treatment group had a postbaseline value for diastolic blood pressure or pulse rate that was outside of the predefined normal limits. A slightly higher percentage of patients had postbaseline values for systolic blood pressure that were below the predefined normal limit (≤90 mmHg), although the percentages were similar among the 3 treatment groups: 4.3% (11/253) of the patients in the

reboxetine group, 4.1% (10/243) of the patients in the placebo group, and 4.1% (10/244) of the patients in the paroxetine group had values for systolic blood pressure that were below the predefined normal limit (≤90 mmHg).

Table 40. Frequency of Patients With at Least One Postbaseline Blood Pressure and/or Pulse Rate Value Outside of the Predefined Limits

Variable	Predefined Limit	RBX		PBO		PAR	
		N*	n (%)†	N*	n (%)†	N*	n (%)†
Systolic BP	≥180 mmHg	253	0	243	0	244	0
	≤90 mmHg	253	11 (4.3)	243	10 (4.1)	244	10 (4.1)
Diastolic BP	≥105 mmHg	252	4 (1.6)	247	7 (2.8)	250	3 (1.2)
	≤50 mmHg	252	2 (0.8)	247	4 (1.6)	250	1 (0.4)
Pulse	≥120 beats/min	251	4 (1.6)	247	1 (0.4)	249	1 (0.4)
	≤50 beats/min	251	0	247	4 (1.6)	249	3 (1.2)

* No. of patients with a normal baseline value and at least one postbaseline measurement.

† No. (%) of patients with a normal baseline value and at least one postbaseline value exceeding the predefined normal limits.

Abbreviations: BP = blood pressure, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Table 6.5

No clinically relevant differences were noted among the treatment groups in the frequency of patients who had vital sign values that were outside of the predefined limits. The majority of the patients in each treatment group who had a postbaseline vital sign that was outside of the predefined limit had only a single abnormal value.

The patients who had values that were outside of the predefined normal limits for vital signs are listed in Appendix 17, Tables 13.1A (systolic blood pressure), 13.1B (diastolic blood pressure) and 13.1C (pulse rate).

9.4.5 Electrocardiograms

9.4.5.1 ECG Abnormalities

The majority of patients in each treatment group had ECG findings that were normal at baseline and at endpoint (defined as the last visit at which the patient was still receiving study medication). The percentage of patients who had normal ECG findings at baseline and abnormal ECG findings at endpoint was 2.8% (6/211) in the reboxetine group, 3.0% (7/232) in the placebo group, and 2.8% (6/211) in the paroxetine group (Section 13, Table 8.2). However, in all of these patients (ie, patients who had normal ECG findings at baseline and abnormal ECG findings at endpoint), the abnormal ECG findings met the predefined criteria for "abnormal, but not clinically relevant" ECG findings, as defined by eResearchTechnology, the central laboratory that evaluated the ECGs.

ECG results are summarized by category of abnormality (ie, arrhythmia, conduction, morphology, myocardial infarction, rhythm, ST segment, T waves, and U waves) in

Section 13, Table 8.4. Patients who had abnormal postbaseline ECG findings are listed in Appendix 17, Table 13.5.

9.4.5.2 Effects of Treatment on Heart Rate, PR, QRS, QT, and QTc Intervals

9.4.5.2.1 Mean Change from Baseline

No statistically significant differences were observed among the treatment groups in the mean change from baseline values for QRS interval at days 28 and 56. Statistically significant differences were observed among the treatment groups in the mean change from baseline values for the PR, QT, QTc (Fridericia), and QTc (Bazett) intervals at days 28 and 56 (Table 41). However, for PR, QT, and QTc (Fridericia) intervals, the mean change in the reboxetine group represented a decrease from baseline values (ie, no prolongation of the intervals was observed). In addition, the mean values at days 28 and 56 remained within the normal ranges for each of the intervals. When the QT interval was corrected for heart rate using Bazett's correction method, the reboxetine group showed a mean increase from baseline QTc values. However, given that reboxetine causes an increase in heart rate and that Bazett's formula is known to overestimate the actual QTc values in the presence of increased heart rate, Fridericia's correction method can be considered to be the more appropriate correction method for the evaluation of reboxetine. Therefore, although statistically significant differences were observed among the treatment groups in the mean change from baseline PR, QT, QTc (Fridericia), and QTc (Bazett) intervals, the results were not considered to be clinically significant.

Table 41. Mean Change From Baseline ECG Intervals at Day 56

	RBX N=192†		PBO N=218†		PAR N=203†		
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change	P Value‡
PR interval (msec)	151.182	-5.620	154.472	-0.555	151.596	-0.591	0.0005*
QRS interval (msec)	87.469	-0.344	88.023	0.261	87.419	0.463	0.5313
QT interval (msec)	376.557	-27.714	379.601	-4.133	377.335	-1.773	<.0001*
QTc interval (msec) (Bazett's)§	402.001	9.639	397.330	1.139	396.171	3.232	0.0002*
QTc interval (msec) (Fridericia's)	392.968	-3.679	391.072	-0.677	389.503	1.569	0.0166*
Heart rate (bpm)	69.755	15.000	66.720	1.945	67.212	1.488	<.0001*

* $p \leq 0.05$

† Number of intent-to-treat patients with the specified ECG measurement at screen and at day 56.

‡ Differences among the treatment groups were tested using a one-way analysis of variance.

§ It should be noted that Bazett's formula overestimates the actual QTc values in the presence of increased heart rate.

Abbreviations: bpm = beats per minute, ECG = electrocardiogram, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Table 8.1

Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline ECG heart rate on days 28 and 56 (Section 13, Table 8.1). In the pairwise comparison, the mean change from baseline ECG heart rate was significantly greater in the reboxetine group than in the placebo group on days 28 and 56. At the end of the study (day 56), the mean increase from baseline ECG heart rate was 15.0 beats per minute in the reboxetine group, 1.9 beats per minute in the placebo group, and 1.5 beats per minute in the paroxetine group.

Section 13, Table 8.1, provides summary statistics for ECG intervals.

9.4.5.2.2 Values Outside of Predefined Limits

The majority of patients in each treatment group had values for ECG intervals that were within the predefined normal limits. The frequency of patients who had values that were outside of the predefined limits for heart rate, PR, QRS, QT, or QTc intervals is summarized in Table 42.

Table 42. Frequency of Patients With At Least One Postbaseline ECG Interval Exceeding the Predefined Limits

Parameter	Limit	RBX		PBO		PAR	
		N*	n (%)†	N*	n (%)†	N*	n (%)†
Bradycardia	≤50 beats/min	223	0	227	8 (3.5)	214	6 (2.8)
Tachycardia	≥120 beats/min	223	0	227	0	214	0
PR Interval	≤110 msec	231	6 (2.6)	237	3 (1.3)	223	1 (0.4)
	≥210 msec	231	0	237	2 (0.8)	223	2 (0.9)
QRS Interval	≤30 msec	230	0	234	0	222	0
	≥110 msec	230	2 (0.9)	234	2 (0.9)	222	1 (0.5)
QT Interval	≥470 msec	233	0	238	0	224	0
QTc Interval (Bazett's)	≥450 msec (males) ≥470 msec (females)	233	2 (0.9)	237	1 (0.4)	224	1 (0.4)
QTc Interval (Fridericia's)	≥450 msec (males) ≥470 msec (females)	233	1 (0.4)	238	1 (0.4)	224	0

* No. of patients with a normal baseline value and at least one postbaseline measurement

† No. (%) of patients with a normal baseline value and at least one postbaseline ECG value outside of predefined limits.

Abbreviations: ECG = electrocardiogram, PAR = paroxetine, PBO = placebo, RBX = reboxetine

Source: Section 13, Table 8.3

Two reboxetine-treated patients (patient nos. 1607 and 2139) had postbaseline values for QTc (Bazett's) that exceeded the predefined limits. However, both of these patients also had an increase in heart rate. Given that Bazett's formula is known to overestimate the actual QTc values in the presence of increased heart rate, Fridericia's correction method can be considered to be the more appropriate correction method. Only one reboxetine-treated patient (patient no. 2139) had a QTc interval that exceeded the predefined limit, based on both Bazett's and Fridericia's correction methods. In this patient, who presented with left

bundle branch block at screen, the elevated value for QTc (Fridericia) (460.4 msec) at day 56 was slightly above the predefined limit of 450 msec.

Patients who had postbaseline values that exceeded the predefined limits for ECG intervals are listed in Appendix 17, Table 13.4.

9.4.6 Exposure in Utero

Despite the fact that patients who were pregnant were to be excluded from the study and that clear instructions were given to the patients to practice effective contraception, 2 pregnancies (one in the reboxetine group and one in the placebo group) occurred during the study. Available information for each case is summarized below:

9.4.6.1 Reboxetine

Patient No.: 1024
Investigator: Klapper (No. 39081)
Treatment: Reboxetine

This 36-year-old female patient was randomized to reboxetine on 7 August 2000. She had a history of a tubal pregnancy in 1987. The concomitant medication record indicated that she was taking multivitamins. No serum pregnancy test was performed on this patient at screen because of a site error (the sample was sent, but the laboratory requisition was not marked). On 21 August 2000, the patient performed a home urine pregnancy test, which was positive. A follow-up serum pregnancy test was performed by Planned Parenthood (date unknown), which confirmed the result of the home urine pregnancy test. The patient was discontinued from the study (date of last dose, 22 August 2000). The patient was assessed at the treatment-termination visit on 29 August 2000. At this time, a serum pregnancy test was performed by the central laboratory, and the result confirmed the earlier positive results. The first day of the patient's last menstrual period was 28 June 2000. The estimated date of conception was 10 July 2000. At the time of the initial exposure to study medication, the gestational age was estimated to be 4 weeks. No pregnancy-related complications had been reported as of 28 November 2000. The investigator considered this event to be unrelated to the study medication.

9.4.6.2 Placebo

Patient No.: 1657
Investigator: Downs (No. 33915)
Treatment: Placebo

This 34-year-old female patient was randomized to placebo on 23 August 2000. She had a history of using oral contraceptives and the barrier method to prevent pregnancy. The concomitant medication record indicated that she was taking an oral contraceptive during the study. At the end-of-treatment visit on 18 October 2000, the patient's serum pregnancy test result was positive. The test was repeated on 23 October 2000, and the result was again positive. The patient indicated that the first day of her last menstrual period was 24 September 2000. She claimed to have been using oral contraceptives and barrier

contraception during this time. An elective abortion was performed on 4 November 2000. The investigator considered the event to be unrelated to the study medication.

9.4.7 Safety Conclusions

Treatment-emergent signs and symptoms were reported in a similar percentage of patients in each of the treatment groups (90.5% in the reboxetine group, 81.9% in the placebo group, and 88.2% in the paroxetine group).

Overall, the adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. The most frequently reported TESS (reported in at least 5% of reboxetine-treated patients and at least 2 times more frequently in the reboxetine-treated patients than in the placebo-treated patients) were dry mouth, constipation, anorexia, insomnia, asthenia, chills, sweating, and vasodilatation. In the paroxetine group, the most frequently reported TESS (reported in at least 5% of paroxetine-treated patients and at least 2 times more frequently in the paroxetine-treated patients than in the placebo-treated patients) were constipation, nausea, anorexia, somnolence, asthenia, reaction unevaluable, accidental injury, and sweating.

Of the TESS that were reported in ≥5% of male or female reboxetine-treated patients, nausea, anorexia, diarrhea, rash, and vasodilatation were reported at least 2 times more frequently in the reboxetine-treated female patients than in the reboxetine-treated male patients, whereas decreased libido, impotence, abnormal ejaculation, urination impaired, urinary retention, dysuria, and weight loss were reported at least 2 times more frequently in the reboxetine-treated male patients than in the reboxetine-treated female patients. Symptoms of restricted urine flow (ie, urinary retention, urination impaired, or urinary frequency) were reported in 16.7% (13/78) of male reboxetine-treated patients in this study. However, all reports of urinary retention, urination impaired, or urinary frequency were mild to moderate in intensity, and only 2 patients in the reboxetine group discontinued treatment due to one of these events.

Of the TESS that were reported in ≥5% of male or female paroxetine-treated patients, nausea and infection were reported at least 2 times more frequently in the paroxetine-treated female patients than in the paroxetine-treated male patients, whereas decreased libido, back pain, and impotence were reported at least 2 times more frequently in the paroxetine-treated male patients than in the paroxetine-treated female patients.

No deaths were reported during this study. Serious TESS were reported in a similar percentage of patients in each of the 3 treatment groups: 1.5% (4/264) of reboxetine-treated patients, 0.4% (1/254) of placebo-treated patients, and 1.5% (4/262) of paroxetine-treated patients.

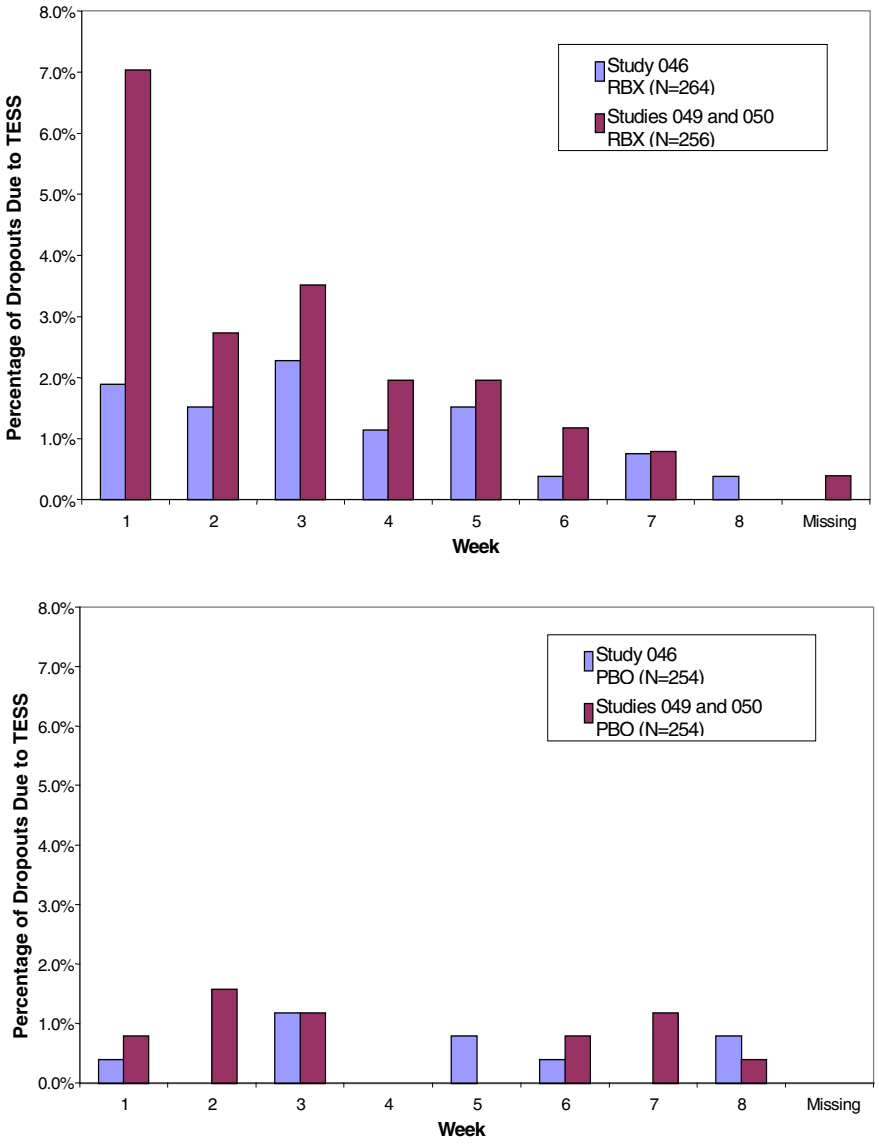
The percentage of patients who discontinued treatment due to TESS at any time during the treatment period was higher in the reboxetine (9.8%; 26/264) and paroxetine (8.4%; 22/262) groups than in the placebo (3.5%; 9/254) group. The most frequently reported TESS that led

to discontinuation of reboxetine treatment was insomnia, which led to discontinuation of treatment in 2.3% of reboxetine-treated patients. The most frequently reported TESS that led to discontinuation of paroxetine treatment was headache, which led to discontinuation of treatment in 1.5% of paroxetine-treated patients.

The rates of discontinuation due to TESS that were observed in this study were much lower than the rates that were observed in earlier US studies of reboxetine (protocols 049 [26] and 050 [27]). In the reboxetine group, the rate of discontinuations due to TESS decreased from 19.5% (50/256) in the earlier studies (combined data from protocols 049 and 050) to 9.8% (26/264) in this study. In the placebo group, the rate of discontinuations due to TESS decreased from 6.7% (17/254) in the earlier studies to 3.5% (9/254) in this study.

During the first week of treatment in this study, when reboxetine was administered at a dose of 4 mg/day (half of the usual recommended dose of 8 mg/day), the rate of discontinuations due to TESS in the reboxetine group (1.9%; 5/264) was substantially lower than the rate that was observed during the first week of studies 049 and 050 (7.0%; 18/256) (Figure 4, top panel). The rate of discontinuations due to TESS in this study decreased slightly during week 2 (1.5%; 4/264) and increased slightly during week 3 (2.3%; 6/264). However, these rates remained lower than the rates that were observed during weeks 2 (2.7%; 7/256) and 3 (3.5%; 9/256) of studies 049 and 050. These results indicate that the 1-week dose-escalation period for reboxetine was successful in reducing the rate of discontinuations due to TESS. The lower rate of discontinuation during weeks 2 and 3 of this study may indicate that the patients became acclimated to the effects of the drug during the 1-week dose-escalation period, or it may reflect improved management of symptoms by the site personnel, compared with earlier studies. The rates of discontinuation due to TESS in the placebo group were generally low, both in this study and in the combined data from studies 049 and 050 (Figure 4, bottom panel). The results that were observed in this study (study 046) are similar to the results that were observed in study 047 [36], which also included a 1-week dose-escalation period for reboxetine.

Figure 4. Discontinuations Due to TESS, by Week of Discontinuation: Comparison of Data From Study 047 With Combined Data from Studies 049 and 050



In addition to the improvements that were observed in the rate of discontinuation due to TESS in the reboxetine group in this study, improvements in the number and severity of TESS were also observed during the 1-week dose-escalation period for reboxetine. In this study (N=264), a total of 490 TESS were reported in the reboxetine group during the first 7 days of treatment, when reboxetine was administered at a dose of 4 mg/day. Of these events, 51.2% (251/490) were mild, 43.3% (212/490) were moderate, and 5.5% (27/490) were severe in intensity. In contrast, in the earlier US studies of reboxetine (combined data from protocols 049 [26] and 050 [27]; N=256), a total of 726 TESS were reported during the first 7 days of treatment, when reboxetine was administered at a dose of 8 mg/day. Of these

events, 49.2% (357/726) were mild, 39.1% (284/726) were moderate, and 11.7% (85/726) were severe in intensity. Thus, the overall number of TESS that were reported in the reboxetine group was reduced during the first week of this study (when reboxetine was administered at a dose of 4 mg/day), compared with studies 049 and 050 (when reboxetine was administered at a dose of 8 mg/day). In addition, the percentage of TESS that were severe in intensity was reduced, and the percentage of TESS that were mild or moderate in intensity was increased, during the first week of this study, compared with studies 049 and 050. The 1-week dose-escalation period for reboxetine is the most likely reason for the improvements that were observed in the profile of TESS during the first week of treatment in this study. These results are consistent with the results that were observed in study 047 [36], which also included a 1-week dose-escalation period for reboxetine.

The majority of patients in each treatment group had postbaseline hematology and chemistry values that were within the predefined normal ranges. No evidence of a treatment-related effect was noted on any hematologic or chemistry assay.

No statistically significant differences were observed among the treatment groups in the mean change from baseline values for sitting systolic blood pressure at day 56. Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline values for sitting diastolic blood pressure at each visit. At the end of the study (day 56), the mean change from baseline diastolic blood pressure was +1.8 mmHg in the reboxetine group, -1.1 mmHg in the placebo group, and +0.2 mmHg in the paroxetine group.

Statistically significant differences were also observed among the 3 treatment groups in the mean change from baseline body weight at days 14, 21, 28, and 56. At the end of the study (day 56), the mean change from baseline body weight was -4.2 lb in the reboxetine group, +0.3 lb in the placebo group, and -1.0 lb in the paroxetine group.

Although statistically significant differences were observed among the treatment groups in the mean change from baseline values for QTc (Fridericia), the mean change in the reboxetine group represented a decrease from baseline values (ie, no prolongation of the intervals was observed). In addition, the mean values at days 28 and 56 remained within the normal range.

Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline values for pulse rate and ECG heart rate. At the end of the study (day 56), the mean change from baseline pulse rate was +8.0 beats per minute in the reboxetine group, +0.5 beats per minute in the placebo group, and –2.3 beats per minute in the paroxetine group, whereas the mean change from baseline ECG heart rate was +15.0 beats per minute in the reboxetine group, +1.9 beats per minute in the placebo group, and +1.5 beats per minute in the paroxetine group. However, few reboxetine-treated patients (1.6%; 4/251) had postbaseline values for pulse rate that were above the predefined limit (≥120 beats/min), and no reboxetine-treated patients had postbaseline values for ECG heart rate that were above the predefined limit (≥120 beats/min).

10 DISCUSSION AND OVERALL CONCLUSIONS

This phase III, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study was conducted in 787 patients who suffered from MDD without psychotic features, as diagnosed using criteria defined by the DSM-IV. The primary objective of the study was to demonstrate that the antidepressant efficacy of reboxetine, administered at a dose of 4 mg/day during the first week and at a dose of 8 to 10 mg/day during the following 7 weeks, is superior to that of placebo, as determined by a 2-way ANOVA of the mean change from baseline in the MADRS total score at day 56 in the ITT patient population.

During the first week of treatment, reboxetine was administered at a dose of 4 mg/day, which is half of the usual recommended dose of 8 mg/day. This dose-escalation period was included in the study design to assess whether the relatively high rate of early discontinuations due to adverse events that had been observed in earlier US studies of reboxetine (protocols 049 [26] and 050 [27]) could be reduced by reducing the starting dose of reboxetine. During weeks 2 through 4, reboxetine was administered at a dose of 8 mg/day. After 4 weeks of treatment, the reboxetine dose could be increased to 10 mg/day in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. Paroxetine was administered at the recommended dose of 20 mg/day during the first 4 weeks of treatment. After 4 weeks of treatment, the paroxetine dose could be increased to 40 mg/day in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose.

A total of 787 patients were enrolled in the study and were randomized to receive treatment with reboxetine (265 patients), placebo (257 patients), or paroxetine (265 patients). The ITT population, which includes all patients who received at least one dose of study medication, includes 264 reboxetine-treated patients, 254 placebo-treated patients, and 262 paroxetine-treated patients.

Overall, the patient population in this study was reflective of the general population of patients with depression [35]. The patients in the study ranged in age from 18 to 65 years, and the majority of the patients were female and white. No statistically significant differences were noted among the treatment groups in the severity of depression at baseline, as judged by the mean total scores for the MADRS, the HAM-D, the CGI Severity of Illness, or the SASS.

This study failed to meet the protocol-specified primary objective. Although the mean decrease from baseline in the MADRS total score was significantly greater in the paroxetine group than in the placebo group at day 56 in the LOCF analysis, no significant differences were observed between the reboxetine and placebo groups on the change from baseline in the MADRS total score. Statistically significant differences, favoring paroxetine over placebo, were also observed on a number of the secondary antidepressant efficacy endpoints. No significant differences were observed between the reboxetine and placebo groups on any of the antidepressant efficacy endpoints, although the response in the reboxetine group was always at least equal to, or numerically better than, the response in the placebo group.

Despite the fact that this study (study 046) and a previously conducted study (study 047 [36]) were conducted according to the same study design, the results of the 2 studies differed markedly. Study 047 demonstrated that reboxetine was significantly superior to placebo on the primary efficacy endpoint and on a number of secondary efficacy endpoints, whereas this study showed no statistically significant differences between reboxetine and placebo on any of the antidepressant efficacy endpoints. This difference in overall study results can be attributed largely to a difference in the placebo response, which was much higher in this study (mean change from baseline in the MADRS total score, –14.4) than in study 047 (mean change from baseline in the MADRS total score, –12.3). In contrast, the response in the reboxetine group in this study (mean change from baseline in the MADRS total score, –14.7) was very consistent with the results in study 047 (mean change from baseline in the MADRS total score, –14.5). Therefore, the failure to demonstrate a statistically significant difference between the reboxetine and placebo groups in this study can be attributed to an increased placebo response, not a decreased reboxetine response. In the paroxetine group, the response in this study (mean change from baseline in the MADRS total score, –16.8) was slightly higher than the response in study 047 (mean change from baseline in the MADRS total score, –15.3). This slight increase enabled the paroxetine group to overcome the increased placebo response in this study, resulting in a significant difference between paroxetine and placebo.

The failure to distinguish an active drug from placebo in antidepressant studies is not uncommon, as demonstrated by the negative studies that were reported as part of the development programs of many approved antidepressant drugs [10]. In general, placebo response rates of 28% to 40% have been reported in patients with MDD [37]. In contrast, the placebo response rate in this study was 55.1% (based on the HAM-D response rate).

To identify the factors that might have contributed to the high placebo response in this study, retrospective exploratory analyses were conducted using visual tools, such as Spotfire.net™, to explore possible patterns or trends in the data, with the intention that more formal statistical analyses would be performed if any trends were observed. Subset analyses were conducted for the following variables to identify possible trends in placebo response: demographics, social situation, previous history of depression, characteristics of present depressive episode, severity of depression at baseline, and discontinuations due to TESS. Because the placebo response rates were similar in the subsets described above, no formal statistical analyses were undertaken.

The results from the secondary measures of energy and social function indicate that quality of life improved in all treatment groups during the study. Statistically significant differences were observed among the 3 treatment groups on the mean change from baseline in the SASS total score on days 28, 42, and 56 in both the LOCF and OC analyses, with reboxetine producing a significantly greater increase in the SASS total score than placebo on days 42 (LOCF analysis) and 56 (LOCF and OC analyses) and paroxetine producing a significantly greater increase in the SASS total score than placebo on days 28, 42, and 56 (LOCF and OC analyses).

On the other secondary measures of energy and social function, including the MOS SF-36 Social Functioning and Vitality scales and the MFI General Fatigue subscale, no statistically

significant differences were observed among the 3 treatment groups at endpoint (day 56). However, on the MOS SF-36 Social Functioning scale, reboxetine produced a significantly greater increase than placebo on day 42 (OC analysis) and paroxetine produced a significantly greater increase than placebo on days 28 (LOCF and OC analyses) and 42 (OC analysis).

Overall, the adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. The most frequently reported TESS (reported in at least 5% of reboxetine-treated patients and at least 2 times more frequently in the reboxetine-treated patients than in the placebo-treated patients) were dry mouth, constipation, anorexia, insomnia, asthenia, chills, sweating, and vasodilatation. In the paroxetine group, the most frequently reported TESS (reported in at least 5% of paroxetine-treated patients and at least 2 times more frequently in the paroxetine-treated patients than in the placebo-treated patients) were constipation, nausea, anorexia, somnolence, asthenia, reaction unevaluable, accidental injury, and sweating. The majority of TESS that were reported by patients in each treatment group were mild to moderate in intensity.

The percentage of patients who discontinued treatment due to TESS at any time during the treatment period was higher in the reboxetine (9.8%; 26/264) and paroxetine (8.4%; 22/262) groups than in the placebo (3.5%; 9/254) group.

The rates of discontinuation due to TESS that were observed in this study were much lower than the rates that were observed in earlier US studies of reboxetine (protocols 049 [26] and 050 [27]). In the reboxetine group, the rate of discontinuations due to TESS decreased from 19.5% (50/256) in the earlier studies (combined data from protocols 049 and 050) to 9.8% (26/264) in this study. In the placebo group, the rate of discontinuations due to TESS decreased from 6.7% (17/254) in the earlier studies to 3.5% (9/254) in this study.

During the first week of treatment in this study, when reboxetine was administered at a dose of 4 mg/day (half of the usual recommended dose of 8 mg/day), the rate of discontinuations due to TESS in the reboxetine group (1.9%; 5/264) was substantially lower than the rate that was observed during the first week of studies 049 and 050 (7.0%; 18/256). The rate of discontinuations due to TESS in this study decreased slightly during week 2 (1.5%; 4/264) and increased slightly during week 3 (2.3%; 6/264). However, these rates remained lower than the rates that were observed during weeks 2 (2.7%; 7/256) and 3 (3.5%; 9/256) of studies 049 and 050. These results indicate that the 1-week dose-escalation period for reboxetine was successful in reducing the rate of discontinuations due to TESS. The lower rate of discontinuation during weeks 2 and 3 of this study may indicate that the patients became acclimated to the effects of the drug during the 1-week dose-escalation period, or it may reflect improved management of symptoms by the site personnel, compared with earlier studies. The results that were observed in this study (study 046) are similar to the results that were observed in study 047 [36], which also included a 1-week dose-escalation period for reboxetine.

In addition to the improvements that were observed in the rate of discontinuation due to TESS in the reboxetine group in this study, improvements in the number and severity of

TESS were also observed during the 1-week dose-escalation period for reboxetine. A total of 490 TESS were reported in the reboxetine group (N=264) during the first week of this study (when reboxetine was administered at a dose of 4 mg/day), whereas 726 TESS were reported in the reboxetine group (N=256) during the first week of studies 049 and 050 (when reboxetine was administered at a dose of 8 mg/day). In addition, the percentage of TESS that were severe in intensity was reduced during the first week of this study (5.5%; 27/490), compared with studies 049 and 050 (11.7%; 85/726). The 1-week dose-escalation period for reboxetine is the most likely reason for the improvements that were observed in the profile of TESS during the first week of treatment in this study. These results are consistent with the results that were observed in study 047 [36], which also included a 1-week dose-escalation period for reboxetine.

Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline values for sitting diastolic blood pressure at each visit. At the end of the study (day 56), the mean change from baseline diastolic blood pressure was +1.8 mmHg in the reboxetine group, -1.1 mmHg in the placebo group, and +0.2 mmHg in the paroxetine group.

Consistent with the results of previous studies, the mean change from baseline values for pulse rate and ECG heart rate were significantly greater in the reboxetine group than in the placebo group throughout the study. At the end of the study (day 56), the mean change from baseline pulse rate was +8.0 beats per minute in the reboxetine group, +0.5 beats per minute in the placebo group, and –2.3 beats per minute in the paroxetine group, whereas the mean change from baseline ECG heart rate was +15.0 beats per minute in the reboxetine group, +1.9 beats per minute in the placebo group, and +1.5 beats per minute in the paroxetine group. However, few reboxetine-treated patients (1.6%; 4/251) had postbaseline values for pulse rate that were above the predefined limit (≥120 beats/min), and no reboxetine-treated patients had postbaseline values for ECG heart rate that were above the predefined limit (≥120 beats/min).

In conclusion, this phase III, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study failed to demonstrate that the antidepressant efficacy of reboxetine is superior to that of placebo, as determined by the mean change from baseline in the MADRS total score at day 56 in the ITT patient population, the primary endpoint. The adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. No new safety concerns associated with the use of reboxetine were identified.

11 ACKNOWLEDGMENTS

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