Studie 047

(M/2020/0047)

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/2020/0047

Previous Reports of the Study:
Final Report Originally Issued 3 November 2000; Amended 6 February 2001

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	8 May 2000
Trial Completion Date	22 September 2000
Sponsor's Responsible Medical Officer	Mark T. Brown, MD Clinical Development Therapeutic Area CNS Pharmacia & Upjohn Inc Kalamazoo, Michigan 49001
Development Phase of Trial	III
Authors of the Report	Mark T. Brown, MD Sally A. Brinkman, BS Jacqueline K. Reisner, MS Clayton R. Rowland, PhD

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.)

Clinical Program Leader

Mark T. Brown, MD
Clinical Development
Therapeutic Area CNS
Pharmacia & Upjohn Inc
Kalamazoo, Michigan 49001

Signature Date

Clinical Trials Associate

Sally A. Brinkman, BS
Clinical Development
Therapeutic Area CNS
Pharmacia & Upjohn Inc
Kalamazoo, Michigan 49001

Signature Date

Statistician

Jacqueline K. Reisner, MS
Clinical Biostatistics II
Pharmacia & Upjohn Inc
Kalamazoo, Michigan 49001

Signature Date

Outcomes Research Associate Director

Clayton R. Rowland, PhD
Outcomes Research
Pharmacia & Upjohn Inc
Kalamazoo, Michigan 49001

Signature Date

Therapeutic Area Clinical Director

C. Eugene Wright III, PharmD, PhD
Clinical Development
Therapeutic Area CNS
Pharmacia & Upjohn Inc
Kalamazoo, Michigan 49001

Signature Date

2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 68 principal investigators participated in this trial at 68 centers in the United States. 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/2020/0047

Investigators and Study Centers: This multicenter study was conducted by the following 68 principal investigators at 68 study centers in the United States: Lawrence Adler (Glen Burnie, MD), Lenard A. Adler (New York, NY), Don Anderson (Loma Linda, CA), James G. Barbee (New Orleans, LA), Dominic Barberio (Dewitt, MI), Louise Beckett (Oklahoma City, OK), Cynthia A. Berry (Swansea, MA), Robert J. Bielski (Okemos, MI), Steven Bowman (Clearwater, FL), David Brown (Austin, TX), Steven J. Bupp (Tucson, AZ), Cal Cohn (Houston, TX), Bruce Corser (Cincinnati, OH), Henry F. Crabbe (New Haven, CT), Adnan Dahdul (West Springfield, MA), Jeffrey Danziger (Winter Park, FL), Charles DeBattista (Stanford, CA), G. Michael Dempsey (Albuquerque, NM), Michael W. DePriest (Las Vegas, NV), John M. Downs (Memphis, TN), Steven M. Eisen (Philadelphia, PA), Joseph C. Fanelli (Oakbrook, IL), James M. Ferguson (Salt Lake City, UT), John W. Goethe (Hartford, CT), James Grimm (Eugene, OR), Daniel Grosz (Northridge, CA), Frances Haines (East Providence, RI), Barbara A. Harris (Cave Creek, AZ), James Hartford (Cincinnati, OH), Radwan Haykal (Memphis, TN), Peter Holland (Boca Raton, FL), David Houlihan (Dubuque, IA), Robert H. Howland (Pittsburgh, PA), Geoffrey Hyde (Bend, OR), Ari Kiev (New York, NY), Jeffrey H. Klopper (Duluth, GA), Michael David Lesem (Bellaire, TX), Robert E. Litman (Rockville, MD), Peter D. Londborg (Seattle, WA), Julio C. Machado (Miami, FL), Harris H. McIlwain (Tampa, FL), David Morin (Bristol, TN), Patrick O'Neill (New Orleans, LA), Leslie R. Pedersen Lundt (Boise, ID), B. Ashok Raj (St. Petersburg, FL), Mark H. Rapaport (La Jolla, CA), Robert Riesenberg (Atlanta, GA), Peter M. Ripley (South Yarmouth, MA), Robert Risinger (Milwaukee, WI), Jeffrey Ross (Chicago, IL), David Sack (Cerritos, CA), Elias Sarkis (Gainesville, FL), Frederick W. Schaerf (Fort Myers, FL), Jeffrey S. Simon (Brown Deer, WI), Ward Smith (Portland, OR), Michael Solloway (Jacksonville, FL), Dwight St. Clair (Wichita, KS), Abbey Strauss (Boynton Beach, FL), Richard L. Suddath (Boulder, CO), Leslie Taylor (Middletown, WI), Richard Templeton (Lanham, MD), Kathleen Toups (Lafayette, CA), Mahmoud Wahba (Kansas City, MO), Charles Walker (Tampa, FL), Teresa Walsh (Eugene, OR), Thomas Walshe (Wellesley Hills, MA), Edd L. Wilbanks (Shreveport, LA), Robin Wooten (Lakeland, FL).

Publication (reference): none

Studied period (years):
Date of first enrollment: 8 May 2000
Date of last patient visit: 22 September 2000

Phase of development: III

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

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 774 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 774 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 258 reboxetine-treated patients, 252 placebo-treated patients, and 260 paroxetine-treated patients, for a total of 770 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.

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

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 38,507 or 38,417) 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 38,503 or 38,413) 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.

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

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:
The mean decrease from baseline in the MADRS total score (primary endpoint) was significantly greater in the reboxetine group (-14.5) than in the placebo group (-12.3) at day 56 in the LOCF analysis ($p=0.016$). The mean decrease from baseline in the MADRS total score was also significantly greater in the paroxetine group (-15.3) than in the placebo group (-12.3) at day 56 in the LOCF analysis ($p<0.001$).

The statistically significant difference between the reboxetine and placebo groups on the protocol-specified primary endpoint confirms that the study was successful in achieving the 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. The statistically significant difference between the paroxetine and placebo groups on the protocol-specified primary endpoint (change from baseline in the MADRS total score) confirms that the study population was a valid population in which to assess the antidepressant efficacy of the study medication.

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

The significantly positive results that were observed on the primary (LOCF) analysis of the mean change from baseline in the MADRS total score were supported by significantly positive results on the secondary analyses (OC, ANCOVA, and GEE analyses) of the primary endpoint.

As summarized in the following table, the significantly positive results on the primary endpoint were also supported by significantly positive results on a number of the key secondary measures of antidepressant efficacy, including the mean change from baseline in the HAM-D Item 1 score (which focuses solely on the depressed mood of the patient), in the HAM-D Retardation Cluster score (which focuses on the depressed mood and the associated psychomotor effects of depression), and in the CGI Severity of Illness score. Thus, the antidepressant efficacy of reboxetine was confirmed on a number of different scales, including instrumental rating scales (MADRS and prespecified items/clusters of the HAM-D) and a clinician rating scale (CGI). On all measures of antidepressant efficacy, the results in the reboxetine group were numerically superior to the results in the placebo group, and the pattern of improvement was consistent with an antidepressant effect for reboxetine.

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

	Results by Treatment Group			**P Values**		
	RBX N=258	**PBO N=252**	**PAR N=260**	**Overall**	**RBX vs PBO**	**PAR vs PBO**
Primary Endpoint						
MADRS total score, mean change from baseline	-14.5	-12.3	-15.3	0.0021*	0.0162*	0.0006*
Secondary Endpoints						
Mean Change from Baseline						
HAM-D Item 1	-1.4	-1.2	-1.5	0.0019*	0.0243*	0.0005*
HAM-D Retardation Cluster	-4.1	-3.2	-3.9	0.0021*	0.0013*	0.0043*
CGI Severity of Illness	-1.5	-1.2	-1.5	0.0045*	0.0085*	0.0025*
HAM-D Total Score	-11.0	-10.1	-11.8	0.0506	--	--
% Responders or Remitters						
MADRS Response	53.4	45.2	61.6	0.0018*	0.0672	0.0004*
MADRS Remission	47.5	42.7	54.1	0.0411*	0.2541	0.0133*
HAM-D Response	50.4	45.2	52.9	0.2691	--	--
HAM-D Remission	45.8	42.3	45.0	0.7552	--	--
CGI Global Improvement Response	54.0	49.0	64.0	0.0045*	0.3094	0.0012*

* $p \leq 0.05$

-- 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

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

The results of the OC analyses (a secondary analysis) of the secondary antidepressant efficacy endpoints were similar to the results of the LOCF analyses. A notable difference between the results of these analyses was in the MADRS response rate, which showed a trend toward significance, in favor of reboxetine over placebo, at day 56 in the LOCF analysis (p=0.067); this difference reached statistical significance at day 56 in the OC analysis (p=0.024).

The results from the secondary measures of energy and social function, including the SASS, the MOS SF-36 Social Functioning and Vitality scales, and the MFI General Fatigue subscale, clearly indicate that quality of life improved in all treatment groups during the study. The improvements that were observed in the active treatment groups were numerically superior to the improvement that was observed in the placebo group, although the differences were not statistically significant. The relatively high placebo response may have contributed to the failure to distinguish a statistically significant difference among the 3 treatment groups.

Taken together, the results from this study clearly demonstrate the efficacy of reboxetine for the treatment of patients with depression.

SAFETY RESULTS:
Treatment-emergent signs and symptoms were reported in a slightly higher percentage of patients in the active treatment groups (87.2%; 225/258 in the reboxetine group and 91.5%; 238/260 in the paroxetine group) than in the placebo group (79.8%; 201/252).

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, chills, sweating, vasodilatation, and abnormality of accommodation (primarily blurred vision). In 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, dizziness, somnolence, and sweating. The majority of TESS that were reported by patients in each treatment group were mild to moderate in intensity.

No deaths were reported during this study. Serious TESS were reported in a similar percentage of patients in each of the 3 treatment groups: 1.6% (4/258) of reboxetine-treated patients, 1.2% (3/252) of placebo-treated patients, and 1.5% (4/260) of paroxetine-treated patients.

The percentage of patients who discontinued treatment due to TESS was higher in the paroxetine group (11.9%; 31/260) than in the reboxetine (7.8%; 20/258) or placebo (4.0%; 10/252) groups. The most frequently reported TESS that led to discontinuation of reboxetine treatment was headache, which led to discontinuation of treatment in 1.9% (5/258) of reboxetine-treated patients. The most frequently reported TESS that led to discontinuation of paroxetine treatment was nausea, which led to discontinuation of treatment in 2.3% (6/260) of paroxetine-treated patients.

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

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 97-CRBX-049 and 97-CRBX-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 7.8% (20/258) 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 4.0% (10/252) 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 (1.6%; 4/258) 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 remained at 1.6% (4/258) during week 2 and increased slightly during week 3 (1.9%; 5/258). 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.

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 496 TESS were reported in the reboxetine group (N=258) 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, and the percentage of TESS that were mild in intensity was increased, during the first week of this study (5.8% [29/496] severe; 59.7% [296/496] mild), compared with studies 049 and 050 (11.7% [85/726] severe; 49.2% [357/726] mild). 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.

No statistically significant differences were observed among the treatment groups in the mean change from baseline values for sitting systolic or diastolic blood pressure.

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 the placebo group throughout the study. At the end of the study (day 56), the mean change from baseline pulse rate was +5.7 beats per minute in the reboxetine group, -0.3 beats per minute in the placebo group, and –1.0 beats per minute in the paroxetine group, whereas the mean change from baseline ECG heart rate was +13.5 beats per minute in the reboxetine group, +0.3 beats per minute in the placebo group, and +1.4 beats per minute in the paroxetine group. However, few reboxetine-treated patients (0.8%; 2/248) 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). No statistically significant differences were observed among the treatment groups in the mean change from baseline values for QTc, based on Fridericia's correction method.

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

CONCLUSION:
In conclusion, this phase III, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study demonstrated 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 results on the secondary endpoints further supported the antidepressant efficacy of reboxetine. 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. Overall, the results demonstrate that reboxetine is effective and well-tolerated for the treatment of patients with major depressive disorder.

Date of the report: Issued 3 November 2000; Amended 6 February 2001

TABLE OF CONTENTS

APPENDICES

Study Information

Patient Data Listings

Case Report Forms

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 1-3), a "working protocol," which incorporates Amendments 1 through 3, was provided to the investigators. The copy of the protocol that is provided in Appendix 4 is the "working protocol" that was provided to the investigators.

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.

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 [10]. 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 roughly a quarter of depressions relate predominantly to noradrenergic problems, a quarter 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 [11].

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) [12, 13]. 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. 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 [14], 014 [15], and 091 [16]) and in a long-term, double-blind, placebo-controlled study (protocol 013 [17]). 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] [18]) were noted in one study [15]. 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/2020/0047) was conducted to test the hypothesis that reboxetine is effective for the treatment of depression in a US 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.

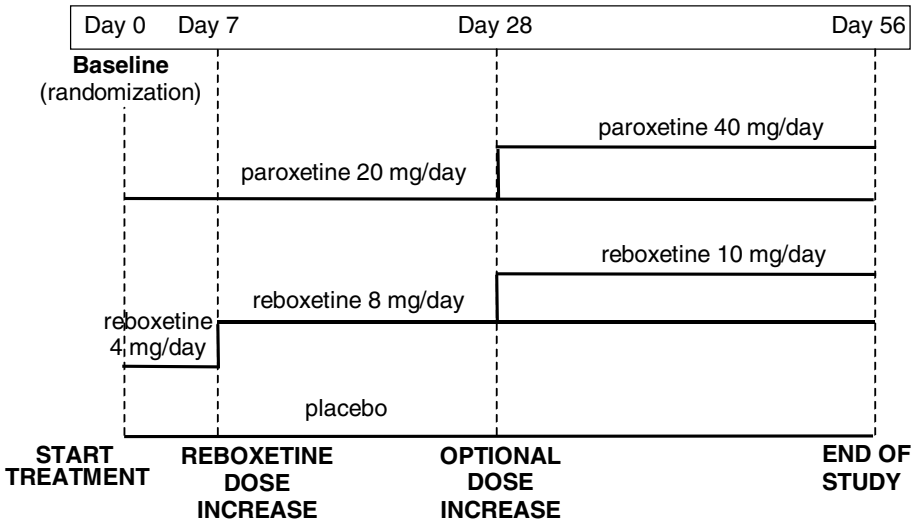
8 METHODS

8.1 Overall Study Design and Plan

This phase III, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study was conducted in 774 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] [19]) 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 [20]. 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 [21, 22, 23, 24].

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 [25] and 97-CRBX-050 [26]) 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)†	38,506 38,416
Paroxetine	40 mg (one 40-mg tablet)	SmithKline Beecham, (repackaged by P&U)†	38,507 38,417
Placebo	--	P&U	38,503 38,413

* 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 [25] and 050 [26]) 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 [27].

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/2020/0047) 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							
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 [28], 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 [21], 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 [20]. 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 [21, 22, 23, 24]. 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 [29] 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 [30] 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 [18] 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 [18]. 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) [18]. 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 [28], 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 [31, 32] 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.
- 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). The specific 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)

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 [33] 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 [25]) 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/2020/0047 were detailed in 4 amendments. The protocol and protocol amendments are in Appendix 4.* 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 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.

* Because of the extensive changes that were made to the protocol before any patients were enrolled in the study (changes detailed in Amendments 1-3), a "working protocol," which incorporates Amendments 1 through 3, was provided to the investigators. The copy of the protocol that is provided in Appendix 4 is the "working protocol" that was provided to the investigators.

8.8.1.2 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 requirements for pharmacokinetic assays and the laboratory assay for platelet serotonin were removed from the study.
- The background and the statistics sections of the protocol were rewritten to support the new primary and secondary objectives of the study.

8.8.1.3 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").

8.8.1.4 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.

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 774 patients were enrolled in the study and were randomized to receive treatment with reboxetine (258 patients), placebo (254 patients), or paroxetine (262 patients). The ITT population, which includes all patients who received at least one dose of study medication, includes 258 reboxetine-treated patients, 252 placebo-treated patients, and 260 paroxetine-treated patients.

The percentage of patients who completed the 8-week treatment period was similar among the treatment groups (73% reboxetine, 77% placebo, and 72% paroxetine). The reasons for study discontinuation are summarized in Table 5.

Table 5. Patient Disposition

	RBX		PBO		PAR	
	n	%*	n	%*	n	%*
Number of patients						
Randomized	258	100.0	254	100.0	262	100.0
Intent to treat†	258	100.0	252	99.2	260	99.2
Completed study	189	73.3	196	77.2	188	71.8
Discontinued study	69	26.7	58	22.8	74	28.2
Reason for discontinuation						
Adverse event	20	7.8	10	3.9	29	11.1
Protocol violation	2	0.8	0	0	1	0.4
Consent withdrawn	15	5.8	12	4.7	14	5.3
Lost to follow-up	29	11.2	23	9.1	29	11.1
Protocol-specific withdrawal criteria	0	0	2	0.8	0	0
Lack of efficacy	2	0.8	10	3.9	0	0
Progression of disease	0	0	1	0.4	1	0.4
Improvement	1	0.4	0	0	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

Adverse events led to discontinuation of treatment* in a higher percentage of paroxetine-treated patients (11.1%; 29/262) than reboxetine- (7.8%; 20/258) or placebo- (3.9%; 10/254) treated patients. (Discontinuations due to adverse events are discussed in Section 9.4.2.3.)

The most common reason for discontinuation of study medication was "lost to follow-up," which occurred in a comparable number of patients in each treatment group: 11.2% (29/258) of the reboxetine-treated patients, 9.1% (23/254) of the placebo-treated patients, and 11.1% (29/262) of the paroxetine-treated patients were lost to follow-up.

Lack of efficacy led to discontinuation of treatment in a higher percentage of placebo-treated patients (3.9%; 10/254) than reboxetine- (0.8%; 2/258) or paroxetine- (0%; 0/262) treated

* 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. Three paroxetine-treated patients (patient nos. 2774, 2884, and 2203) who were included in Table 30 and in Table 38 were not included in Table 5, because their treatment termination records did not indicate that they had discontinued due to adverse events (either because of a CRF error [patient no. 2774], missing data/data-entry error [patient no. 2884], or because the primary reason for discontinuation was something other than an adverse event [patient no. 2203, who discontinued due to progression of disease]). One other paroxetine-treated patient (patient no. 2850) was 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.

patients. All other reasons for discontinuation were generally comparable between the 3 treatment groups.

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 4 patients who were randomized for treatment but who were not included in the ITT group are listed in Appendix 15, Table 11.1.

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	258	11 (4.3)	252	20 (7.9)	260	9 (3.5)
Patient age >65 years	258	0	252	0	260	1 (0.4)†
Dose of study medication exceeding the protocol-specified dosage regimen						
>10 to <12 mg/day RBX or >40 to <50 mg/day PAR	258	29 (11.2)			260	21 (8.1)
≥12 mg/day RBX or ≥50 mg/day PAR	258	12 (4.7)			260	11 (4.2)
Positive urine drug screen‡	255	3 (1.2)	248	4 (1.6)	258	5 (1.9)
Positive serum pregnancy test at screen§	164	0	187	0	158	2 (1.3)

* 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.

† This patient (patient no. 2404) was 66 years of age.

‡ 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.

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

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

Although the protocol specified that female patients who had a positive serum pregnancy test at screen were to be excluded from the study, 2 patients had a positive test at screen and were

enrolled in the study. One of the patients (patient no. 2745) had a miscarriage shortly before the screening visit; the second patient (patient no. 2753) had an elective abortion shortly before the screening visit. Subsequent serum pregnancy tests for these patients were negative. Therefore, in these 2 patients, the positive pregnancy tests were considered to be false-positive test results.

As indicated in Table 6, data from the medication record CRFs indicated that 41 reboxetine-treated patients and 32 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. Of the 23 cases in which patients appeared to have received ≥12 mg/day of reboxetine or ≥50 mg/day of paroxetine, 8 cases represented data-entry errors or CRF errors. In 5 of the remaining cases, the same date was recorded as both the date of last intake in one week and the date of first intake in the following week, resulting in an elevated value for the average daily dose on that date only. The remaining 10 patients who did receive ≥12 mg/day of reboxetine (6 patients) or ≥50 mg/day of paroxetine (4 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	2206	44	13.7
		45-55	16.7
	2312	32-43	22.0
		44-57	20.0
	2357	31-34	15.4
	2470	35	14.4
		36	28.8
		37-40	19.3
	2494	17	13.3
		30	13.1
		31	14.3
		44	13.4
		45	12.9
	2606	45-54	12.7
Paroxetine	2072	29-39	69.1
	2307	29-56	80.0
	2355	29-39	79.2
		40-42	42.9
	2623	33-45	61.5

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

Source: Appendix 14, Table 10.2B

Only 2 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. 2312 in the reboxetine group reported increased somnolence and impotence (duration, 1 day) and patient no. 2623 in the paroxetine group reported agitation (duration, 1 day). 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 774 patients who were randomized into the study, 770 patients (258 reboxetine-treated, 252 placebo-treated, and 260 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

Differences among the treatment groups at screen were noted in the mean age of patients, which was slightly lower in the placebo group (37.1 years) than in the reboxetine (39.3 years) or paroxetine (39.8 years) groups. Likewise, the percentage of male patients was slightly lower in the placebo group (17.9%) than in the reboxetine (26.0%) or paroxetine (28.1%) groups. However, although these differences were statistically significant, they were generally small and are unlikely to be clinically relevant.

Overall, the patient population in this study was reflective of the general population of patients with depression [34]. The patients in the study ranged in age from 18 to 66 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=258	PBO N=252	PAR N=260	P Value†
Age, years	Mean ± SD	39.3 ± 11.6	37.1 ± 11.0	39.8 ± 10.8	0.0137*
	Range	20 - 65	18 - 65	19 - 66	
Sex: n (%)	Male	67 (26.0%)	45 (17.9%)	73 (28.1%)	0.0172*
	Female	191 (74.0%)	207 (82.1%)	187 (71.9%)	
Race: n (%)	White	221 (85.7%)	210 (83.3%)	218 (83.8%)	0.4770
	Black	27 (10.5%)	31 (12.3%)	23 (8.8%)	
	Asian	4 (1.6%)	3 (1.2%)	5 (1.9%)	
	Other	6 (2.3%)	8 (3.2%)	14 (5.4%)	

* $p \leq 0.05$

† 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

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, occupation, living situation, 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 mid- to late twenties at the time of onset of their illness and to have had a mean of 3 to 4 previous depressive episodes. The mean duration of the last depressive episode was 74 weeks in the reboxetine group, 67 weeks in the placebo group, and 89 weeks in the paroxetine group (Table 9).

Table 9. Previous History of Depression

Variable	RBX N=258	PBO N=252	PAR N=260	P Value*
Age (years) at onset of major depression				
Mean ± SD	27.4 ± 13.3	25.5 ± 11.9	27.6 ± 13.0	0.1226
Range	0 - 64	0 - 57	0 - 61	
Number of previous episodes				
Mean ± SD	4.0 ± 9.4	3.1 ± 4.9	3.5 ± 8.0	0.4092
Range	0 - 76	0 - 30	0 - 70	
Approximate duration of last episode (weeks)				
Mean ± SD	74.0 ± 231.0	67.2 ± 120.2	88.9 ± 233.6	0.5291
Range	0 - 3016	0 - 780	0 - 2652	
Previous hospitalization for depression				
No. (%) of patients who were ever hospitalized	34 (13.2%)	35 (13.9%)	27 (10.4%)	0.4450
No. of hospitalizations				0.3459
Mean ± SD	1.7 ± 1.3	1.3 ± 0.9	1.7 ± 1.7	
Range	0 - 5	1 - 5	0 - 8	
Age at first hospitalization				0.8458
Mean ± SD	26.5 ± 13.1	25.9 ± 10.0	27.6 ± 9.8	
Range	1 - 53	12 - 55	9 - 46	

* 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 8.5% (22/258) of reboxetine-treated patients, 6.0% (15/252) of placebo-treated patients, and 8.8% (23/260) of paroxetine-treated patients (Table 10).

Table 10. Previous Use of Psychotropic Medication Other Than Antidepressants

	RBX N=258		PBO N=252		PAR N=260	
	n	%*	n	%*	n	%*
Any psychotropic medication other than antidepressants	35	13.6	29	11.5	39	15.0
Benzodiazepines	22	8.5	15	6.0	23	8.8
Anxiolytics other than benzodiazepines	3	1.2	5	2.0	6	2.3
Anti-psychotics	1	0.4	2	0.8	1	0.4
Lithium	2	0.8	1	0.4	4	1.5
Other	7	2.7	7	2.8	5	1.9

* 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 (>94%) 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 134 weeks in the reboxetine group, 107 weeks in the placebo group, and 133 weeks in the paroxetine group. For the majority of patients in each group, the present episode was judged to represent a recurrence of a similar previous condition (67% in the reboxetine group, 66% in the placebo group, and 66% in the paroxetine group). Most patients (≥70%) in each group had precipitating stress associated with their present episode.

Table 11. Characteristics of the Present Depressive Episode

	RBX N=258	PBO N=252	PAR N=260	P Value†
No. (%) of patients by treatment status immediately prior to screen				
No treatment	249 (96.5%)	238 (94.4%)	257 (98.8%)	0.0222*
Outpatient treatment only	9 (3.5%)	14 (5.6%)	3 (1.2%)	
Approximate duration of present episode				
Mean ± SD (weeks)	133.9 ± 275.6	107.3 ± 186.9	133.2 ± 305.7	0.4254
Range (weeks)	2 - 3120	2 - 1248	2 - 2652	
No. (%) of patients whose present episode was diagnosed as:				
Single episode	84 (32.6%)	86 (34.1%)	89 (34.2%)	0.9036
Recurrent episode	174 (67.4%)	166 (65.9%)	171 (65.8%)	
No. (%) of patients whose present episode was best characterized as:				
Exacerbation of chronic condition	32 (12.4%)	32 (12.7%)	32 (12.3%)	0.9927
Recurrence of similar previous conditions	136 (52.7%)	126 (50.0%)	135 (51.9%)	
Significantly different from any previous conditions	11 (4.3%)	12 (4.8%)	14 (5.4%)	
First occurrence, no previous psychiatric diagnosis	79 (30.6%)	82 (32.5%)	79 (30.4%)	
No. (%) of patients for whom precipitating stress was:				
Absent	65 (25.2%)	70 (27.8%)	62 (23.8%)	0.7868
Probably present	95 (36.8%)	96 (38.1%)	97 (37.3%)	
Definitely present	98 (38.0%)	86 (34.1%)	101 (38.8%)	

* $p \leq 0.05$

† 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, 2.4, 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=258	PBO N=252	PAR N=260	P Value*
MADRS total score				
No. of patients	258	252	260	0.1209
Mean ± SD	29.8 ± 6.1	28.9 ± 5.8	28.8 ± 6.1	
Range	9 - 44	8 - 42	12 - 43	
21-Item HAM-D total score				
No. of patients	258	252	260	0.5515
Mean ± SD	24.2 ± 4.9	23.7 ± 4.8	23.9 ± 5.4	
Range	11 - 39	8 - 37	9 - 37	
CGI Severity of Illness score				
No. of patients	258	251	259	0.5610
Mean ± SD	4.3 ± 0.6	4.3 ± 0.6	4.3 ± 0.6	
Range	2 - 6	3 - 6	3 - 6	
SASS total score				
No. of patients	257	252	260	0.2325
Mean ± SD	27.5 ± 7.4	27.7 ± 7.4	28.6 ± 7.9	
Range	7 - 50	6 - 50	10 - 50	

* 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: 72.9% (188/258) of patients in the reboxetine group, 77.0% (194/252) of patients in the placebo group, and 80.4% (209/260) 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, systemic antihistamines, oral calcium, estrogens, homeopathic medicines, multivitamins, combination nonnarcotic analgesics, nonsteroidal anti-inflammatory agents, oral contraceptives, salicylates, systemic sympathomimetics, 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% (217/258) of patients in the reboxetine group, 87.7% (221/252) of patients in the placebo group, and 89.2% (232/260) 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, antacids, antianxiety medications, systemic antihistamines, oral calcium, estrogens, histamine H2 antagonists, homeopathic medicines, multivitamins, nonbarbiturate sedatives and hypnotics, combination nonnarcotic analgesics, nonsteroidal anti-inflammatory agents, oral contraceptives, salicylates, systemic sympathomimetics, 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 discussed 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 60% of the 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	248	4.0	255	17.7
14	235	7.6	228	19.2
21	224	7.7	222	19.5
28	211	7.8	215	20.1
42	202	9.2	207	32.0
56	191	8.8	187	33.0

* 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 Primary Analysis

The mean decrease from baseline in the MADRS total score was significantly greater in the reboxetine group (-14.5) than in the placebo group (-12.3) at day 56 in the LOCF analysis (p=0.016) (Table 14 and Figure 2). The mean decrease from baseline in the MADRS total score was also significantly greater in the paroxetine group (-15.3) than in the placebo group (-12.3) at day 56 in the LOCF analysis (p<0.001).

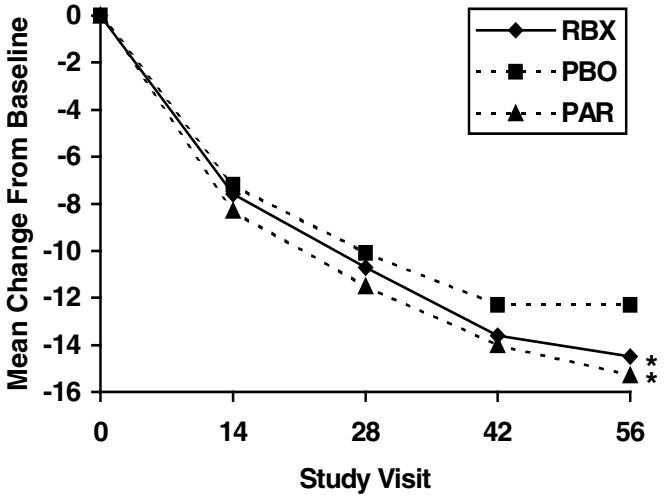
Table 14. Mean Change From Baseline in the MADRS Total Score

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	258	29.8	234	-7.6	238	-10.7	238	-13.6	238	-14.5
		PBO	252	28.9	236	-7.2	239	-10.1	239	-12.3	239	-12.3
		PAR	260	28.8	241	-8.3	241	-11.5	241	-14.0	242	-15.3
	P Values‡	Among Treatments	0.0957		0.2734		0.1556		0.0794		0.0021*	
		RBX vs. PBO	0.0555		0.5340		0.4008		0.1051		0.0162*	
		PAR vs. PBO	0.9208		0.1106		0.0545		0.0304*		0.0006*	
Observed Cases	Mean Change From Baseline	RBX	258	29.8	234	-7.6	211	-11.4	196	-15.3	190	-16.5
		PBO	252	28.9	236	-7.2	223	-10.5	212	-13.1	200	-13.8
		PAR	260	28.8	241	-8.3	215	-12.4	198	-15.9	192	-17.5
	P Values‡	Among Treatments	0.0957		0.2734		0.0435*		0.0064*		0.0016*	
		RBX vs. PBO	0.0555		0.5340		0.2315		0.0171*		0.0160*	
		PAR vs. PBO	0.9208		0.1106		0.0123*		0.0028*		0.0005*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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

All 3 of the treatment groups showed decreases in the MADRS total score from the first on-treatment evaluation (day 14); however, the differences among the treatments did not reach statistical significance in the LOCF analysis until day 56.

Figure 2. Mean Change From Baseline in the MADRS Total Score (LOCF Analysis)



Source: Section 13, Table 4.1C

* $p \leq 0.05$ in pairwise comparison of reboxetine and placebo or paroxetine and placebo

The statistically significant difference between the reboxetine and placebo groups on the protocol-specified primary endpoint confirms that the study was successful in achieving the 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.

The statistically significant difference between the paroxetine and placebo groups on the protocol-specified primary endpoint (change from baseline in the MADRS total score) confirms that the study population was a valid population in which to assess the antidepressant efficacy of the study medication.

9.3.1.2 Secondary Analyses of the Primary Endpoint

9.3.1.2.1 Observed Case Analysis

The results of the secondary OC analysis of the mean change from baseline in the MADRS total score supported the results of the primary LOCF analysis, showing statistically significant differences between reboxetine and placebo and between paroxetine and placebo

at day 56. In contrast to the LOCF analysis, statistically significant differences were observed among the treatment groups in the OC analysis on days 28, 42, and 56, with reboxetine producing a significantly greater decrease in the MADRS total score than placebo on days 42 and 56 and paroxetine producing a significantly greater decrease in the MADRS total score than placebo on days 28, 42, and 56 (Table 14).

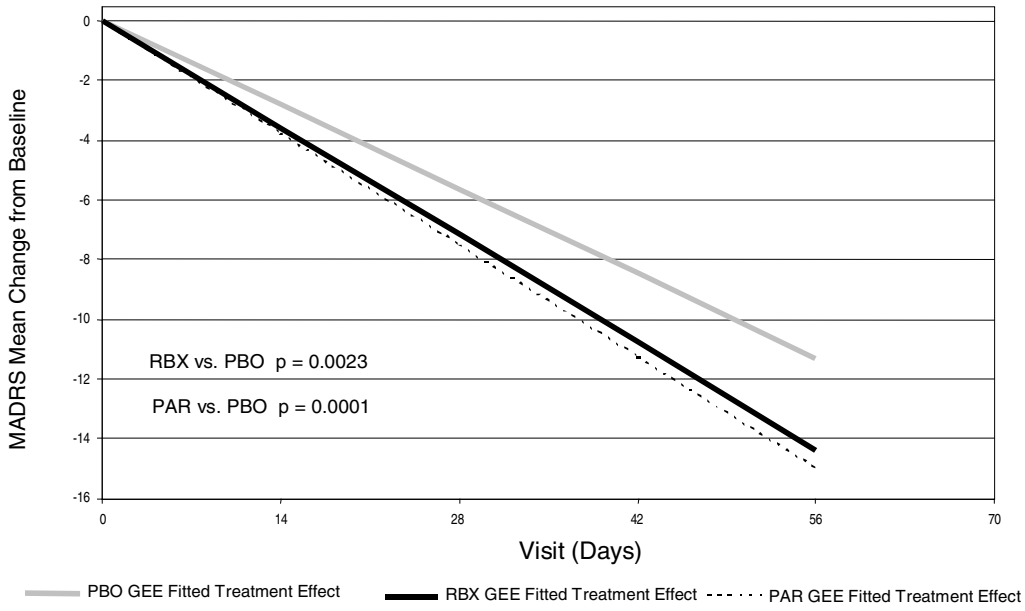
9.3.1.2.2 Analysis of Covariance

When the results of the mean change from baseline in the MADRS total score were adjusted for baseline severity as a covariate, the difference between the reboxetine and placebo groups at day 56 remained statistically significant (p=0.027 in the LOCF analysis and p=0.028 in the OC analysis) (Section 13, Tables 4.4A, 4.4B, and 4.4C). These results thus confirm the treatment effects that were observed in the LOCF and OC analyses.

9.3.1.2.3 Analysis by General 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. 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).

Figure 3. 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

Figure 3 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. The difference between the reboxetine and placebo groups in the average rate of change (ie, slope) was -0.06 points per day (p=0.0023), whereas the difference between the paroxetine and placebo groups in the average rate of change (ie, slope) was -0.07 points per day (p=0.0001). Multiplying the average rate of change per day by the number of days of the study (56), the difference between reboxetine and placebo at day 56 is estimated to be 3.3 points, and the difference between paroxetine and placebo at day 56 is estimated to be 4.0 points. These results thus confirm the antidepressant effects of reboxetine and paroxetine, compared with placebo.

9.3.1.2.4 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=258		PBO N=252		PAR N=260	
	n	Mean Change	n	Mean Change	n	Mean Change
Day 14	24	-3.9	13	-5.2	24	-4.8
Day 28	13	-7.5	10	-6.7	15	-6.4
Day 42	11	-10.8	16	-3.2	11	-12.2

* 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

Among the patients who discontinued reboxetine treatment early, only the patients whose last assessment was on day 14 showed an improvement that was less than the improvement that was observed in the placebo group. However, the paroxetine-treated patients whose last assessment was on day 14 also showed an improvement that was less than the improvement that was observed in the placebo group. It should be noted that, because of the 1-week dose-escalation period, the reboxetine-treated patients had received only 1 week of treatment at the therapeutic dose of 8 mg/day of reboxetine, whereas the paroxetine-treated patients had received 2 weeks of treatment at the therapeutic dose of 20 mg/day, at the time of the day-14 evaluation.

Consistent with the improvements that were observed in the MADRS scores at the last assessment for patients in the active treatment groups who discontinued early, few patients (0.8%; 2/258) in the reboxetine group and no patients in the paroxetine group (0/262) discontinued due to lack of efficacy, whereas 3.9% (10/254) of the patients in the placebo group discontinued due to lack of efficacy (see Section 9.1.1 for a summary of patient disposition).

Overall, the improvements that were observed in the MADRS scores among the patients in the active treatment groups who discontinued early from the study demonstrate a treatment effect (defined as a mean decrease in the MADRS total score at last assessment that was greater in the active treatment group than in the placebo group) in the reboxetine-treated patients whose last assessment was on days 28 or 42 and in the paroxetine-treated patients whose last assessment was on day 42. These results confirm that the antidepressant effects that were observed for reboxetine and paroxetine at day 56 represent true treatment effects that were not biased by early discontinuations due to poor efficacy.

9.3.2 Continuous Secondary Measures of Antidepressant Efficacy

9.3.2.1 HAM-D Total Score

No statistically significant difference was observed among the 3 treatment groups on the mean change from baseline in the HAM-D total score at day 56 in the LOCF analysis (p=0.051) (Table 16). Both of the active treatment groups demonstrated a mean change from baseline in the HAM-D total score that was numerically superior to the mean change that was observed in the placebo group. However, the relatively high placebo response may have contributed to the failure to distinguish a statistically significant difference among the 3 treatment groups on the LOCF analysis.

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	258	24.2	233	-5.9	238	-8.2	238	-10.5	238	-11.0
		PBO	252	23.7	234	-6.5	239	-8.3	239	-9.8	239	-10.1
		PAR	260	23.9	240	-7.2	241	-9.6	241	-11.1	242	-11.8
	P Values‡	Among Treatments	0.3589		0.1257		0.0532		0.1115		0.0506	
		RBX vs. PBO	0.1527		0.3913		0.8307		0.1789		0.1553	
		PAR vs. PBO	0.4973		0.2461		0.0282*		0.0390*		0.0150*	
Observed Cases	Mean Change From Baseline	RBX	258	24.2	233	-5.9	211	-8.7	196	-11.7	189	-12.3
		PBO	252	23.7	234	-6.5	223	-8.6	211	-10.3	200	-11.3
		PAR	260	23.9	240	-7.2	213	-10.3	196	-12.5	192	-13.3
	P Values‡	Among Treatments	0.3589		0.1257		0.0120*		0.0084*		0.0458*	
		RBX vs. PBO	0.1527		0.3913		0.6492		0.0449*		0.1563	
		PAR vs. PBO	0.4973		0.2461		0.0053*		0.0025*		0.0134*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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

In the OC analysis, the mean decrease from baseline in the HAM-D total score was numerically greater in the reboxetine group (-12.3) than in the placebo group (-11.3) at day 56, although the results were not statistically significant. The mean decrease from baseline in the HAM-D total score was significantly greater in the paroxetine group (-13.3) than in the placebo group (-11.3) at day 56 (p=0.013) in the OC analysis.

The lack of a significant difference between the reboxetine and placebo groups on the HAM-D total score at day 56 is not unexpected, given the nonsedating properties of reboxetine. As discussed in Section 9.3.5, the HAM-D total score reflects the

multidimensional properties of the scale. In addition to the core symptoms of depression, the HAM-D awards points for associated symptoms that may or may not be related to depression. For example, the HAM-D rewards treatments that are sedating and penalizes those that are nonsedating, since lower scores on the sleep items (HAM-D Items 4, 5, and 6) count as improvement. This scale thus may work to the advantage of an antidepressant, such as paroxetine, which has sedating properties and to the disadvantage of an antidepressant, such as reboxetine, which is nonsedating.

9.3.2.2 HAM-D Item-1 Score

The mean decrease from baseline in the HAM-D Item 1 (depressed mood) score was significantly greater in the reboxetine group (-1.4) than in the placebo group (-1.2) at day 56 in the LOCF analysis (p=0.024) (Table 17). The mean decrease from baseline in the HAM-D Item 1 score was also significantly greater in the paroxetine group (-1.5) than in the placebo group (-1.2) at day 56 in the LOCF analysis (p<0.001).

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	258	2.7	234	-0.8	238	-1.1	238	-1.3	238	-1.4
		PBO	252	2.6	236	-0.6	239	-0.9	239	-1.1	239	-1.2
		PAR	260	2.6	241	-0.9	241	-1.2	241	-1.4	242	-1.5
	P Values‡	Among Treatments	0.0583		0.0281*		0.0391*		0.0041*		0.0019*	
		RBX vs. PBO	0.0869		0.1064		0.1546		0.1028		0.0243*	
		PAR vs. PBO	0.5737		0.0080*		0.0111*		0.0009*		0.0005*	
Observed Cases	Mean Change From Baseline	RBX	258	2.7	234	-0.8	211	-1.2	196	-1.4	190	-1.6
		PBO	252	2.6	236	-0.6	223	-1.0	211	-1.2	200	-1.3
		PAR	260	2.6	241	-0.9	214	-1.3	199	-1.6	192	-1.7
	P Values‡	Among Treatments	0.0583		0.0281*		0.0128*		0.0002*		0.0045*	
		RBX vs. PBO	0.0869		0.1064		0.1066		0.0422*		0.0374*	
		PAR vs. PBO	0.5737		0.0080*		0.0033*		0.0001*		0.0012*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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

Consistent with the results of the LOCF analysis, the OC analysis also demonstrated that the mean decrease from baseline in the HAM-D Item 1 score was significantly greater in the reboxetine group (-1.6) than in the placebo group (-1.3) at day 56 (p=0.037). The significant difference between the reboxetine and placebo groups was observed at day 42 and continued through day 56 (Table 17).

In contrast to the HAM-D total score, which awards points for associated symptoms that may or may not be related to depression, Item 1 of the HAM-D focuses solely on the depressed mood of the patient. Therefore, the statistically significant differences between the reboxetine and placebo groups on the HAM-D Item 1 score confirm the statistically significant differences that were observed on the protocol-specified primary endpoint (mean change from baseline in the MADRS total score) and provide strong evidence for the antidepressant effect of reboxetine.

9.3.2.3 HAM-D Retardation Cluster Score

The mean decrease from baseline in the HAM-D Retardation Cluster (Items 1, 7, 8, and 14 [29, 30]) score was significantly greater in the reboxetine group (-4.1) than in the placebo group (-3.2) at day 56 in the LOCF analysis (p=0.001) (Table 18). The mean decrease from baseline in the HAM-D Retardation Cluster score was also significantly greater in the paroxetine group (-3.9) than in the placebo group (-3.2) at day 56 in the LOCF analysis (p=0.004).

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	258	7.8	234	-2.1	238	-3.0	238	-3.7	238	-4.1
		PBO	252	7.6	236	-1.8	239	-2.6	239	-3.1	239	-3.2
		PAR	260	7.6	241	-2.0	241	-2.9	241	-3.5	242	-3.9
	P Values‡	Among Treatments	0.1360		0.5138		0.1234		0.0861		0.0021*	
		RBX vs. PBO	0.0902		0.2827		0.0650		0.0335*		0.0013*	
		PAR vs. PBO	0.9590		0.3651		0.0910		0.1090		0.0043*	
Observed Cases	Mean Change From Baseline	RBX	258	7.8	234	-2.1	211	-3.2	196	-4.1	190	-4.6
		PBO	252	7.6	236	-1.8	223	-2.7	211	-3.3	200	-3.6
		PAR	260	7.6	241	-2.0	214	-3.1	199	-3.9	192	-4.5
	P Values‡	Among Treatments	0.1360		0.5138		0.0619		0.0156*		0.0011*	
		RBX vs. PBO	0.0902		0.2827		0.0518		0.0103*		0.0012*	
		PAR vs. PBO	0.9590		0.3651		0.0347*		0.0165*		0.0015*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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

Consistent with the results of the LOCF analysis, the OC analysis also demonstrated that the mean decrease from baseline in the HAM-D Retardation Cluster score was significantly greater in the reboxetine group (-4.6) than in the placebo group (-3.6) at day 56 (p=0.001).

The significant difference between the reboxetine and placebo groups was observed at day 42 and continued through day 56 (Table 18).

The HAM-D Retardation Cluster (Items 1, 7, 8, and 14) represents a symptom cluster that is primarily focussed on the depressed mood and the associated psychomotor effects of depression. The statistically significant differences between the reboxetine and placebo groups on the HAM-D Retardation Cluster score confirm the statistically significant differences that were observed on the HAM-D Item 1 score and on the protocol-specified primary endpoint (mean change from baseline in the MADRS total score). Taken together, these results provide strong evidence for the antidepressant effect of reboxetine.

9.3.2.4 CGI Severity of Illness

The mean decrease from baseline in the CGI Severity of Illness score was significantly greater in the reboxetine group (-1.5) than in the placebo group (-1.2) at day 56 in the LOCF analysis (p=0.009) (Table 19). The mean decrease from baseline in the CGI Severity of Illness score was also significantly greater in the paroxetine group (-1.5) than in the placebo group (-1.2) at day 56 in the LOCF analysis (p=0.003).

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	258	4.3	234	-0.6	238	-0.9	238	-1.2	238	-1.5
		PBO	251	4.3	235	-0.5	238	-0.8	238	-1.1	238	-1.2
		PAR	259	4.3	241	-0.7	241	-1.0	241	-1.4	242	-1.5
	P Values‡	Among Treatments	0.4408		0.1637		0.0299*		0.0125*		0.0045*	
		RBX vs. PBO	0.2203		0.4373		0.2434		0.1441		0.0085*	
		PAR vs. PBO	0.7589		0.0587		0.0082*		0.0031*		0.0025*	
Observed Cases	Mean Change From Baseline	RBX	258	4.3	234	-0.6	211	-1.0	196	-1.4	189	-1.7
		PBO	251	4.3	235	-0.5	222	-0.8	212	-1.2	199	-1.4
		PAR	259	4.3	241	-0.7	216	-1.1	199	-1.6	192	-1.7
	P Values‡	Among Treatments	0.4408		0.1637		0.0181*		0.0012*		0.0092*	
		RBX vs. PBO	0.2203		0.4373		0.2405		0.0799		0.0103*	
		PAR vs. PBO	0.7589		0.0587		0.0048*		0.0002*		0.0063*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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

Consistent with the results of the LOCF analysis, the OC analysis also demonstrated that the mean decrease from baseline in the CGI Severity of Illness score was significantly greater in the reboxetine group (-1.7) than in the placebo group (-1.4) at day 56 (p=0.010).

The statistically significant differences between the reboxetine and placebo groups on the CGI Severity of Illness score confirm the statistically significant differences that were observed on the HAM-D Item 1 score, the HAM-D Retardation Cluster score, and the MADRS total score. Together, these results provide strong evidence for the antidepressant effect of reboxetine.

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

No statistically significant differences were observed among the 3 treatment groups in the HAM-D response rate at day 56 in either the LOCF (p=0.269) or OC analyses (p=0.111) (Table 20). Both of the active treatment groups demonstrated a HAM-D response rate that was numerically superior to the response rate that was observed in the placebo group. However, the relatively high placebo response may have contributed to the failure to distinguish a statistically significant difference among the 3 treatment groups.

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	18.9	83	34.9	110	46.2	120	50.4
		PBO	49	20.9	81	33.9	102	42.7	108	45.2
		PAR	61	25.4	95	39.4	120	49.8	128	52.9
	P Values‡	Among Treatments	0.1518		0.4103		0.3605		0.2691	
		RBX vs. PBO	0.5239		0.6800		0.4546		0.2550	
		PAR vs. PBO	0.2257		0.2039		0.1509		0.1123	
Observed Cases	Response rate†	RBX	44	18.9	79	37.4	99	50.5	109	57.7
		PBO	49	20.9	79	35.4	95	45.0	100	50.0
		PAR	61	25.4	92	43.2	112	57.1	116	60.4
	P Values‡	Among Treatments	0.1518		0.2130		0.0524		0.1107	
		RBX vs. PBO	0.5239		0.5642		0.3106		0.1631	
		PAR vs. PBO	0.2257		0.0971		0.0138*		0.0452*	

* $p \leq 0.05$

† 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.

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

No statistically significant differences were observed among the 3 treatment groups in the HAM-D remission rate at day 56 in either the LOCF (p=0.755) or OC analyses (p=0.589) (Table 21). Both of the active treatment groups demonstrated a HAM-D remission rate that was numerically superior to the remission rate that was observed in the placebo group. However, the relatively high placebo response may have contributed to the failure to distinguish a statistically significant difference among the 3 treatment groups.

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	38	16.3	61	25.6	99	41.6	109	45.8
		PBO	37	15.8	68	28.5	87	36.4	101	42.3
		PAR	50	20.8	79	32.8	101	41.9	109	45.0
	P Values‡	Among Treatments	0.2175		0.2700		0.4092		0.7552	
		RBX vs. PBO	0.9863		0.6232		0.2510		0.4527	
		PAR vs. PBO	0.1437		0.2805		0.2431		0.6148	
Observed Cases	Remission rate†	RBX	38	16.3	59	28.0	90	45.9	99	52.4
		PBO	37	15.8	66	29.6	81	38.4	94	47.0
		PAR	50	20.8	77	36.2	95	48.5	100	52.1
	P Values‡	Among Treatments	0.2175		0.1614		0.1037		0.5891	
		RBX vs. PBO	0.9863		0.7769		0.1450		0.3960	
		PAR vs. PBO	0.1437		0.1280		0.0424*		0.4336	

* $p \leq 0.05$

† 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.

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

The MADRS response rate showed a trend toward significance, in favor of reboxetine over placebo, at day 56 in the LOCF analysis (p=0.067); this difference reached statistical significance at day 56 in the OC analysis (p=0.024) (Table 22). The MADRS response rate was significantly greater in the paroxetine group than in the placebo group at day 56 in both the LOCF and OC analyses.

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	42	17.9	74	31.1	111	46.6	127	53.4
		PBO	46	19.5	79	33.1	104	43.5	108	45.2
		PAR	61	25.3	100	41.5	128	53.1	149	61.6
	P Values‡	Among Treatments	0.0622		0.0346*		0.1073		0.0018*	
		RBX vs. PBO	0.6044		0.6786		0.5150		0.0672	
		PAR vs. PBO	0.0913		0.0559		0.0374*		0.0004*	
Observed Cases	Response rate†	RBX	42	17.9	73	34.6	102	52.0	118	62.1
		PBO	46	19.5	78	35.0	99	46.7	100	50.0
		PAR	61	25.3	94	43.7	117	59.1	134	69.8
	P Values‡	Among Treatments	0.0622		0.0559		0.0416*		0.0005*	
		RBX vs. PBO	0.6044		0.9476		0.3630		0.0243*	
		PAR vs. PBO	0.0913		0.0480*		0.0125*		0.0002*	

* $p \leq 0.05$

† 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.

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

The MADRS remission rate was numerically greater in the reboxetine group than in the placebo group, although the differences were not statistically significant in either the OC or LOCF analyses at day 56 (Table 23). The MADRS remission rate was significantly greater in the paroxetine group than in the placebo group at day 56 in both the LOCF and OC analyses.

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	43	18.4	72	30.3	99	41.6	113	47.5
		PBO	42	17.8	65	27.2	97	40.6	102	42.7
		PAR	48	19.9	85	35.3	113	46.9	131	54.1
	P Values‡	Among Treatments	0.7663		0.1359		0.3304		0.0411*	
		RBX vs. PBO	0.9106		0.4190		0.8560		0.2541	
		PAR vs. PBO	0.5227		0.0514		0.1659		0.0133*	
Observed Cases	Remission rate†	RBX	43	18.4	71	33.6	89	45.4	103	54.2
		PBO	42	17.8	63	28.3	93	43.9	96	48.0
		PAR	48	19.9	82	38.1	105	53.0	121	63.0
	P Values‡	Among Treatments	0.7663		0.0574		0.1263		0.0150*	
		RBX vs. PBO	0.9106		0.2247		0.8422		0.2478	
		PAR vs. PBO	0.5227		0.0194*		0.0626		0.0057*	

* $p \leq 0.05$

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

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

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

The CGI Global Improvement response rate was numerically greater in the reboxetine group than in the placebo group, although the differences were not statistically significant in either the OC or LOCF analyses at day 56 (Table 24). The CGI Global Improvement response rate was significantly greater in the paroxetine group than in the placebo group at day 56 in both the LOCF and OC analyses.

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	48	20.5	82	34.6	123	51.9	128	54.0
		PBO	52	22.0	77	32.2	111	46.4	117	49.0
		PAR	69	28.6	108	44.8	140	58.1	155	64.0
	P Values‡	Among Treatments	0.0710		0.0109*		0.0536		0.0045*	
		RBX vs. PBO	0.6308		0.6003		0.3293		0.3094	
		PAR vs. PBO	0.0807		0.0052*		0.0161*		0.0012*	
Observed Cases	Response rate†	RBX	48	20.5	79	37.6	114	58.2	116	61.4
		PBO	52	22.0	75	33.6	107	50.2	109	54.5
		PAR	69	28.6	103	47.7	131	65.8	140	72.9
	P Values‡	Among Treatments	0.0710		0.0046*		0.0064*		0.0007*	
		RBX vs. PBO	0.6308		0.4380		0.1683		0.1651	
		PAR vs. PBO	0.0807		0.0017*		0.0016*		0.0003*	

* $p \leq 0.05$

† 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.

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

No statistically significant differences were observed among the 3 treatment groups in the mean change from baseline in the SASS total score at day 56 in either the LOCF (p=0.174) or OC analyses (p=0.315) (Table 25). Both of the active treatment groups demonstrated a mean change from baseline in the SASS total score that was numerically superior to the mean change that was observed in the placebo group (increasing scores indicate improvement).

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	257	27.5	234	3.3	238	4.8	238	6.6	238	7.3
		PBO	252	27.7	236	2.4	239	3.9	239	5.6	239	6.1
		PAR	260	28.6	240	3.2	240	5.2	240	6.6	241	7.3
	P Values‡	Among Treatments	0.1464		0.1887		0.1016		0.2216		0.1743	
		RBX vs. PBO	0.7336		0.0935		0.1229		0.1145		0.1000	
		PAR vs. PBO	0.1357		0.1417		0.0400*		0.1572		0.1114	
Observed Cases	Mean Change From Baseline	RBX	257	27.5	234	3.3	210	5.0	196	7.0	189	8.2
		PBO	252	27.7	236	2.4	222	4.0	212	5.9	200	6.9
		PAR	260	28.6	240	3.2	216	5.6	199	7.3	192	8.2
	P Values‡	Among Treatments	0.1464		0.1887		0.0481*		0.1397		0.3148	
		RBX vs. PBO	0.7336		0.0935		0.1776		0.1874		0.2085	
		PAR vs. PBO	0.1357		0.1417		0.0140*		0.0532		0.1708	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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

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=0.158) or OC analyses (p=0.083) (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	255	17.39	231	-1.92	236	-2.85	236	-3.65	236	-3.92
		PBO	251	17.17	233	-1.85	238	-2.43	238	-3.19	238	-3.33
		PAR	259	16.95	236	-1.76	239	-2.75	239	-3.30	240	-3.52
	P Values‡	Among Treatments	0.0881		0.8653		0.2400		0.3337		0.1577	
		RBX vs. PBO	0.2074		0.6069		0.1330		0.1395		0.0551	
		PAR vs. PBO	0.3560		0.9015		0.1558		0.5128		0.2878	
Observed Cases	Mean Change From Baseline	RBX	255	17.39	231	-1.92	206	-3.17	193	-4.07	187	-4.57
		PBO	251	17.17	233	-1.85	221	-2.52	207	-3.38	199	-3.62
		PAR	259	16.95	236	-1.76	214	-3.12	195	-3.88	190	-4.21
	P Values‡	Among Treatments	0.0881		0.8653		0.0539		0.1834		0.0834	
		RBX vs. PBO	0.2074		0.6069		0.0478*		0.0843		0.0296*	
		PAR vs. PBO	0.3560		0.9015		0.0297*		0.1631		0.1320	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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=0.300) or OC analyses (p=0.488) (Table 27). Both of the active treatment groups demonstrated a mean change from baseline that was numerically superior to the mean change that was observed in the placebo group (increasing scores indicate improvement).

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	256	33.89	234	17.70	239	21.31	239	26.32	239	27.58
		PBO	252	34.92	236	14.41	239	20.35	239	23.90	239	23.85
		PAR	258	39.20	238	16.74	239	20.94	240	25.68	241	25.63
	P Values‡	Among Treatments	0.0091*		0.4191		0.6998		0.3491		0.2996	
		RBX vs. PBO	0.4014		0.1917		0.4598		0.1857		0.1211	
		PAR vs. PBO	0.0336*		0.4168		0.4700		0.2404		0.4025	
Observed Cases	Mean Change From Baseline	RBX	256	33.89	234	17.70	209	22.71	197	29.42	190	30.85
		PBO	252	34.92	236	14.51	222	21.68	210	25.65	200	26.63
		PAR	258	39.20	238	16.74	214	22.12	199	27.53	191	28.82
	P Values‡	Among Treatments	0.0091*		0.4191		0.6310		0.2078		0.4877	
		RBX vs. PBO	0.4014		0.1917		0.4799		0.0829		0.2327	
		PAR vs. PBO	0.0336*		0.4168		0.3629		0.2482		0.6124	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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

The differences between the treatment groups at baseline, when the paroxetine group showed a mean total score (39.20) that was higher than the mean total scores in the reboxetine (33.89) or placebo (34.92) groups (p=0.009), may have contributed to the difficulty of demonstrating a statistically significant difference among the treatment groups in the mean change from baseline in the total score of the MOS SF-36 Social Functioning scale at day 56.

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=0.170) or OC analyses (p=0.255) (Table 28). Both of the active treatment groups demonstrated a mean change from baseline that was numerically superior to the mean change that was observed in the placebo group (increasing scores indicate improvement).

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	256	19.36	233	13.05	237	18.88	237	25.72	237	26.35
		PBO	252	19.90	236	12.82	239	16.92	239	21.17	239	21.44
		PAR	259	21.87	237	13.46	238	19.39	239	23.97	240	24.71
	P Values‡	Among Treatments	0.1178		0.9693		0.4388		0.2018		0.1704	
		RBX vs. PBO	0.8159		0.9827		0.4974		0.0831		0.0785	
		PAR vs. PBO	0.0978		0.8210		0.1998		0.2122		0.1456	
Observed Cases	Mean Change From Baseline	RBX	256	19.36	233	13.05	208	20.43	194	28.12	188	29.47
		PBO	252	19.90	236	12.82	221	17.76	210	22.90	199	24.02
		PAR	259	21.87	237	13.46	212	21.11	198	26.77	190	27.95
	P Values‡	Among Treatments	0.1178		0.9693		0.2194		0.1646		0.2546	
		RBX vs. PBO	0.8159		0.9827		0.4291		0.0877		0.1276	
		PAR vs. PBO	0.0978		0.8210		0.0819		0.1211		0.1876	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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 was successful in meeting 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. The fact that similar results were observed for the active comparator paroxetine confirms that the study population was a valid population in which to assess the antidepressant efficacy of the study medication.

The significantly positive results that were observed on the primary (LOCF) analysis of the mean change from baseline in the MADRS total score were supported by significantly positive results on the secondary analyses (OC, ANCOVA, and GEE analyses) of the primary endpoint. Furthermore, even among the patients in the active treatment groups who discontinued early from the study, a treatment effect (defined as a mean decrease in the MADRS total score at last assessment that was greater in the active treatment group than in the placebo group) was observed in the reboxetine-treated patients whose last assessment was on days 28 or 42 and in the paroxetine-treated patients whose last assessment was on day 42. Thus, the antidepressant effects that were observed for reboxetine and paroxetine at day 56 represent true treatment effects that were not biased by early discontinuations due to poor efficacy.

As summarized in Table 29, the significantly positive results on the primary endpoint were also supported by significantly positive results on a number of the key secondary measures of antidepressant efficacy, including the mean change from baseline in the HAM-D Item 1 score (which focuses solely on the depressed mood of the patient), in the HAM-D Retardation Cluster score (which focuses on the depressed mood and the associated psychomotor effects of depression), and in the CGI Severity of Illness score. Thus, the antidepressant efficacy of reboxetine was confirmed on a number of different scales, including instrumental rating scales (MADRS and prespecified items/clusters of the HAM-D) and a clinician rating scale (CGI).

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

	Results by Treatment Group			P Values		
	RBX N=258	PBO N=252	PAR N=260	Overall	RBX vs PBO	PAR vs PBO
Primary Endpoint						
MADRS total score, mean change from baseline	-14.5	-12.3	-15.3	0.0021*	0.0162*	0.0006*
Secondary Endpoints						
Mean Change From Baseline						
HAM-D Item 1	-1.4	-1.2	-1.5	0.0019*	0.0243*	0.0005*
HAM-D Retardation Cluster	-4.1	-3.2	-3.9	0.0021*	0.0013*	0.0043*
CGI Severity of Illness	-1.5	-1.2	-1.5	0.0045*	0.0085*	0.0025*
HAM-D Total Score	-11.0	-10.1	-11.8	0.0506	--	--
% Responders or Remitters						
MADRS Response	53.4	45.2	61.6	0.0018*	0.0672	0.0004*
MADRS Remission	47.5	42.7	54.1	0.0411*	0.2541	0.0133*
HAM-D Response	50.4	45.2	52.9	0.2691	--	--
HAM-D Remission	45.8	42.3	45.0	0.7552	--	--
CGI Global Improvement Response	54.0	49.0	64.0	0.0045*	0.3094	0.0012*

* $p \leq 0.05$

-- 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

The results of the other secondary antidepressant efficacy endpoints, which include the HAM-D total score, the HAM-D response and remission rates, the MADRS response and remission rates, and the CGI Global Improvement response rate, also support the results of the primary efficacy endpoint. Although the differences between reboxetine and placebo were not statistically significant on the LOCF analyses of these endpoints, in all cases the results in the reboxetine group were numerically superior to the results in the placebo group, and the pattern of improvement was consistent with an antidepressant effect for reboxetine.

The results of the OC analyses (a secondary analysis) of the secondary antidepressant efficacy endpoints were similar to the results of the LOCF analyses. A notable difference between the results of these analyses was in the MADRS response rate, which showed a trend toward significance, in favor of reboxetine over placebo, at day 56 in the LOCF analysis (p=0.067); this difference reached statistical significance at day 56 in the OC analysis (p=0.024).

Published data and expert opinion support the use of the MADRS as a sensitive measurement of symptom change and antidepressant drug effect in clinical trials [21]. In the MADRS, categories of degree are precisely described, items are restricted to only those symptoms that

are considered to be the core symptoms of depressive syndromes, and items representing somatic complaints are reduced [20]. The superior ability of the MADRS over the HAM-D to distinguish between subjects who are likely to experience somatic side effects from treatment and those who are less likely to experience somatic side effects have been demonstrated in several trials [21, 22, 23, 24, 35]. The results of this study also confirm the choice of the MADRS as the better scale for assessing the antidepressant efficacy of a nonsedating drug, such as reboxetine.

Although no significant differences were observed between the reboxetine and placebo groups on the mean change from baseline in the HAM-D total score, this lack of a significant difference was not unexpected, given the nonsedating properties of reboxetine. The HAM-D was primarily designed to measure the severity of depression [36, 29, 37, 38]. Although it is widely used in clinical trials, it has never been established that the HAM-D total score, which reflects the multidimensional properties of the scale, is a reliable index of symptom status or change [39, 40, 41, 42, 43, 44]. In addition to the core symptoms of depression, the HAM-D awards points for associated symptoms that may or may not be related to depression. For example, the HAM-D rewards treatments that are sedating and penalizes those that are nonsedating, since lower scores on the sleep items (HAM-D Items 4, 5, and 6) count as improvement. This scale thus works to the advantage of an antidepressant, such as paroxetine, which has sedating properties and to the disadvantage of an antidepressant, such as reboxetine, which is nonsedating.

The results from the secondary measures of energy and social function, including the SASS, the MOS SF-36 Social Functioning and Vitality scales, and the MFI General Fatigue subscale, clearly indicate that quality of life improved in all treatment groups during the study. The improvements that were observed in the active treatment groups were numerically superior to the improvement that was observed in the placebo group, although the differences were not statistically significant. The relatively high placebo response may have contributed to the failure to distinguish a statistically significant difference among the 3 treatment groups.

Taken together, the results from this study clearly demonstrate the efficacy of reboxetine for the treatment of patients with depression.

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 slightly higher percentage of patients in the active treatment groups (87.2% in the reboxetine group and 91.5% in the paroxetine group) than in the placebo group (79.8%). The percentage of patients who discontinued due to TESS was higher in the paroxetine group (11.9%) than in the reboxetine (7.8%) or placebo (4.0%) groups. 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=258		PBO N=252		PAR N=260	
	n	%	n	%	n	%
Patients with at least one TESS	225	87.2	201	79.8	238	91.5
Drug-related*	206	79.8	167	66.3	214	82.3
Serious	4	1.6	3	1.2	4	1.5
Patients who discontinued due to TESS	20	7.8	10	4.0	31	11.9

* 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=258		PBO N=252		PAR N=260	
	n	%	n	%	n	%
Patients with at least one TESS	**225**	**87.2**	**201**	**79.8**	**238**	**91.5**
Digestive	168	65.1	108	42.9	153	58.8
Nervous	140	54.3	84	33.3	153	58.8
Body	123	47.7	118	46.8	128	49.2
Skin	61	23.6	25	9.9	35	13.5
Urogenital	45	17.4	28	11.1	41	15.8
Cardiovascular	38	14.7	13	5.2	25	9.6
Special Senses	35	13.6	14	5.6	17	6.5
Respiratory	26	10.1	30	11.9	26	10.0
Musculo-skeletal	10	3.9	6	2.4	6	2.3
Metabolic and nutritional	6	2.3	7	2.8	6	2.3
Hemic and lymphatic	4	1.6	2	0.8	2	0.8
Endocrine	0	0	1	0.4	0	0

* 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=258		PBO N=252		PAR N=260	
	n	%	n	%	n	%
DIGESTIVE						
Dry mouth	110	42.6	34	13.5	53	20.4
Constipation	65	25.2	14	5.6	31	11.9
Nausea	35	13.6	31	12.3	72	27.7
Anorexia	28	10.9	2	0.8	19	7.3
Diarrhea	14	5.4	36	14.3	38	14.6
Dyspepsia	14	5.4	10	4.0	12	4.6
Vomiting	6	2.3	9	3.6	10	3.8
Flatulence	5	1.9	8	3.2	8	3.1
Increased appetite	5	1.9	7	2.8	2	0.8
Tooth disorder	5	1.9	6	2.4	1	0.4
Eructation	3	1.2	1	0.4	0	0
Gastroenteritis	3	1.2	1	0.4	2	0.8
Thirst	2	0.8	2	0.8	3	1.2
NERVOUS						
Insomnia	78	30.2	32	12.7	58	22.3
Dizziness	30	11.6	15	6.0	34	13.1
Somnolence	19	7.4	13	5.2	48	18.5
Anxiety	16	6.2	16	6.3	15	5.8
Nervousness	15	5.8	9	3.6	14	5.4
Paresthesia	10	3.9	4	1.6	4	1.5
Thinking abnormal	10	3.9	4	1.6	3	1.2
Hypertonia	9	3.5	2	0.8	4	1.5
Agitation	6	2.3	2	0.8	4	1.5
Confusion	5	1.9	0	0	4	1.5
Abnormal dreams	4	1.6	4	1.6	7	2.7
Akathisia	4	1.6	1	0.4	7	2.7
Tremor	4	1.6	4	1.6	7	2.7
Depression	3	1.2	5	2.0	4	1.5
Euphoria	3	1.2	0	0	0	0
Libido decreased	3	1.2	2	0.8	10	3.8
Sleep disorder	3	1.2	2	0.8	5	1.9
Hyperkinesia	2	0.8	0	0	3	1.2
Emotional lability	1	0.4	3	1.2	0	0
Hypesthesia	1	0.4	3	1.2	3	1.2

continued

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

COSTART Body System/Preferred Term*	RBX N=258		PBO N=252		PAR N=260	
	n	%	n	%	n	%
BODY						
Headache	66	25.6	66	26.2	69	26.5
Asthenia	23	8.9	15	6.0	30	11.5
Infection	18	7.0	18	7.1	11	4.2
Chills	14	5.4	3	1.2	7	2.7
Abdominal pain	11	4.3	16	6.3	13	5.0
Accidental injury	11	4.3	9	3.6	7	2.7
Back pain	8	3.1	12	4.8	10	3.8
Chest pain	6	2.3	3	1.2	5	1.9
Pain	6	2.3	6	2.4	6	2.3
Abdomen enlarged	4	1.6	4	1.6	4	1.5
Allergic reaction	3	1.2	0	0	5	1.9
Fever	3	1.2	2	0.8	2	0.8
Reaction unevaluable	3	1.2	1	0.4	6	2.3
Flu syndrome	2	0.8	5	2.0	4	1.5
Generalized edema	1	0.4	7	2.8	0	0
SKIN						
Sweating	40	15.5	10	4.0	26	10.0
Rash	8	3.1	3	1.2	3	1.2
Hair disorder	3	1.2	1	0.4	0	0
Pruritus	3	1.2	4	1.6	4	1.5
UROGENITAL						
Urination impaired	10	3.9	0	0	2	0.8
Impotence	7	2.7	0	0	3	1.2
Urinary retention	7	2.7	1	0.4	2	0.8
Dysmenorrhea	6	2.3	3	1.2	1	0.4
Abnormal ejaculation	5	1.9	0	0	6	2.3
Urinary frequency	5	1.9	5	2.0	6	2.3
Urinary tract infection	4	1.6	2	0.8	2	0.8
Abnormal sexual function	2	0.8	0	0	3	1.2
Vaginal moniliasis	1	0.4	3	1.2	0	0
Anorgasmia	0	0	0	0	12	4.6
Breast pain	0	0	4	1.6	0	0
CARDIOVASCULAR						
Vasodilatation	18	7.0	2	0.8	9	3.5
Palpitation	7	2.7	6	2.4	7	2.7
Tachycardia	5	1.9	2	0.8	2	0.8
SPECIAL SENSES						
Abnormality of accommodation	14	5.4	3	1.2	6	2.3
Taste perversion	6	2.3	2	0.8	5	1.9
Dry eyes	4	1.6	1	0.4	1	0.4

continued

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

COSTART Body System/Preferred Term*	RBX N=258		PBO N=252		PAR N=260	
	n	%	n	%	n	%
Conjunctivitis	3	1.2	0	0	1	0.4
RESPIRATORY						
Pharyngitis	11	4.3	8	3.2	6	2.3
Rhinitis	5	1.9	4	1.6	3	1.2
Sinusitis	5	1.9	5	2.0	8	3.1
Cough increased	3	1.2	3	1.2	4	1.5
Bronchitis	1	0.4	3	1.2	0	0
Dyspnea	1	0.4	3	1.2	5	1.9
Yawn	0	0	3	1.2	5	1.9
MUSCULO-SKELETAL						
Leg cramps	5	1.9	0	0	2	0.8
Myalgia	3	1.2	4	1.6	1	0.4
METABOLIC AND NUTRITIONAL						
Weight loss	3	1.2	0	0	3	1.2
Weight gain	0	0	4	1.6	0	0

* 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, chills, sweating, vasodilatation, and abnormality of accommodation (primarily blurred vision).

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, dizziness, somnolence, 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 16.7% (43/258) of the patients in the reboxetine group, in 11.5% (29/252) of the patients in the placebo group, and in 18.8% (49/260) 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=258 n (%)		PBO N=252 n (%)		PAR N=260 n (%)	
	Mild/Mod	Severe	Mild/Mod	Severe	Mild/Mod	Severe
Patients with at least one TESS	**182 (70.5)**	**43 (16.7)**	**172 (68.3)**	**29 (11.5)**	**189 (72.7)**	**49 (18.8)**
DIGESTIVE						
Dry mouth	106 (41.1)	4 (1.6)	34 (13.5)	0	49 (18.8)	4 (1.5)
Constipation	60 (23.3)	5 (1.9)	13 (5.2)	1 (0.4)	27 (10.4)	4 (1.5)
Nausea	35 (13.6)	0	31 (12.3)	0	62 (23.9)	10 (3.8)
Anorexia	28 (10.9)	0	2 (0.8)	0	18 (7.0)	1 (0.4)
Diarrhea	14 (5.4)	0	34 (13.5)	2 (0.8)	34 (13.1)	4 (1.5)
Dyspepsia	14 (5.4)	0	10 (4.0)	0	11 (4.2)	1 (0.4)
NERVOUS						
Insomnia	64 (24.8)	14 (5.4)	26 (10.3)	6 (2.4)	53 (20.4)	5 (1.9)
Dizziness	30 (11.6)	0	15 (6.0)	0	28 (10.8)	6 (2.3)
Somnolence	18 (7.0)	1 (0.4)	13 (5.2)	0	45 (17.3)	3 (1.2)
Anxiety	15 (5.8)	1 (0.4)	13 (5.2)	3 (1.2)	13 (5.0)	2 (0.8)
Nervousness	13 (5.0)	2 (0.8)	7 (2.8)	2 (0.8)	10 (3.8)	4 (1.5)
BODY						
Headache	60 (23.3)	6 (2.3)	60 (23.8)	6 (2.4)	60 (23.1)	9 (3.5)
Asthenia	22 (8.5)	1 (0.4)	14 (5.6)	1 (0.4)	28 (10.8)	2 (0.8)
Infection	16 (6.2)	2 (0.8)	17 (6.7)	1 (0.4)	11 (4.2)	0
Chills	14 (5.4)	0	3 (1.2)	0	6 (2.3)	1 (0.4)
Abdominal pain	10 (3.9)	1 (0.4)	14 (5.6)	2 (0.8)	11 (4.2)	2 (0.8)
SKIN						
Sweating	35 (13.6)	5 (1.9)	10 (4.0)	0	24 (9.2)	2 (0.8)
CARDIOVASCULAR						
Vasodilatation	18 (7.0)	0	1 (0.4)	1 (0.4)	8 (3.1)	1 (0.4)
SPECIAL SENSES						
Abnormality of accommodation	13 (5.0)	1 (0.4)	3 (1.2)	0	6 (2.3)	0

* 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 15.

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

	Week 1*			Weeks 2-8*		
	RBX N=258	PBO N=252	PAR N=260	RBX N=258	PBO N=252	PAR N=260
Total number of TESS; n (%)†						
Mild	296 (59.7)	120 (60.0)	199 (49.9)	278 (49.2)	271 (58.4)	306 (54.4)
Moderate	171 (34.5)	68 (34.0)	155 (38.8)	245 (43.4)	161 (34.7)	210 (37.3)
Severe	29 (5.8)	12 (6.0)	45 (11.3)	42 (7.4)	31 (6.7)	47 (8.3)
Not reported	0	0	0	0	1 (0.2)	0
Total	496 (100)	200 (100)	399 (100)	565 (100)	464 (100)	563 (100)
Percentage of patients with at least one TESS; n (%)‡						
Mild	68 (26.4)	62 (24.6)	72 (27.7)	59 (22.9)	72 (28.6)	59 (22.7)
Moderate	86 (33.3)	43 (17.1)	82 (31.5)	98 (38.0)	79 (31.3)	98 (37.7)
Severe	20 (7.8)	9 (3.6)	21 (8.1)	26 (10.1)	22 (8.7)	31 (11.9)
Total	174 (67.4)	114 (45.2)	175 (67.3)	183 (70.9)	173 (68.7)	188 (72.3)

* 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 group (496) than in the paroxetine (399) or placebo (200) groups. However, the percentage of events that were severe in intensity was higher in the paroxetine group (11.3%; 45/399) than in the reboxetine (5.8%; 29/496) or placebo (6.0%; 12/200) groups during the first week of treatment.

The percentage of patients who experienced at least one TESS during the first week of treatment was similar among the active treatment groups (67.4% in the reboxetine group and 67.3% in the paroxetine group) and was higher in the active treatment groups than in the placebo group (45.2%). Likewise, the percentage of patients who experienced at least one TESS that was severe in intensity during the first week of treatment was similar among the active treatment groups (7.8% in the reboxetine group and 8.1% in the paroxetine group) and was higher in the active treatment groups than in the placebo group (3.6%).

Among the TESS that started during weeks 2 through 8, both the total number of TESS and the percentage of patients who experienced at least one TESS were similar among the active

treatment groups and were higher in the active treatment groups than in the placebo group (Table 15).

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=191	Male N=67	Female N=207	Male N=45	Female N=187	Male N=73
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one TESS	**165 (86.4)**	**60 (89.6)**	**166 (80.2)**	**35 (77.8)**	**171 (91.4)**	**67 (91.8)**
DIGESTIVE						
Dry mouth	84 (44.0)	26 (38.8)	29 (14.0)	5 (11.1)	39 (20.9)	14 (19.2)
Constipation	45 (23.6)	20 (29.9)	14 (6.8)	0	23 (12.3)	8 (11.0)
Nausea	29 (15.2)	6 (9.0)	30 (14.5)	1 (2.2)	61 (32.6)	11 (15.1)
Anorexia	20 (10.5)	8 (11.9)	1 (0.5)	1 (2.2)	15 (8.0)	4 (5.5)
Diarrhea	10 (5.2)	4 (6.0)	33 (15.9)	3 (6.7)	30 (16.0)	8 (11.0)
Dyspepsia	13 (6.8)	1 (1.5)	7 (3.4)	3 (6.7)	9 (4.8)	3 (4.1)
Flatulence	5 (2.6)	0	7 (3.4)	1 (2.2)	2 (1.1)	6 (8.2)
Tooth disorder	5 (2.6)	0	3 (1.4)	3 (6.7)	0	1 (1.4)
NERVOUS						
Insomnia	57 (29.8)	21 (31.3)	27 (13.0)	5 (11.1)	37 (19.8)	21 (28.8)
Dizziness	20 (10.5)	10 (14.9)	10 (4.8)	5 (11.1)	29 (15.5)	5 (6.8)
Somnolence	16 (8.4)	3 (4.5)	8 (3.9)	5 (11.1)	33 (17.6)	15 (20.5)
Anxiety	11 (5.8)	5 (7.5)	14 (6.8)	2 (4.4)	11 (5.9)	4 (5.5)
Nervousness	8 (4.2)	7 (10.4)	8 (3.9)	1 (2.2)	11 (5.9)	3 (4.1)
Hypertonia	5 (2.6)	4 (6.0)	2 (1.0)	0	4 (2.1)	0
Tremor	4 (2.1)	0	3 (1.4)	1 (2.2)	3 (1.6)	4 (5.5)
Libido decreased	1 (0.5)	2 (3.0)	2 (1.0)	0	2 (1.1)	8 (11.0)
BODY						
Headache	51 (26.7)	15 (22.4)	52 (25.1)	14 (31.1)	54 (28.9)	15 (20.5)
Asthenia	18 (9.4)	5 (7.5)	10 (4.8)	5 (11.1)	22 (11.8)	8 (11.0)
Infection	17 (8.9)	1 (1.5)	15 (7.2)	3 (6.7)	8 (4.3)	3 (4.1)
Chills	12 (6.3)	2 (3.0)	2 (1.0)	1 (2.2)	6 (3.2)	1 (1.4)
Accidental injury	11 (5.8)	0	9 (4.3)	0	5 (2.7)	2 (2.7)
Abdominal pain	8 (4.2)	3 (4.5)	11 (5.3)	5 (11.1)	8 (4.3)	5 (6.8)
Back pain	8 (4.2)	0	11 (5.3)	1 (2.2)	7 (3.7)	3 (4.1)
UROGENITAL						
Urination impaired	1 (0.5)	9 (13.4)	0	0	0	2 (2.7)
Impotence	0	7 (10.4)	0	0	0	3 (4.1)
Urinary retention	0	7 (10.4)	1 (0.5)	0	0	2 (2.7)
Abnormal ejaculation	0	5 (7.5)	0	0	0	6 (8.2)
SKIN						
Sweating	30 (15.7)	10 (14.9)	9 (4.3)	1 (2.2)	16 (8.6)	10 (13.7)
CARDIOVASCULAR						
Vasodilatation	14 (7.3)	4 (6.0)	2 (1.0)	0	8 (4.3)	1 (1.4)

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=191	Male N=67	Female N=207	Male N=45	Female N=187	Male N=73
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
RESPIRATORY						
Pharyngitis	7 (3.7)	4 (6.0)	7 (3.4)	1 (2.2)	5 (2.7)	1 (1.4)
SPECIAL SENSES						
Abnormality of accommodation	9 (4.7)	5 (7.5)	2 (1.0)	1 (2.2)	6 (3.2)	0

* 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, clinically relevant between-gender differences were observed in the frequency of urination impaired, impotence, urinary retention, and abnormal ejaculation, which were reported 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 functional limitation of bladder outflow (ie, urinary retention [10.4%; 7/67], urination impaired [13.4%; 9/67], or urinary frequency [3.0%; 2/67]), only one patient reported more than one of these individual symptoms (patient no. 2466, who reported both urinary frequency and urination impaired). Therefore, the frequency of male reboxetine-treated patients who reported at least one symptom of functional limitation of bladder outflow was 25.4% (17/67) in this study. All reports of urinary retention, urination impaired, or urinary frequency were mild to moderate in intensity, and only one patient in the reboxetine group discontinued treatment due to one of these events (patient no. 2153 discontinued due to impaired urination). In addition, the concomitant medication records indicate that only one of these reboxetine-treated patients received medication (ie, Flomax [tamsulosin hydrochloride], Cardura [doxazosin mesylate], or Hytrin [terazosin hydrochloride]) for the urinary symptoms: patient no. 2752 was treated with tamsulosin hydrochloride for urinary hesitancy. None of the reboxetine-treated male patients were known to have required urinary catheterization for treatment of symptoms of functional limitation of bladder outflow.

Of the TESS that were reported in ≥5% of male or female paroxetine-treated patients, clinically relevant between-gender differences were observed in the frequency of nausea and dizziness, which were reported more frequently in the paroxetine-treated female patients than in the paroxetine-treated male patients, and in the frequency of decreased libido and abnormal ejaculation, which were reported 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 79.8% (206/258) of reboxetine-treated patients, 66.3% (167/252) of placebo-treated patients, and 82.3% (214/260) 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=258		PBO N=252		PAR N=260	
	n	%	n	%	n	%
Patients with at least one drug-related TESS	**206**	**79.8**	**167**	**66.3**	**214**	**82.3**
DIGESTIVE						
Dry mouth	107	41.5	31	12.3	52	20.0
Constipation	61	23.6	14	5.6	26	10.0
Nausea	34	13.2	24	9.5	63	24.2
Anorexia	26	10.1	2	0.8	19	7.3
Dyspepsia	13	5.0	5	2.0	10	3.8
Diarrhea	6	2.3	28	11.1	26	10.0
NERVOUS						
Insomnia	71	27.5	27	10.7	51	19.6
Dizziness	28	10.9	13	5.2	30	11.5
Somnolence	18	7.0	13	5.2	47	18.1
Anxiety	14	5.4	14	5.6	13	5.0
Nervousness	13	5.0	8	3.2	14	5.4
BODY						
Headache	49	19.0	50	19.8	53	20.4
Asthenia	20	7.8	10	4.0	26	10.0
SKIN						
Sweating	39	15.1	10	4.0	23	8.8
CARDIOVASCULAR						
Vasodilatation	14	5.4	2	0.8	8	3.1

* 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, dyspepsia, insomnia, dizziness, 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: nausea, anorexia, dizziness, 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: 1.6% (4/258) of reboxetine-treated patients, 1.2% (3/252) of placebo-treated patients, and 1.5% (4/260) 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=258		PBO N=252		PAR N=260	
	n	%	n	%	n	%
At least one serious TESS	**4**	**1.6**	**3**	**1.2**	**4**	**1.5**
BODY						
Chest pain	2	0.8	0	0	1	0.4
Allergic reaction	1	0.4	0	0	0	0
Headache†	1	0.4	0	0	0	0
Abdominal pain	0	0	0	0	1	0.4
Accidental injury	0	0	1	0.4	1	0.4
CARDIOVASCULAR						
Hypertension	1	0.4	0	0	0	0
DIGESTIVE						
Vomiting	0	0	0	0	1	0.4
NERVOUS						
Depression	1	0.4	0	0	1	0.4
SKIN						
Sweating	0	0	0	0	1	0.4
UROGENITAL						
Unintended pregnancy	0	0	2	0.8	1	0.4

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

† After the database had been closed for this study, this event (headache in patient no. 2826) was determined to not be a serious adverse event.

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, one event (chest pain in patient no. 2772 in the reboxetine group) was judged by the investigator to have been caused by the study medication.* The patient recovered from the chest pain (see narrative summary 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).

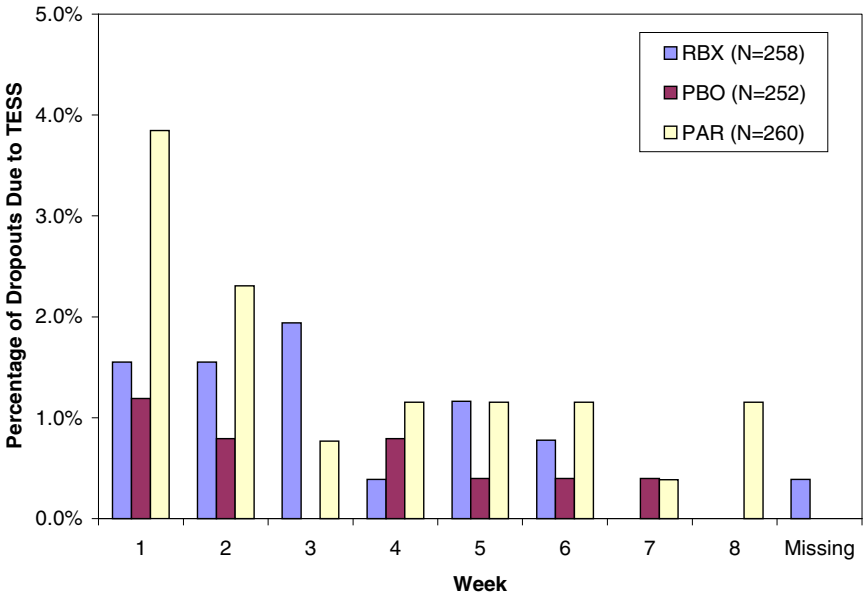
9.4.2.3 Discontinuations Due to Treatment-Emergent Signs and Symptoms

The percentage of patients who discontinued treatment due to TESS at any time during the treatment period was higher in the paroxetine group (11.9%; 31/260) than in the reboxetine (7.8%; 20/258) or placebo (4.0%; 10/252) groups (Section 13, Table 5.5).

* A second drug-related TESS that was reported as a serious event (headache in patient no. 2826 in the reboxetine group) was retrospectively determined to not be a serious event.

During the first week of treatment, when reboxetine was administered at a dose of 4 mg/day, the rate of discontinuations due to TESS was higher in the paroxetine group (3.8%; 10/260) than in the reboxetine (1.6%; 4/258) or placebo (1.2%; 3/252) groups (Figure 4). 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 remained constant (1.6%; 4/258) in the reboxetine group and decreased in the paroxetine (2.3%; 6/260) and placebo (0.8%; 2/252) groups. During the third week of treatment, the rate of discontinuations due to TESS increased slightly in the reboxetine group (1.9%; 5/258) and decreased in the paroxetine (0.8%; 2/260) and placebo (0%; 0/252) groups. After the third week of treatment, the rate of discontinuations due to TESS was ≤1.2% in all treatment groups.

Figure 4. 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=258		PBO N=252		PAR N=260	
	n	%	n	%	n	%
At least one TESS that led to discontinuation	**20**	**7.8**	**10**	**4.0**	**31**	**11.9**
BODY						
Headache	5†	1.9	4	1.6	3	1.2
NERVOUS						
Dizziness	2	0.8	0	0	4	1.5
Depression	1	0.4	3	1.2	2	0.8
Somnolence	1	0.4	0	0	4	1.5
Insomnia	0	0	1	0.4	4	1.5
Nervousness	0	0	2	0.8	3	1.2
DIGESTIVE						
Nausea	2	0.8	0	0	6	2.3

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

† After the database had been closed for this study, the report of headache in patient no. 2826 in the reboxetine group was determined to not be the reason for discontinuation of study medication in this patient (rather, the patient discontinued due to adverse events of chest pain and hypertension).

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 headache, which led to discontinuation of treatment in 1.9% of reboxetine-treated patients. The most frequently reported TESS that led to discontinuation of paroxetine treatment was nausea, which led to discontinuation of treatment in 2.3% 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 1.2% (3/258) of reboxetine-treated patients (chest pain in patient no. 2772, depression in patient no. 2169, and hypertension and chest pain in patient no. 2826*) and in 0.8% (2/260) of paroxetine-treated patients (depression in patient no. 2787 and accidental injury in patient no. 2636); no placebo-treated patients discontinued due to serious TESS (Section 13, Table 5.9).

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

* As noted in Table 38, after the database had been closed for this study, the report of headache in patient no. 2826 in the reboxetine group was determined to not be the reason for discontinuation of study medication in this patient (rather, the patient discontinued due to adverse events of chest pain and hypertension).

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 (other than unintended pregnancy) are presented below; narrative summaries for the patients who became pregnant during the study are in Section 9.4.6, Exposure in Utero. 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.: *2008*
Investigator: *Adler (No. 42035)*
Treatment: *Reboxetine*
Event: *Allergic reaction to Dilaudid (Allergic reaction)*

This 36-year-old female was randomized to reboxetine on 7 June 2000. The patient had no pertinent medical history other than seasonal and bee-sting allergies. Concomitant medications included Differin (adapalene), Preparation H (phenylephrine hydrochloride), and Ativan (lorazepam). Percocet (oxycodone hydrochloride/acetaminophen) was prescribed for a severe left-ankle sprain on 4 July 2000 and was discontinued on 9 July 2000. On day 6 of the study (13 June 2000), the patient was seen in the emergency room for severe back pain and was given Dilaudid (hydromorphone hydrochloride) and morphine for pain control. Following the administration of Dilaudid, the patient displayed signs of a possible allergic reaction to Dilaudid, manifested as hives, nausea, and vomiting. The adverse medication reaction led to patient hospitalization for 2 days. She fully recovered from this event on day 7 (14 June 2000) and was discharged on the same day with a diagnosis of kidney stones (nephrolithiasis). The blind was maintained during this event, and the study medication was not interrupted. The investigator considered this event to be unrelated to the study medication.

Patient No.: *2169*
Investigator: *Riesenberg (No. 40676)*
Treatment: *Reboxetine*
Event: *Worsening of depression (Depression)*

This 37-year-old female was randomized to reboxetine on 17 May 2000. On 5 June 2000 (day 19 of study), the patient experienced worsening of depressive symptoms with auditory hallucinations and was hospitalized. At that time, she was permanently discontinued from the study. The investigator indicated that the patient had not recovered but was in a chronic condition. The investigator considered the event to be unrelated to the study medication.

Patient No.: *2772*
Investigator: *Downs (No. 33915)*
Treatment: *Reboxetine*
Event: *Chest tightness (Chest pain)*

This 53-year-old female was randomized to reboxetine on 5 July 2000. The patient's history included blurred vision while taking Zoloft (sertraline hydrochloride) and mild hypertension on screening (140/88 mmHg) and at baseline (140/74 mmHg). Baseline ECG was within normal limits. Concomitant medication included Claritin (loratadine) for sinus congestion and Tylenol (acetaminophen) Migraine for migraine headaches. On 16 July 2000 (study day 11), the patient experienced blurred vision and permanently discontinued study medication. On 17 July 2000 (study day 12), the blurred vision continued and she developed chest tightness, profuse sweating, and increased blood pressure (138/102 mmHg). She was examined by a local physician who performed an ECG. She was then referred by the local physician to a cardiologist who performed a thallium-treadmill test and lab work-up. The local physician notified the study site verbally that cardiac tests were negative. The patient recovered on 19 July 2000. She had sequelae of fuzzy/hazy vision. The investigator considered the event to be related to study medication.

Patient No.: *2826*
Investigator: *Solloway (No. 43068)*
Treatment: *Reboxetine*
Event: *Chest pain with hypertension (Chest pain, Hypertension)*

This 44-year-old female patient was randomized to reboxetine on 19 July 2000. She had a history of a cholecystectomy, gastric stapling in 1986, and breast reduction. She had also been seen in the emergency room on 9 August 2000 for lower abdominal pain and vaginal bleeding. She was given a prescription for Percocet (oxycodone hydrochloride/acetaminophen) for the pain and was sent home with a diagnosis of bleeding uterine fibroids. On 10 August 2000, the patient permanently discontinued the study medication. Concomitant medications included omeprazole for gastroesophageal reflux disease, Equate for headaches, and Percocet (oxycodone hydrochloride/acetaminophen) for abdominal pain. On 12 August 2000 (study day 24) the patient presented to the emergency room with a chief complaint of unremitting mid-chest pain, described as a dull pressure. The event was moderate in severity and was associated with slight nausea and shortness of breath. She was given nitroglycerin (sublingual), which did not relieve her pain. Upon admission to the hospital for elevated blood pressure (196/107 mmHg), her pain had decreased from a score of 7 out of 10 to a score of 1 to 2 out of 10. Labs (including cardiac-enzyme profile), stress test, portable chest X-ray, and upper gastrointestinal series revealed no significant abnormalities. The patient was discharged on 14 August 2000 (study day 26) and was considered to be fully recovered. She was discharged on Zantac (ranitidine hydrochloride) and still had 8 days left of the Percocet prescription. The patient was referred to a cardiologist for cardiac work-up.

On 16 August 2000 the patient went to a different hospital because of chest tightness and was admitted for evaluation. During the hospital admission, myocardial infarction was ruled out. An echocardiogram was normal and an exercise stress test was unremarkable. Hypertension was treated with atenolol. The attending physician noted that it was unlikely that cardiac ischemia was the cause of the exertional shortness of breath/chest pain. The patient recovered and was discharged on 18 August 2000, with instructions for follow up. The investigator considered the events to be unrelated to study medication.

9.4.2.4.2 Placebo

Patient No.: *2650*
Investigator: *Dahdul (No. 38900)*
Treatment: *Placebo*
Event: *Fractured right humerus (Accidental injury)*

This 32-year-old female was randomized to placebo on 8 June 2000. On 11 June 2000, she was involved in a motorcycle accident. When the driver lost control of the motorcycle on a curve, the patient (who was a passenger) was thrown from the motorcycle and hit a pole. Follow-up exam revealed a right humerus fracture that required hospitalization and surgery (open reduction and internal fixation). The patient recovered and completed the study without interruption of study medication. The investigator considered the event to be unrelated to study medication.

9.4.2.4.3 Paroxetine

Patient No.: *2415*
Investigator: *Raj (No. 42042)*
Treatment: *Paroxetine*
Event: *Chest pain, Abdominal pain, Vomiting, Profuse sweating (Chest pain, Abdominal pain, Vomiting, Sweating)*

This 64-year-old male patient was randomized to paroxetine on 23 May 2000. The patient had a history of quintuple coronary artery bypass graft in 1991, hypertension since 1995, myocardial infarction in 1998, and asbestos exposure in 1980. Concomitant medications included nifedipine for hypertension. On 14 July 2000, the patient went walking in greater than 90-degree temperatures and developed stomach and chest pains, profuse sweating, and vomiting. He went to the emergency room where he was admitted for work-up. After lab and ECG results were reviewed, a myocardial infarction was ruled out and he was treated with intravenous heparin sodium, aspirin (ASA), Norvasc (amlodipine besylate), and beta-blocker therapy for unstable angina. The patient refused cardiac catheterization. He was discharged with full recovery on 17 July 2000 and was encouraged to follow up with cardiac catheterization or a nuclear stress test with his personal physician. Discharge medications included Nitro-Dur every morning, one ASA/day, Plavix (clopidogrel bisulfate) 75 mg daily, nitroglycerin 0.4 mg sublingually as needed for chest pain, Tenormin (atenolol) 25 mg every evening, and Norvasc 2.5 mg twice daily. The blind was maintained, and study medication

was not interrupted. The patient completed the study on 19 July 2000. The investigator considered the event to be unrelated to the study medication.

Patient No.: *2636*
Investigator: *Beckett (No. 43228)*
Treatment: *Paroxetine*
Event: *Fall (Accidental injury)*

This 53-year-old female was randomized to paroxetine on 23 June 2000. No pertinent medical history was noted. On 3 August 2000, the patient was hospitalized for a broken nose. A computed tomography (CT) scan and lab results were obtained, but no further information was received. The blind was maintained, and study medication was not interrupted during hospitalization. However, after the patient was discharged from the hospital, she did not return to the study clinic and did not return telephone calls, despite numerous attempts by the clinic staff to reach her by telephone. Therefore, the patient was discontinued from the study due to hospitalization, her work situation, and the length of time during which the study medication had not been taken. The investigator considered the event to be unrelated to the study medication.

Patient No.: *2787*
Investigator: *Machado (No. 43053)*
Treatment: *Paroxetine*
Event: *Suicidal ideation (Depression)*

This 46-year-old female was randomized to paroxetine on 27 June 2000. She was on no concomitant medication. A history of recurrent Major Depressive Disorder was noted. The current episode started in April 2000. On 6 August 2000, the patient telephoned the study clinic and reported suicidal ideation that was vague and nonspecific. She was crying and was judged to be markedly agitated and distraught. No specific suicide plans were reported.

Crisis intervention was performed via telephone conversations, with an initial duration of contact of approximately 30 minutes. Her daughter also participated in this intervention. The patient's condition gradually improved, and it was determined that there was no imminent suicidal risk. The patient was to be supervised by her daughter and other family members. Two follow-up calls were made at 1.5-hour intervals, and the patient's condition appeared to remain stable. An appointment was made for her to come into the office the next day (7 August 2000) for a follow-up evaluation. The next day, the patient called the office to cancel the appointment due to personal issues. She indicated that she was feeling much better, and she rescheduled the appointment for 8 August 2000. On that day, the patient again called to cancel her appointment. Issues of suicidality were examined; no significant concerns were identified. An office visit on 10 August 2000 revealed no further suicidal ideation. However, due to this episode and to marked fluctuations in mood and emotional liability, the patient was withdrawn from the study. The patient was started on Celexa (citalopram hydrobromide) (20 mg/day) and was referred to a psychiatric center for further

evaluation and treatment. 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).

Although statistically significant differences were noted among the treatment groups in the mean change from baseline values for hemoglobin and erythrocytes at day 28, the changes were greater in the placebo group (changes of $-0.064 \times 10^6/\mu L$ for erythrocytes and -0.23 g/dL for hemoglobin) than in the reboxetine (changes of $-0.004 \times 10^6/\mu L$ for erythrocytes and -0.04 g/dL for hemoglobin) or paroxetine (changes of $-0.045 \times 10^6/\mu L$ for erythrocytes and -0.11 g/dL for hemoglobin) groups. The mean values remained within normal ranges, and none of these changes was considered to be clinically meaningful.

Statistically significant differences were also noted among the treatment groups in the mean change from baseline values for platelet count at days 28 and 56. Differences were due to a slight mean increase in the reboxetine group (change of $12.6 \times 10^3/\mu L$) and slight mean decreases in the placebo (change of $-5.7 \times 10^3/\mu L$) and paroxetine (change of $-2.9 \times 10^3/\mu L$) 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 10.5% 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,

AST, bilirubin, creatinine, glucose, potassium, sodium, or carbon dioxide content (Section 13, Table 7.2).

Although statistically significant differences were noted among the treatment groups in the mean change from baseline values for alkaline phosphatase and serum chloride at day 56, the changes were greater in the placebo group (changes of –2.04 U/L for alkaline phosphatase and 0.80 mEq/L for chloride) than in the reboxetine (changes of 1.80 U/L for alkaline phosphatase and 0.01 mEq/L for chloride) or paroxetine (changes of 0.74 U/L for alkaline phosphatase and 0.09 mEq/L for chloride) groups. The mean values remained within normal ranges, and none of these changes was considered to be clinically meaningful.

Statistically significant differences were also noted among the treatment groups in the mean change from baseline values for blood urea nitrogen at day 28. Differences were due to a slight mean increase in the placebo group (change of 0.37 mg/dL) and to slight mean decreases in the reboxetine (change of –0.52 mg/dL) and paroxetine (change of -0.31 mg/dL) groups between baseline and day 28. No statistically significant differences were noted among the 3 treatment groups in the mean change from baseline values for blood urea nitrogen at day 56. The mean values at day 28 remained within normal ranges, and none of these changes was considered to be clinically meaningful.

Statistically significant differences were also noted among the treatment groups in the mean change from baseline values for uric acid at days 28 and 56. Differences at day 56 were due to a slightly greater mean decrease in the reboxetine group (change of –0.24 mg/dL) than in the placebo (change of –0.03 mg/dL) or paroxetine (change of -0.01 mg/dL) 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 7.2, 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 serum chloride and glucose values, fewer than 10% of patients in any treatment group had postbaseline chemistry values that were outside of normal ranges.

Serum chloride values that exceeded the predefined limit (>108 mEq/L) were reported in comparable proportions of patients in each treatment group: 9.0% (19/211) of the patients in the reboxetine group, 12.6% (27/214) of the patients in the placebo group, and 10.2% (22/215) of the patients in the paroxetine group had chloride values that exceeded the predefined limit. 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 also reported in comparable proportions of patients in each treatment group: 17.7% (36/203) of the patients in the reboxetine group, 15.8% (32/202) of the patients in the placebo group, and 17.7% (37/209) 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	217	3 (1.4)	227	2 (0.9)	227	6 (2.6)
Total Bilirubin	219	6 (2.7)	228	1 (0.4)	229	1 (0.4)
ALT	213	7 (3.3)	222	14 (6.3)	223	10 (4.5)
AST	218	5 (2.3)	224	10 (4.5)	226	7 (3.1)
Creatinine	221	0	226	1 (0.4)	227	2 (0.9)
BUN	217	0	220	4 (1.8)	220	2 (0.9)

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

No statistically significant differences were observed among the treatment groups in the mean change from baseline values for sitting systolic or diastolic blood pressure (Section 13, Tables 6.1 and 6.2).

Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline pulse rate at each visit (Section 13, Table 6.3). 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 +5.7 beats per minute in the reboxetine group, -0.3 beats per minute in the placebo group, and –1.0 beats per minute in the paroxetine group.

Statistically significant differences were also observed among the 3 treatment groups in the mean change from baseline body weight at each visit (Section 13, Table 6.4). In the pairwise comparison, the mean change from baseline body weight 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 body weight was -3.9 lb in the reboxetine group, +2.0 lb in the placebo group, and -0.8 lb in the paroxetine group.

9.4.4.2 Values Outside of Predefined Normal Limits

As shown in Table 40, fewer than 2% 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: 6.1% (15/244) of the patients in the reboxetine group, 6.2% (15/242) of the patients in the placebo group, and 5.3% (13/246) 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

		RBX		PBO		PAR	
Variable	Predefined Limit	N*	n (%)†	N*	n (%)†	N*	n (%)†
Systolic BP	≥180 mmHg	244	1 (0.4)	242	1 (0.4)	246	2 (0.8)
	≤90 mmHg	244	15 (6.1)	242	15 (6.2)	246	13 (5.3)
Diastolic BP	≥105 mmHg	245	1 (0.4)	244	1 (0.4)	250	2 (0.8)
	≤50 mmHg	245	4 (1.6)	244	1 (0.4)	250	2 (0.8)
Pulse	≥120 beats/min	248	2 (0.8)	245	0	249	0
	≤50 beats/min	248	1 (0.4)	245	2 (0.8)	249	4 (1.6)

* 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 2.5% (5/200) in the reboxetine group, 3.2% (7/218) in the placebo group, and 4.8% (10/209) in the paroxetine group (Section 13, Table 8.2). The majority of these 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. Only 1 patient (patient no. 2365 in the paroxetine group) had a normal ECG at baseline and an abnormal ECG finding postbaseline (day 28) that was classified as clinically relevant. The ECG abnormality that was observed at day 28 was myocardial infarction in septal leads (V1, V2, [V3]). However, the ECG evaluation at day 56 was normal for this patient, and no cardiovascular-related adverse events were reported during the study.

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

Statistically significant differences were observed among the treatment groups in the mean change from baseline values for the PR and QT intervals at days 28 and 56 and for the QRS interval at day 56 (Table 41). However, for each of these 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. Therefore, although statistically significant differences were observed among the treatment groups in the mean change from baseline PR, QRS, and QT intervals, the results were not considered to be clinically significant.

When the QT interval was corrected for heart rate using Fridericia's correction method, no statistically significant differences were observed among the treatment groups in the mean change from baseline values for the corrected QT interval (QTc). When the QT interval was corrected for heart rate using Bazett's correction method, statistically significant differences were observed among the treatment groups in the mean change 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.

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 13.5 beats per minute in the reboxetine group, 0.3 beats per minute in the placebo group, and 1.4 beats per minute in the paroxetine group.

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

	RBX N=182†		PBO N=202†		PAR N=191†		
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change	P Value‡
PR interval (msec)	154.758	-8.571	151.075	0.896	154.476	-3.717	<.0001*
QRS interval (msec)	86.896	-0.198	85.426	2.401	87.466	1.115	0.0051*
QT interval (msec)	379.516	-23.857	375.673	-0.906	378.346	-3.686	<.0001*
QTc interval (msec) (Bazett's)§	403.579	10.453	406.948	-0.589	403.078	0.395	<.0001*
QTc interval (msec) (Fridericia's)	395.093	-1.787	395.968	-0.738	394.308	-0.985	0.8538
Heart rate (bpm)	69.049	13.544	71.545	0.277	69.435	1.356	<.0001*

* $p \leq 0.05$

† Number of intent-to-treat patients with the specified ECG measurement at screen and at day 56. For PR interval, N=201 for the placebo group 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

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	205	0	227	5 (2.2)	217	4 (1.8)
Tachycardia	≥120 beats/min	205	0	227	0	217	0
PR Interval	≤110 msec	209	1 (0.5)	227	2 (0.9)	224	1 (0.4)
	≥210 msec	209	0	227	2 (0.9)	224	1 (0.4)
QRS Interval	≤30 msec	209	0	228	0	223	0
	≥110 msec	209	3 (1.4)	228	0	223	7 (3.1)
QT Interval	≥470 msec	214	0	229	0	227	0
QTc Interval (Bazett's)	≥450 msec (males) ≥470 msec (females)	214	3 (1.4)	227	2 (0.9)	225	0
QTc Interval (Fridericia's)	≥450 msec (males) ≥470 msec (females)	214	1 (0.5)	229	0	227	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

Three reboxetine-treated patients (patient nos. 2510, 2040, and 2638) had postbaseline values for QTc (Bazett's) that exceeded the predefined limits. However, all 3 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. In 2 of the 3 patients who had an elevated value for QTc (Bazett's), the values for QTc (Fridericia) were within the normal range. Only one patient (patient no. 2638) had a QTc interval that exceeded the predefined limit, based on both the Bazett's and the Fridericia's correction methods. However, the elevated value for QTc (Fridericia) (476 msec) was only slightly above the predefined limit of 470 msec at day 28, and the value returned to normal (423 msec) at day 56.

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, 4 pregnancies (2 in the paroxetine group and 2 in the placebo group) occurred during the study. Available information for each case is summarized below:

9.4.6.1 Paroxetine

Patient No: *2029*
Investigator: *Beckett (No. 43228)*
Treatment: *Paroxetine*
Event: *Exposure in Utero*

This 38-year-old female was randomized to paroxetine on 1 June 2000. She took the last dose of study medication on 26 July 2000. The final patient assessment was performed on 27 July 2000 (study day 56). The study termination laboratory assays, which included a serum pregnancy test, were conducted on 4 August 2000. Pregnancy was confirmed on 7 August 2000. Her last menstrual period was 7 July 2000 and conception date was estimated as 29 July 2000 (study day 58). This patient will be followed until completion of the pregnancy. So far, no pregnancy-related complications have been reported. The patient was on Levlite (birth-control pills) during the study. Other concomitant medications were aspirin (2 days for menstrual cramps) and Ventolin (for asthma; started medication before entry into the study).

Patient No: *2377*
Investigator: *Pedersen-Lundt (No. 45907)*
Treatment: *Paroxetine*
Event: *Exposure in Utero*

This 37 year-old female was randomized to paroxetine on 8 June 2000. She suspected pregnancy and discontinued study medication on 13 June 2000 (study day 5). On 21 June 2000, a home pregnancy test was positive. Her last menstrual period was on 7 June 2000. As recorded on the Exposure-in-Utero form, the patient estimated that her date of conception was 5 May 2000. The patient contacted the site and was advised to discontinue study medication and to visit the clinic for an urine pregnancy test. Pregnancy was confirmed on 21 June 2000. The final patient assessment was performed on 27 June 2000. This patient will be followed until completion of the pregnancy. So far, no pregnancy-related complications have been reported.

9.4.6.2 Placebo

Patient No: *2361*
Investigator: *Hyde (No. 43463)*
Treatment: *Placebo*
Event: *Exposure in Utero*

This 36 year-old female was randomized to placebo on 1 June 2000. She took the last dose of study medication on 27 July 2000. The final patient assessment was performed on

27 July 2000 (study day 56) together with the study termination laboratory assays, which included a serum pregnancy test. She was treated with Paxil at the day-56 visit. Pregnancy was confirmed on 31 July 2000 (patient was using double-barrier birth control method), and telephone contact with the patient revealed that her last menstrual period was on 24 June 2000 (approximately study day 23). This patient has had no subsequent contact with the investigator or the study site and has been lost to follow-up.

Patient No: *2761*
Investigator: *Strauss (No. 42044)*
Treatment: *Placebo*
Event: *Exposure in Utero*

This 23 year-old female was randomized to placebo on 12 July 2000. She took the last dose of study medication on 6 September 2000. The final patient assessment was performed on 6 September 2000 (study day 56) together with the study termination laboratory assays, which included a serum pregnancy test. The serum pregnancy test was positive and this result was confirmed by a repeat serum pregnancy test at the request of the investigator. Her last menstrual period was 27 July 2000, the estimated date of conception was 10 August 2000, and the estimated date of delivery is 3 May 2001. This patient will be followed until completion of pregnancy. So far, no pregnancy-related complications have been reported. The concomitant medications taken during the study were Tylenol and Ibuprofen for headaches and a laxative (not specified) for constipation.

9.4.7 Safety Conclusions

Treatment-emergent signs and symptoms were reported in a slightly higher percentage of patients in the active treatment groups (87.2%; 225/258 in the reboxetine group and 91.5%; 238/260 in the paroxetine group) than in the placebo group (79.8%; 201/252).

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, chills, sweating, vasodilatation, and abnormality of accommodation (primarily blurred vision). 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, dizziness, somnolence, and sweating. The majority of TESS that were reported by patients in each treatment group were mild to moderate in intensity.

Of the TESS that were reported in ≥5% of male or female reboxetine-treated patients, clinically relevant between-gender differences were observed in the frequency of urination impaired, impotence, urinary retention, and abnormal ejaculation, which were reported more frequently in the reboxetine-treated male patients than in the reboxetine-treated female patients. Symptoms of functional limitation of bladder outflow (ie, urinary retention,

urination impaired, or urinary frequency) were reported in 25.4% (17/67) 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 one patient 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, clinically relevant between-gender differences were observed in the frequency of nausea and dizziness, which were reported more frequently in the paroxetine-treated female patients than in the paroxetine-treated male patients, and in the frequency of decreased libido and abnormal ejaculation, which were reported more frequently in the paroxetine-treated male patients than in the paroxetine-treated female patients.

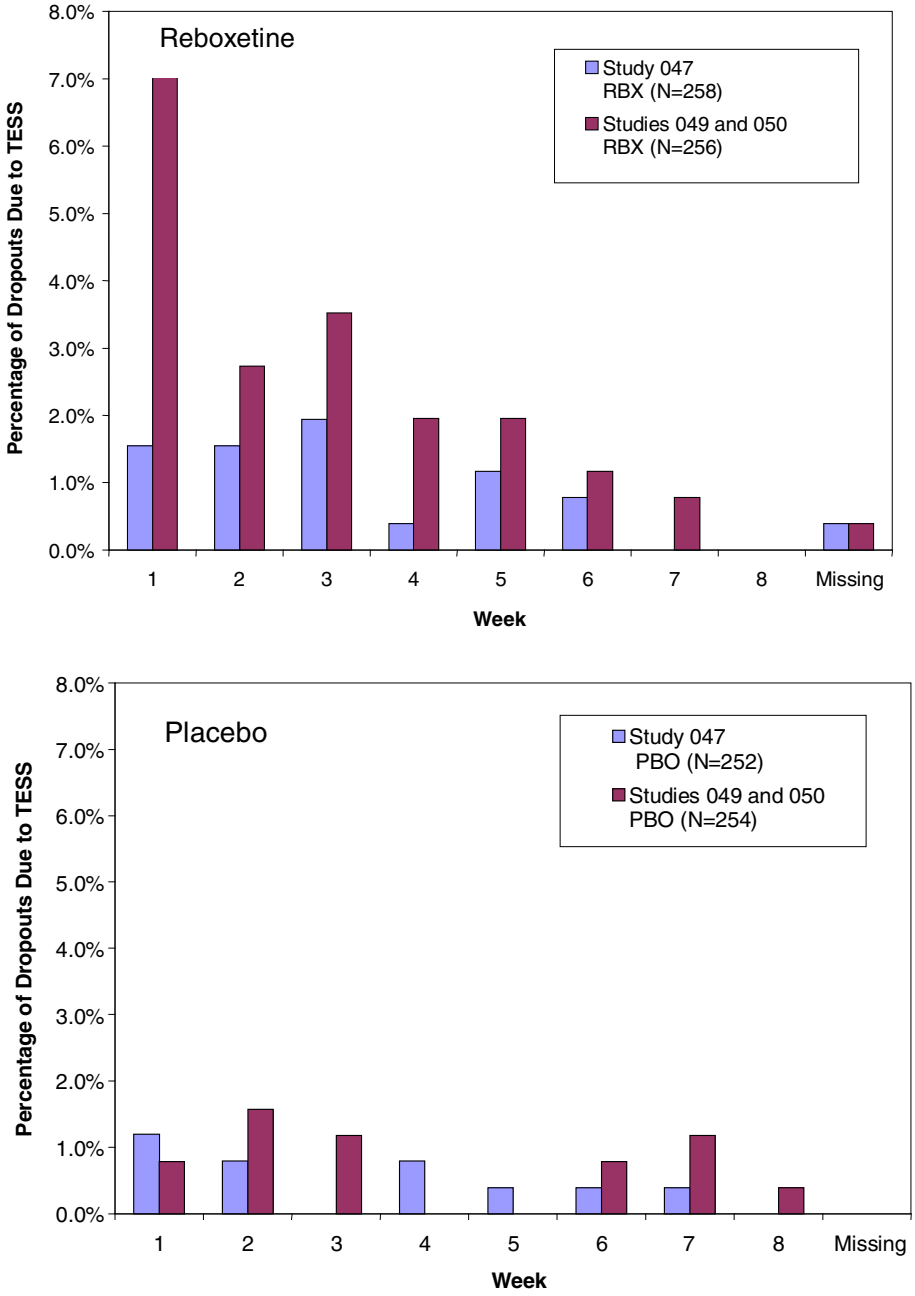
No deaths were reported during this study. Serious TESS were reported in a similar percentage of patients in each of the 3 treatment groups: 1.6% (4/258) of reboxetine-treated patients, 1.2% (3/252) of placebo-treated patients, and 1.5% (4/260) of paroxetine-treated patients.

The percentage of patients who discontinued treatment due to TESS was higher in the paroxetine group (11.9%; 31/260) than in the reboxetine (7.8%; 20/258) or placebo (4.0%; 10/252) groups. The most frequently reported TESS that led to discontinuation of reboxetine treatment was headache, which led to discontinuation of treatment in 1.9% (5/258) of reboxetine-treated patients. The most frequently reported TESS that led to discontinuation of paroxetine treatment was nausea, which led to discontinuation of treatment in 2.3% (6/260) 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 [25] and 050 [26]). 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 7.8% (20/258) in this study. In the placebo group, the rate of discontinuations due to TESS decreased from 5.9% (15/254) in the earlier studies to 4.0% (10/252) 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 (1.6%; 4/258) was substantially lower than the rate that was observed during the first week of studies 049 and 050 (7.0%; 18/256) (Figure 5, top panel). The rate of discontinuations due to TESS in this study remained at 1.6% (4/258) during week 2 and increased slightly during week 3 (1.9%; 5/258). 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 5, bottom panel).

Figure 5. 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=258), a total of 496 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, 59.7% (296/496) were mild, 34.5% (171/496) were moderate, and 5.8% (29/496) were severe in intensity. In contrast, in the earlier US studies of reboxetine (combined data from protocols 049 [25] and 050 [26]; 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 in intensity was increased, during the first week of this study, compared with studies 049 and 050. Furthermore, the percentage of patients who had at least one TESS during the first week was also lower in this study (67.4%; 174/258) than in studies 049 and 050 (77.3%; 198/256). 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.

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 or diastolic blood pressure. Statistically significant differences were observed among the 3 treatment groups in the mean change from baseline body weight at each visit. At the end of the study (day 56), the mean change from baseline body weight was -3.9 lb in the reboxetine group, +2.0 lb in the placebo group, and -0.8 lb in the paroxetine group.

No statistically significant differences were observed among the treatment groups in the mean change from baseline values for QTc, based on Fridericia's correction method.

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 +5.7 beats per minute in the reboxetine group, -0.3 beats per minute in the placebo group, and –1.0 beats per minute in the paroxetine group, whereas the mean change from baseline ECG heart rate was +13.5 beats per minute in the reboxetine group, +0.3 beats per minute in the placebo group, and +1.4 beats per minute in the paroxetine group. However, few reboxetine-treated patients (0.8%; 2/248) 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 774 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 [25] and 050 [26]) 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 774 patients were enrolled in the study and were randomized to receive treatment with reboxetine (258 patients), placebo (254 patients), or paroxetine (262 patients). The ITT population, which includes all patients who received at least one dose of study medication, includes 258 reboxetine-treated patients, 252 placebo-treated patients, and 260 paroxetine-treated patients.

Overall, the patient population in this study was reflective of the general population of patients with depression [34]. The patients in the study ranged in age from 18 to 66 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.

The study was successful in meeting the protocol-specified primary objective. The mean decrease from baseline in the MADRS total score was significantly greater in the reboxetine group than in the placebo group at day 56 in the LOCF analysis (p=0.016). The fact that similar results were observed for the active comparator paroxetine confirms that the study population was a valid population in which to assess the antidepressant efficacy of the study medication. The significantly positive results that were observed on the primary (LOCF) analysis of the mean change from baseline in the MADRS total score were supported by significantly positive results on the secondary analyses (OC, ANCOVA, and GEE analyses) of the primary endpoint.

The significantly positive results on the primary endpoint were also supported by significantly positive results on a number of the key secondary measures of antidepressant efficacy. Reboxetine was shown to be superior to placebo on the mean change from baseline in the HAM-D Item 1 score, the HAM-D Retardation Cluster score, and the CGI Severity of Illness score. Thus, the antidepressant efficacy of reboxetine was confirmed on a number of

different scales, including instrumental rating scales (MADRS and prespecified items/clusters of the HAM-D) and a clinician rating scale (CGI). On all measures of antidepressant efficacy, the results in the reboxetine group were numerically superior to the results in the placebo group, and the pattern of improvement was consistent with an antidepressant effect for reboxetine.

The results from the secondary measures of energy and social function, including the SASS, the MOS SF-36 Social Functioning and Vitality scales, and the MFI General Fatigue subscale, clearly indicate that quality of life improved in all treatment groups during the study. The improvements that were observed in the active treatment groups were numerically superior to the improvement that was observed in the placebo group, although the differences were not statistically significant. The relatively high placebo response may have contributed to the failure to distinguish a statistically significant difference among the 3 treatment groups.

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, chills, sweating, vasodilatation, and abnormality of accommodation (primarily blurred vision). 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, dizziness, somnolence, 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 was higher in the paroxetine group (11.9%; 31/260) than in the reboxetine (7.8%; 20/258) or placebo (4.0%; 10/252) groups.

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 [25] and 050 [26]). 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 7.8% (20/258) 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 4.0% (10/252) 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 (1.6%; 4/258) 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 remained at 1.6% (4/258) during week 2 and increased slightly during week 3 (1.9%; 5/258). 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.

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 496 TESS were reported in the reboxetine group (N=258) 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, and the percentage of TESS that were mild in intensity was increased, during the first week of this study (5.8% [29/496] severe; 59.7% [296/496] mild), compared with studies 049 and 050 (11.7% [85/726] severe; 49.2% [357/726] mild). 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.

No statistically significant differences were observed among the treatment groups in the mean change from baseline values for sitting systolic or diastolic blood pressure.

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 +5.7 beats per minute in the reboxetine group, -0.3 beats per minute in the placebo group, and –1.0 beats per minute in the paroxetine group, whereas the mean change from baseline ECG heart rate was +13.5 beats per minute in the reboxetine group, +0.3 beats per minute in the placebo group, and +1.4 beats per minute in the paroxetine group. However, few reboxetine-treated patients (0.8%; 2/248) 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). No statistically significant differences were observed among the treatment groups in the mean change from baseline values for QTc, based on Fridericia's correction method.

In conclusion, this phase III, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study demonstrated 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 results on the secondary endpoints further supported the antidepressant efficacy of reboxetine. 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. Overall, the results demonstrate that reboxetine is effective and well-tolerated for the treatment of patients with major depressive disorder.

11 ACKNOWLEDGMENTS

The authors thank the many individuals who contributed to the conduct of the study or to the preparation of the study report. In particular, the authors acknowledge the contributions of the following members of the clinical study team: Jill W. Bokros (Clinical Data Integration), John H. Gordon (Clinical Trials Conduct), Timothy D. Holt (Clinical Reporting Systems), and Patricia A. Smanik (Medical Writing).

12 REFERENCE LIST

1. Merikangas KR, Kupfer DJ. Mood disorders: Genetic aspects. In: Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry. 6th ed. Baltimore, MD: Williams & Wilkins; 1995:1102-1116.
2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC, American Psychiatric Association, 1994.
3. Post RM. Mood Disorders: Somatic treatment. In: Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry. 6th ed. Baltimore, MD: Williams & Wilkins; 1995:1152-1178.
4. Nierenberg A, Wright EC. Evolution of remission as the new standard in the treatment of depression. J Clin Psychiatry 1999;60(suppl 22):7-11.
5. Elkin I, Shea MT, Watkins JT, Sotsky SM, Collins JF, Glass DR, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. Arch Gen Psychiatry 1989;46(11):971-82.
6. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. Br Med J 1995;310(b992):1433-88.
7. Montgomery SA, Henry J, McDonald G, Dinan T, Lader M, Hindmarch I, et al. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. Int Clin Psychopharmaco 1994;9(1):47-53.
8. Song F, Freemantle N, Sheldon TA, House A, Watson P, Long A, Mason J. Selective serotonin reuptake inhibitors: Meta-analysis of efficacy and acceptability. Br Med J 1993(13);306(6879):683-7.
9. Montgomery SA. Reboxetine: additional benefits to the depressed patient. J Psychopharmacol 1997;11(suppl 4):S9-15.
10. Healy D, McMonagle T. The enhancement of social functioning as a therapeutic principle in the management of depression. J Psychopharmacol 1997;11(suppl 4):S25-31.
11. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122(5):509-22.
12. Wong EH, Sonders MS, Amara SG, Tinholt PM, Piercey MF, Hoffman WP, et al. Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. Biol Psychiatry 2000;47(9):818-29.

13. Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997;340(2-3):249-58.
14. Dubini A, Ban TA, Money LC. Phase II controlled study of the activity and tolerability of reboxetine in comparison with placebo and desipramine in patients hospitalised for major depressive Disorder. Internal Report FCE 20124/702I, February 1991.
15. Ban TA, Dubini A,Giorgetti C, Petroccione A, Andreoli V, Caillard V, et al. Multicentre, multinational double blind study of the activity and tolerability of reboxetine versus fluoxetine and placebo in patients suffering from Major Depressive Episodes. Internal Report 9550080, December 1995.
16. Ban TA, Morey LC, Fjetland OK, Dubini A. Phase II placebo-controlled clinical study with reboxetine in major depression. Farmitalia Carlo Erba Internal Report FCE 201124/706i, November 1993.
17. Ban TA, Dubini A, Petroccione A, Castiglioni R, Gazner P, Mehilane L, et al. Multicentre, multinational double-blind study of the activity and tolerability of Reboxetine versus placebo in the continuation therapy of major depressive episodes. Pharmacia Internal Report 9550077, December 1995.
18. Bosc M, Dubini A, Polin V. Development and validation of a social functioning scale, the Social Adaptation Self-Evaluation Scale. European Neuropsychopharmacology 1997;7(suppl 1):S57-70 (discussion, S71-73).
19. Mundt JC, Kobac KA, Taylor LV, Mantle JM, Jefferson JW, Katzelnick DJ, Greist JH. Administration of the Hamilton Depression Rating Scale using interactive voice response technology. MD Computing 1998;15(1):31-39.
20. Maier W, Philipp M. Comparative analysis of observer depression scales. Acta Psychiatr Scand 1985;72(3):239-45.
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.
22. Davidson J, Turnbull CD, Strickland R, Miller R, Graves K. The Montgomery-Asberg Depression Scale: reliability and validity. Acta Psychiatr Scand 1986;73:544-8.
23. Davidson J, Turnbull C. The importance of dose in isocarboxazid therapy. J Clin Psychiatry 1984:45(7 Pt 2):49-52.
24. Kearns NP, Cruickshank CA, McGuigan KJ, Riley SA, Shaw SP, Snaith RP. A comparison of depression scales. Br J Psychiatry 1982;141:45-9.
25. Wright CE, Brown MT, Wagner JA, Reisner JK. Reboxetine (PNU-155950E) versus placebo in the treatment of major depressive disorders (Protocol 97-CRBX-049). Pharmacia & Upjohn Study Report a0027738, 16 August 1999.

26. Brown MT, Reisner JK, Wagner JA, Wright CE, Rowland CR. Reboxetine (PNU-155950E) versus placebo and fluoxetine in a controlled, randomized, double-blind, multicenter study of treatment in major depressive disorders (Protocol 97-CRBX-050). Pharmacia & Upjohn study report in preparation.
27. Paxil (paroxetine hydrochloride) [package insert]. Philadelphia, PA: SmithKline Beecham Pharmaceuticals; 1999.
28. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39(3):315-25.
29. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6(4):278-96.
30. Guy W. ECDEU Assessment Manual for Psychopharmacology, 1976, Revised (DHEW Publication No. ADM 76-338). Washington, DC: US Government Printing Office.
31. Ware JE, Sherbourne CD. The MOS 36-item short-term health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473-83.
32. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-item short form health survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31(3):247-63.
33. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73(1):13-22.
34. Blazer D II. Mood Disorders: Epidemiology. In: Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry. 6th ed. Baltimore, MD: Williams & Wilkins; 1995:1079-89.
35. Hammond MF. Rating depression severity in the elderly physically ill patient: reliability and factor structure of the Hamilton and Montgomery-Asberg Depression Rating Scales. Int J Geriatr Psychiatry 1998;13(4):257-61.
36. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
37. Hamilton M. General problems of psychiatric rating scales. In: Pichot P, ed. Psychological measurements in psychopharmacology. Basel, Switzerland: Karger; 1974:125-38.
38. Hamilton M. Standardized assessment and recording of depressive symptoms. Psychiatr Neurol Neurochir 1969;72(2):201-5.
39. Bech P, Allerup P. The Hamilton Depression Scale: evaluation of objectivity using logistic models. Acta Psychiatr Scand 1981;63(3):290-99.

40. Bech P, Allerup P, Reisby N, Gram LF. Assessment of symptom change from improvement curves on the Hamilton Depression Scale in trials with antidepressants. Psychopharmacol 1984;84(2):276-81.

41. Bech P, Gram LF, Dein E, Jacobsen O, Vitger J, Belwig TG. Quantitative rating of depressive states. Acta Psychiatr Scand 1975;51(3):161-70.

42. Gibbons RD, Clark DC, Kupfer DJ. Exactly what does the Hamilton Depression Rating Scale Measure? J Psychiatr Res 1993;27(3):259-73.

43. Maier W, Heuser I, Philipp M, Schlegel S, Buller R, Wetzel H. Improving depression severity assessment - I. Reliability, internal validity and sensitivity to change of three observer depression scales. J Psychiatr Res 1988;22(1):3-12.

44. Maier W, Heuser I, Philipp M, Frommberger U, Demuth W. Improving depression severity assessment - II. Content, concurrent and external validity of three observer depression scales. J Psychiatr Res 1988;22(1):13-9.

Amendment

1 IDENTIFYING INFORMATION FOR AMENDMENT

Amendment Number:	1
Approval Date:	6 February 2001
Product:	PNU-155950E, Reboxetine mesylate

2 IDENTIFYING INFORMATION FOR ORIGINAL DOCUMENT

Document Number:	a0080877
Document Type:	Study Report
Title:	M/2020/0047 Reboxetine, Placebo, and Paroxetine Comparison in Patients With Major Depressive Disorder
Protocol Number:	M/2020/0047
Project / Product Identifier:	PNU-950E-CNS-0005
Authors:	Mark T. Brown, Sally A. Brinkman, Jacqueline K. Reisner, Clayton R. Rowland
Approval Date:	03 November 2000

3 AMENDMENT SUMMARY

The study report for protocol M/2020/0047 was revised to (1) correct errors in the algorithms that were used to calculate the total scores for the Hamilton Rating Scale for Depression (HAM-D) and the Social Adaptation Self-evaluation Scale (SASS), (2) revise the laboratory and electrocardiogram (ECG) data tables by designating the unscheduled pretreatment visits as baseline visits rather than postbaseline unscheduled visits, (3) revise the data tables that present the pregnancy test results to include in the denominator (N) all patients who had a pregnancy test at any visit, rather than only patients who had a pregnancy test at screen (this correction did not change the number of pregnancies that were described in the original report; see Section 9.4.6 [Exposure In Utero] in the original report), and (4) correct a typographical error in the report. The changes that are described in this amendment do not alter the overall conclusions that were reported in the original study report for protocol M/2020/0047.

The revised statistical tables are summarized in Table 1. A more detailed description of the changes that were made and the reasons for the changes is provided in the following sections of this amendment.

Table 1. Summary of Revised Statistical Tables

Table No.	Table Title	Original		Revised	
		Date Produced	No. of Pages	Date Produced	No. of Pages
Section 13					
2.9	Summary of Baseline Data	10/5/2000	2	12/4/2000	2
4.6A	HAM-D Total Score: Mean Change From Baseline - LOCF	10/5/2000	2	1/18/2001	2
4.6C	Summary of HAM-D Change From Baseline	10/5/2000	1	1/18/2001	1
4.7A	HAMD: Responder Status - LOCF	10/5/2000	1	1/18/2001	1
4.7C	Summary of HAM-D Responder Status	10/5/2000	1	1/18/2001	1
4.8A	HAM-D: Remission Status - LOCF	10/5/2000	1	1/18/2001	1
4.8C	Summary of HAM-D Remission Status	10/5/2000	1	1/18/2001	1
4.16A	Social Adaptation Self-Evaluation Scale: Mean Change from Baseline - LOCF	10/5/2000	2	1/18/2001	2
4.16B	Social Adaptation Self-Evaluation Scale: Mean Change from Baseline - Observed	10/5/2000	2	12/4/2000	2
4.16C	Summary of Social Adaptation Self-Evaluation Scale Change From Baseline	10/5/2000	1	1/18/2001	1
7.1	Summary Statistics for Hematology	10/5/2000	20	1/12/2001	10
7.2	Summary Statistics for Chemistry	10/5/2000	26	1/12/2001	14
7.3	Summary of All Patients With Postbaseline Hematology Values Exceeding Normal Ranges	10/5/2000	2	1/12/2001	2
7.4	Summary of All Patients With Postbaseline Chemistry Values Exceeding Normal Ranges	10/5/2000	2	1/12/2001	2
8.1	Summary Statistics for ECG Intervals	11/2/2000	12	1/16/2001	6
8.2	Shift Table for Abnormal/Normal ECG (Baseline vs. Endpoint	10/5/2000	1	1/16/2001	1
8.3	Summary of All Patients With Postbaseline ECG Intervals Exceeding Predefined Limits	11/2/2000	1	1/16/2001	1
Appendix 14					
10.4A	Summary of Protocol Violators With Pregnancy Test Exceeding Normal Ranges	10/19/2000	1	1/12/2001	1
10.4B	Listing of Protocol Violators With Pregnancy Test Exceeding Normal Ranges	10/19/2000	2	1/12/2001	2
Appendix 17					
13.2	Listing of Patients With Postbaseline Hematology Values Exceeding Normal Ranges	10/24/2000	95	1/12/2001	96
13.3	Listing of Patients With Postbaseline Chemistry Values Exceeding Normal Ranges	10/24/2000	125	1/12/2001	125
13.4	Listing of Patients With Postbaseline ECG Intervals Exceeding Predefined Limits	11/2/2000	25	1/16/2001	25

4 SPECIFIC CHANGES

4.1 HAM-D Total Score

4.1.1 Reason for Change

The algorithm that was used to calculate the HAM-D total score was modified to correct the following problem with the last-observation-carried-forward (LOCF) analysis. In the original study report, when the score for a single item of the HAM-D at a nonbaseline visit was missing, then the total score for that visit was assigned a value of missing. The missing total score was then replaced with the total score from the previous nonbaseline visit (ie, the total score from the previous visit was carried forward). With this amendment, the algorithm was changed to carry forward only the score for the individual item that was missing. The total score was then calculated by adding the scores for the items that were not missing to the carried-forward score of the missing item.

After the previously described error was identified and corrected, an additional error in the algorithm for the LOCF analysis was corrected. Although this error did not affect the analysis in the original study report, the data were updated in order to perform the reanalysis correctly. Specifically, the algorithm that was used to determine whether the score for Item 16a (loss of weight, when rated by history) or Item 16b (loss of weight, when actual weight changes are measured) was included in the total score was applied after the LOCF algorithm, when it should have been applied before the LOCF algorithm. As a result, a score from the previous visit may have been carried forward when a score for the current visit was present. For example, if the score for Item 16b was missing and the score for Item 16a was present, then the score for Item 16a was ignored and the score for Item 16b from the previous visit was carried forward. In this amendment, the algorithm was corrected to first assess which item should be used before imputing any values from the previous visit.

4.1.2 Description of Change

Section 13, Tables 4.6A, 4.6C, 4.7A, 4.7C, 4.8A, and 4.8C, were updated using the corrected algorithm for calculating the HAM-D total score.

The text of the report was corrected, as shown below (added text is shown with an underline; deleted text is shown with a strikethrough line).

Section 9.3.2.1 HAM-D Total Score

No statistically significant difference was observed among the 3 treatment groups on the mean change from baseline in the HAM-D total score at day 56 in the LOCF analysis (p=~~0.052~~p=0.051) (Table 16). Both of the active treatment groups demonstrated a mean change from baseline in the HAM-D total score that was numerically superior to the mean

change that was observed in the placebo group. However, the relatively high placebo response may have contributed to the failure to distinguish a statistically significant difference among the 3 treatment groups on the LOCF analysis.

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	258	24.2	233	-5.9	238	-8.2	238	-10.5	238	~~-10.9~~ -11.0
		PBO	252	23.7	234	-6.5	239	-8.3	239	-9.8	239	-10.1
		PAR	260	23.9	240	-7.2	241	~~-9.7~~ -9.6	241	-11.1	242	-11.8
	P Values‡	Among Treatments	0.3589		0.1257		~~0.0348*~~ 0.0532		~~0.0991~~ 0.1115		~~0.0516~~ 0.0506	
		RBX vs. PBO	0.1527		0.3913		~~0.8308~~ 0.8307		~~0.1794~~ 0.1789		~~0.1753~~ 0.1553	
		PAR vs. PBO	0.4973		0.2461		~~0.0192*~~ 0.0282*		~~0.0335*~~ 0.0390*		~~0.0151*~~ 0.0150*	
Observed Cases	Mean Change From Baseline	RBX	258	24.2	233	-5.9	211	-8.7	196	-11.7	189	-12.3
		PBO	252	23.7	234	-6.5	223	-8.6	211	-10.3	200	-11.3
		PAR	260	23.9	240	-7.2	213	-10.3	196	-12.5	192	-13.3
	P Values‡	Among Treatments	0.3589		0.1257		0.0120*		0.0084*		0.0458*	
		RBX vs. PBO	0.1527		0.3913		0.6492		0.0449*		0.1563	
		PAR vs. PBO	0.4973		0.2461		0.0053*		0.0025*		0.0134*	

* $p \leq 0.05$
† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
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

Section 9.3.3.1 HAM-D Response Rate (In-text 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	18.9	83	34.9	110	46.2	120	50.4
		PBO	49	20.9	81	33.9	102	42.7	108	45.2
		PAR	61	25.4	~~96~~ 95	~~39.8~~ 39.4	~~121~~ 120	~~50.2~~ 49.8	128	52.9
	P Values‡	Among Treatments	0.1518		~~0.3541~~ 0.4103		~~0.3145~~ 0.3605		0.2691	
		RBX vs. PBO	0.5239		0.6800		0.4546		0.2550	
		PAR vs. PBO	0.2257		~~0.1714~~ 0.2039		~~0.1260~~ 0.1509		0.1123	
Observed Cases	Response rate†	RBX	44	18.9	79	37.4	99	50.5	109	57.7
		PBO	49	20.9	79	35.4	95	45.0	100	50.0
		PAR	61	25.4	92	43.2	112	57.1	116	60.4
	P Values‡	Among Treatments	0.1518		0.2130		0.0524		0.1107	
		RBX vs. PBO	0.5239		0.5642		0.3106		0.1631	
		PAR vs. PBO	0.2257		0.0971		0.0138*		0.0452*	

* $p \leq 0.05$

† 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.

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

Section 9.3.3.2 HAM-D Remission Rate (In-text 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	38	16.3	61	25.6	99	41.6	109	45.8
		PBO	37	15.8	68	28.5	87	36.4	101	42.3
		PAR	50	20.8	~~80~~ 79	~~33.2~~ 32.8	~~102~~ 101	~~42.3~~ 41.9	109	45.0
	P Values‡	Among Treatments	0.2175		~~0.2258~~ 0.2700		~~0.3780~~ 0.4092		0.7552	
		RBX vs. PBO	0.9863		0.6232		0.2510		0.4527	
		PAR vs. PBO	0.1437		~~0.2376~~ 0.2805		~~0.2068~~ 0.2431		0.6148	
Observed Cases	Remission rate†	RBX	38	16.3	59	28.0	90	45.9	99	52.4
		PBO	37	15.8	66	29.6	81	38.4	94	47.0
		PAR	50	20.8	77	36.2	95	48.5	100	52.1
	P Values‡	Among Treatments	0.2175		0.1614		0.1037		0.5891	
		RBX vs. PBO	0.9863		0.7769		0.1450		0.3960	
		PAR vs. PBO	0.1437		0.1280		0.0424*		0.4336	

* $p \leq 0.05$

† 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.

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

Summary Table in Sections 3 (Synopsis) and 9.3.5 (Efficacy Discussion and Conclusions)

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

	Results by Treatment Group			P Values		
	RBX N=258	PBO N=252	PAR N=260	Overall	RBX vs PBO	PAR vs PBO
Primary Endpoint						
MADRS total score, mean change from baseline	-14.5	-12.3	-15.3	0.0021*	0.0162*	0.0006*
Secondary Endpoints						
Mean Change From Baseline						
HAM-D Item 1	-1.4	-1.2	-1.5	0.0019*	0.0243*	0.0005*
HAM-D Retardation Cluster	-4.1	-3.2	-3.9	0.0021*	0.0013*	0.0043*
CGI Severity of Illness	-1.5	-1.2	-1.5	0.0045*	0.0085*	0.0025*
HAM-D Total Score	~~-10.9~~ -11.0	-10.1	-11.8	~~0.0516~~ 0.0506	--	--
% Responders or Remitters						
MADRS Response	53.4	45.2	61.6	0.0018*	0.0672	0.0004*
MADRS Remission	47.5	42.7	54.1	0.0411*	0.2541	0.0133*
HAM-D Response	50.4	45.2	52.9	0.2691	--	--
HAM-D Remission	45.8	42.3	45.0	0.7552	--	--
CGI Global Improvement Response	54.0	49.0	64.0	0.0045*	0.3094	0.0012*

* p≤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≤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

4.2 SASS Total Score

4.2.1 Reason for Change

The algorithm that was used to calculate the SASS total score should have used the answer to the “yes/no” question ("Do you have an occupation?") as the indicator for whether to include either Item 1 ("If yes, how interested are you in your occupation?") or Item 2 ("If no, how interested are you in your home related activities?") in the total score. Instead, in the original study report, the algorithm incorrectly used Item 1 as the indicator for whether to include Items 1 or 2 in the total score. In this amendment, the error in the algorithm was corrected to use the answer to the “yes/no” question as the indicator.

In addition, an error in the algorithm for the LOCF analysis was corrected. In the original study report, the algorithm to determine whether Item 1 or Item 2 should be included in the total score was applied after the LOCF algorithm, when it should have been applied before the LOCF algorithm. As a result, a score from the previous visit may have been carried forward when a score for the current visit was present. For example, if the scores for both the “yes/no” question ("Do you have an occupation?") and Item 1 were missing and the score for Item 2 was present, then the score for Item 2 was ignored and the score for Item 1 from the previous visit was carried forward. In this amendment, the algorithm was corrected to first assess which item should be used before imputing any values from the previous visit.

4.2.2 Description of Change

Section 13, Tables 2.9, 4.16A, 4.16B, and 4.16C, were updated using the corrected algorithm for calculating the SASS total score.

The text of the report was corrected, as shown below (added text is shown with an underline; deleted text is shown with a strikethrough line).

Section 9.1.4.2.4 Severity of Depression at Baseline (In-text Table 12)

Table 12. Severity of Depression at Baseline

Variable	RBX N=258	PBO N=252	PAR N=260	P Value*
MADRS total score				
No. of patients	258	252	260	0.1209
Mean ± SD	29.8 ± 6.1	28.9 ± 5.8	28.8 ± 6.1	
Range	9 - 44	8 - 42	12 – 43	
21-Item HAM-D total score				
No. of patients	258	252	260	0.5515
Mean ± SD	24.2 ± 4.9	23.7 ± 4.8	23.9 ± 5.4	
Range	11 - 39	8 - 37	9 – 37	
CGI Severity of Illness score				
No. of patients	258	251	259	0.5610
Mean ± SD	4.3 ± 0.6	4.3 ± 0.6	4.3 ± 0.6	
Range	2 - 6	3 - 6	3 – 6	
SASS total score				
No. of patients	257	252	260	0.2205 0.2325
Mean ± SD	~~26.6 ± 7.2~~ 27.5 ± 7.4	~~26.7 ± 7.0~~ 27.7 ± 7.4	~~27.6 ± 7.5~~ 28.6 ± 7.9	
Range	7 - 50	6 - 50	10 – 50	

* 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

Section 9.3.4.1 Social Adaptation Self-evaluation Scale

No statistically significant differences were observed among the 3 treatment groups in the mean change from baseline in the SASS total score at day 56 in either the LOCF (~~p=0.254~~p=0.174) or OC analyses (~~p=0.425~~p=0.315) (Table 25). Both of the active treatment groups demonstrated a mean change from baseline in the SASS total score that was numerically superior to the mean change that was observed in the placebo group (increasing scores indicate improvement).

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	257	~~26.6~~ 27.5	234	~~3.2~~ 3.3	238	4.8	238	~~6.5~~ 6.6	238	7.3
		PBO	252	~~26.7~~ 27.7	236	2.4	239	~~4.0~~ 3.9	239	~~5.7~~ 5.6	239	~~6.3~~ 6.1
		PAR	260	~~27.6~~ 28.6	240	~~3.1~~ 3.2	240	5.2	240	6.6	241	~~7.4~~ 7.3
	P Values‡	Among Treatments	~~0.1402~~ 0.1464		~~0.2675~~ 0.1887		~~0.1194~~ 0.1016		~~0.2808~~ 0.2216		~~0.2538~~ 0.1743	
		RBX vs. PBO	~~0.7990~~ 0.7336		~~0.1307~~ 0.0935		~~0.1694~~ 0.1229		~~0.1624~~ 0.1145		~~0.1641~~ 0.1000	
		PAR vs. PBO	~~0.1174~~ 0.1357		~~0.2025~~ 0.1417		~~0.0436*~~ 0.0400*		~~0.1731~~ 0.1572		~~0.1406~~ 0.1114	
Observed Cases	Mean Change From Baseline	RBX	257	~~26.6~~ 27.5	234	~~3.2~~ 3.3	210	~~4.9~~ 5.0	196	~~6.7~~ 7.0	189	~~7.9~~ 8.2
		PBO	252	~~26.7~~ 27.7	236	2.4	222	4.0	212	~~5.8~~ 5.9	200	~~6.8~~ 6.9
		PAR	260	~~27.6~~ 28.6	240	~~3.1~~ 3.2	216	~~5.4~~ 5.6	199	~~7.0~~ 7.3	192	~~8.0~~ 8.2
	P Values‡	Among Treatments	~~0.1402~~ 0.1464		~~0.2675~~ 0.1887		~~0.0597~~ 0.0481*		~~0.1777~~ 0.1397		~~0.4247~~ 0.3148	
		RBX vs. PBO	~~0.7990~~ 0.7336		~~0.1307~~ 0.0935		~~0.2018~~ 0.1776		~~0.2523~~ 0.1874		~~0.3061~~ 0.2085	
		PAR vs. PBO	~~0.1174~~ 0.1357		~~0.2025~~ 0.1417		~~0.0178*~~ 0.0140*		~~0.0666~~ 0.0532		~~0.2230~~ 0.1708	

* $p \leq 0.05$

† Mean change from baseline value
‡ P values are based on a 2-way ANOVA.
Abbreviations: ANOVA = analysis of variance, LOCF = last observation carried forward, PAR = paroxetine, PBO = placebo, RBX = reboxetine, SASS = Social Adaptation Self-evaluation Scale
Source: Section 13, Tables 4.16A, 4.16B, and 4.16C

4.3 Laboratory and ECG Data

4.3.1 Reason for Change

In addition to the data that were collected during scheduled visits, laboratory and ECG data were also collected during unscheduled visits that occurred after screen and before the date of first dose of study medication. In the original study report, the data that were collected during these unscheduled visits were reported as unscheduled postbaseline visits. In this

amendment, the unscheduled visits that occurred after screen and before the date of first dose of study medication are designated as baseline (pretreatment) visits rather than postbaseline unscheduled visits.

4.3.2 Description of Change

Section 13, Tables 7.1, 7.2, 7.3, 7.4, 8.1, 8.2, and 8.3, and Appendix 17, Tables 13.2, 13.3, and 13.4, were revised to include the unscheduled visits that occurred after screen and before the date of first dose of study medication as baseline (pretreatment) visits rather than postbaseline unscheduled visits. In addition, the summary tables (Section 13, Tables 7.1, 7.2, and 8.1) were revised to include data from only the regularly scheduled visits.

The text of the report was corrected, as shown below (added text is shown with an underline; deleted text is shown with a strikethrough line).

Section 9.4.3.1.1 Mean Change From Baseline (Hematology)

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).

Although statistically significant differences were noted among the treatment groups in the mean change from baseline values for hemoglobin and erythrocytes at day 28, the changes were greater in the placebo group (changes of ~~-0.065x10^6/µL~~ -0.064x10^6/µL for erythrocytes and -0.23 g/dL for hemoglobin) than in the reboxetine (changes of ~~-0.005x10^6/µL~~ -0.004x10^6/µL for erythrocytes and ~~-0.05 g/dL~~ -0.04 g/dL for hemoglobin) or paroxetine (changes of ~~-0.046x10^6/µL~~ -0.045x10^6/µL for erythrocytes and -0.11 g/dL for hemoglobin) groups. The mean values remained within normal ranges, and none of these changes was considered to be clinically meaningful.

Statistically significant differences were also noted among the treatment groups in the mean change from baseline values for platelet count at days 28 and 56. Differences were due to a slight mean increase in the reboxetine group (change of ~~12.0x10^3/µL~~ 12.6x10^3/µL) and slight mean decreases in the placebo (change of –5.7x10^3/µL) and paroxetine (change of ~~-3.0x10^3/µL~~ –2.9x10^3/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 9.4.3.2.1 Mean Change From Baseline (Chemistries)

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, AST, bilirubin, creatinine, glucose, potassium, sodium, or carbon dioxide content (Section 13, Table 7.2).

Although statistically significant differences were noted among the treatment groups in the mean change from baseline values for alkaline phosphatase and serum chloride at day 56, the changes were greater in the placebo group (changes of ~~–2.14 U/L~~ –2.04 U/L for alkaline phosphatase and ~~0.82 mEq/L~~ 0.80 mEq/L for chloride) than in the reboxetine (changes of ~~1.73 U/L~~ 1.80 U/L for alkaline phosphatase and ~~0.04 mEq/L~~ 0.01 mEq/L for chloride) or paroxetine (changes of 0.74 U/L for alkaline phosphatase and 0.09 mEq/L for chloride) groups. The mean values remained within normal ranges, and none of these changes was considered to be clinically meaningful.

Statistically significant differences were also noted among the treatment groups in the mean change from baseline values for blood urea nitrogen at day 28. Differences were due to a slight mean increase in the placebo group (change of ~~0.40 mg/dL~~0.37 mg/dL) and to slight mean decreases in the reboxetine (change of ~~–0.55 mg/dL~~ –0.52 mg/dL) and paroxetine (change of ~~–0.30 mg/dL~~ -0.31 mg/dL) groups between baseline and day 28. No statistically significant differences were noted among the 3 treatment groups in the mean change from baseline values for blood urea nitrogen at day 56. The mean values at day 28 remained within normal ranges, and none of these changes was considered to be clinically meaningful.

Statistically significant differences were also noted among the treatment groups in the mean change from baseline values for uric acid at days 28 and 56. Differences at day 56 were due to a slightly greater mean decrease in the reboxetine group (change of ~~–0.23 mg/dL~~ -0.24 mg/dL) than in the placebo (change of –0.03 mg/dL) or paroxetine (change of -0.01 mg/dL) 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 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 serum chloride and glucose values, fewer than 10% of patients in any treatment group had postbaseline chemistry values that were outside of normal ranges.

Serum chloride values that exceeded the predefined limit (>108 mEq/L) were reported in comparable proportions of patients in each treatment group: 9.0% (19/211) of the patients in the reboxetine group, 12.6% (27/~~215~~214) of the patients in the placebo group, and 10.2% (22/215) of the patients in the paroxetine group had chloride values that exceeded the

predefined limit. 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 also reported in comparable proportions of patients in each treatment group: 17.7% (36/203) of the patients in the reboxetine group, 15.8% (32/202) of the patients in the placebo group, and ~~17.8%~~17.7% (37/~~208~~209) 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	~~216~~ 217	~~2 (0.9)~~ 3 (1.4)	~~228~~ 227	2 (0.9)	227	~~5 (2.2)~~ 6 (2.6)
Total Bilirubin	219	6 (2.7)	~~229~~ 228	1 (0.4)	229	1 (0.4)
ALT	213	7 (3.3)	~~223~~ 222	14 (6.3)	223	~~9 (4.0)~~ 10 (4.5)
AST	218	5 (2.3)	~~225~~ 224	~~10 (4.4)~~ 10 (4.5)	226	~~6 (2.7)~~ 7 (3.1)
Creatinine	221	0	~~227~~ 226	1 (0.4)	227	2 (0.9)
BUN	217	0	~~221~~ 220	4 (1.8)	220	2 (0.9)

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

Section 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 2.5% (5/~~201~~200) in the reboxetine group, 3.2% (7/218) in the placebo group, and 4.8% (10/209) in the paroxetine group (Section 13, Table 8.2). The majority of these 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. Only 1 patient (patient no. 2365 in the paroxetine group) had a normal ECG at baseline and an abnormal ECG finding postbaseline

(day 28) that was classified as clinically relevant. The ECG abnormality that was observed at day 28 was myocardial infarction in septal leads (V1, V2, [V3]). However, the ECG evaluation at day 56 was normal for this patient, and no cardiovascular-related adverse events were reported during the study.

Section 9.4.5.2.2 Values Outside of Predefined Limits (In-text 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	~~206~~205	0	227	5 (2.2)	217	4 (1.8)
Tachycardia	≥120 beats/min	~~206~~205	0	227	0	217	0
PR Interval	≤110 msec	~~210~~209	1 (0.5)	227	2 (0.9)	224	1 (0.4)
	≥210 msec	~~210~~209	0	227	2 (0.9)	224	1 (0.4)
QRS Interval	≤30 msec	~~210~~209	0	228	0	223	0
	≥110 msec	~~210~~209	3 (1.4)	228	0	223	7 (3.1)
QT Interval	≥470 msec	~~215~~214	0	229	0	227	0
QTc Interval (Bazett's)	≥450 msec (males) ≥470 msec (females)	~~215~~214	3 (1.4)	227	2 (0.9)	225	0
QTc Interval (Fridericia's)	≥450 msec (males) ≥470 msec (females)	~~215~~214	1 (0.5)	229	0	227	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

4.4 Pregnancy Tests

4.4.1 Reason for Change

In the original report, the denominator (N) in Appendix 14, Tables 10.4A and 10.4B, included only patients who had a pregnancy test at screen (ie, patients who had a pregnancy test at a postbaseline visit but not at the screen visit were excluded from these tables). The numerator (n) included any patients who were included in the denominator (N) and who had a positive pregnancy test at any visit. Thus, in the original tables, patients who did not have a pregnancy test at screen but who had a positive result on a pregnancy test at a postbaseline visit were excluded from the tables. In this amendment, the tables were revised so that the denominator (N) includes patients who had a pregnancy test at any visit. This correction did

not change the number of pregnancies that were described in the original report (see Section 9.4.6 [Exposure In Utero] in the original report).

4.4.2 Description of Change

Appendix 14, Tables 10.4A and 10.4B, were revised to include in the denominator (N) all patients who had a pregnancy test at any visit.

The text of the report was corrected, as shown below (added text is shown with an underline; deleted text is shown with a strikethrough line). A footnote was added to the in-text Table 6, to explain that this table shows the number of patients who had a positive pregnancy test at screen, whereas Appendix 14, Table 10.4A, summarizes the number of patients who had a positive pregnancy test at any visit.

Section 9.1.2 Protocol Deviations (In-text Table 6)

Table 6. Protocol Deviations

	RBX		PBO		PAR	
	N*	n (%)	N*	n (%)	N*	n (%)
Use of disallowed psychotropic medications	258	11 (4.3)	252	20 (7.9)	260	9 (3.5)
Patient age >65 years	258	0	252	0	260	1 (0.4)†
Dose of study medication exceeding the protocol-specified dosage regimen						
>10 to <12 mg/day RBX or >40 to <50 mg/day PAR	258	29 (11.2)			260	21 (8.1)
≥12 mg/day RBX or ≥50 mg/day PAR	258	12 (4.7)			260	11 (4.2)
Positive urine drug screen‡	255	3 (1.2)	248	4 (1.6)	258	5 (1.9)
Positive serum pregnancy test at screen§	~~148~~ 164	0	~~172~~ 187	0	~~146~~ 158	~~2 (1.4)~~ 2 (1.3)

* 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.

† This patient (patient no. 2404) was 66 years of age.

‡ 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.

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

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

4.5 Typographical Error

A typographical error in the text of the report was corrected, as shown below (added text is shown with an underline; deleted text is shown with a strikethrough line).

Section 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 8.5% (22/258) of reboxetine-treated patients, 6.0% (15/252) of ~~paroxetine~~placebo-treated patients, and 8.8% (23/260) of ~~placebo~~ paroxetine-treated patients (Table 10).