Studie 052

(97-CRBX-052)

Studienbericht

Pharmacia & Upjohn

PNU-155950E
Reboxetine Mesylate

CLINICAL RESEARCH
Protocol 97-CRBX-052

09 September 2004

Reboxetine (PNU-155950E) *vs* Paroxetine in a Double-Blind, Multinational Study of Treatment in Major Depressive Disorder.

Final Report of the Study
97-CRBX-052

Previous Reports of the Study:
None

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

Trial Initiation Date	29 June 1999
Trial Completion Date	08 November 2000
Global Director, CNS	Gerri E. Schwartz, PhD Clinical Development Therapeutic Area CNS Pharmacia & Upjohn, Inc. Peapack, New Jersey 07977
Medical Director	Joel Krasnow, M.D.
Development Phase of Trial	IIIB
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1 SIGNATURE PAGE

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

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2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 42 principal investigators participated in this trial at 42 centers in the United Kingdom, Germany, Italy, Sweden, Denmark, Spain, Portugal, Belgium, and Austria. Appendix 2 lists the investigators and their affiliations, and curricula vitae for each are located in the master file at the Market Companies. Appendix 1 contains the signature of the sponsor's responsible medical officer.

Laboratory tests were performed at SmithKline Beecham Clinical Laboratories (Middlesex, England and Van Nuys, CA for the drug/alcohol screen), that later changed its name to Quest Diagnostics part way through the study.

3 SYNOPSIS

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

Title of study:
Reboxetine (PNU-15590E) *vs* paroxetine in a double-blind, multinational study of treatment in major depressive disorder

Protocol number:
97-CRBX-052

Investigators and Study Centers:
The study was conducted at 41 study centers, including 9 centers in the United Kingdom, 7 centers in Germany, 5 centers in Italy, 6 centers in Belgium, 4 centers in Spain, 4 centers in Portugal, 2 centers in Sweden, 2 centers in Denmark, and 2 centers in Austria (see Appendix 2 for a complete list).

Publication (reference):
none

Studied period (years):
Date of first enrollment: 29 June 1999
Date of last patient visit: 08 November 2000

Phase of development:
IIIB

Objectives

Primary:
To assess efficacy and tolerability of reboxetine in comparison with paroxetine in patients suffering from Major Depressive Disorder (MDD) as determined by the Hamilton Rating Scale for Depression (HAM-D) scale.

Secondary:
To assess efficacy of reboxetine in comparison with paroxetine in patients suffering from MDD as determined by the Montgomery-Asberg Depression Rating Scale (MADRS), Medical Outcomes Study Short-Form Health Survey (36 items) (SF-36), Clinical Global Impression (CGI), Social Adaptation Self-evaluation Scale (SASS) scales, and the Rush Sexual Inventory (RSI) scales.

Methodology:
This phase III, multicenter, randomized, double-blind, active-controlled, parallel-group study was conducted in 325 patients (randomized population) aged 18 to 68 years who suffered from MDD without psychotic features, as diagnosed using criteria defined by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) [2]. Written informed consent was obtained for each patient prior to entry into the study. Patients were required to have a screening total score of ≥22 and ≤35 on the 17-Item HAM-D that was confirmed at the baseline visit after an appropriate washout period based on the type of previously used psychoactive medication(s). Eligible patients were randomized to receive 8 weeks of treatment with reboxetine (8mg/day, days 0-27; 8-10mg/day, days 28-56) or paroxetine (20mg/day, days 0-27; 20-40mg/day, days 28-56). The optional dose increase to 10mg/day of reboxetine or 40mg/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. If the investigator considered it safe and preferable, patients were given the option to continue on blinded treatment (at the same dose as day 56) for up to 16 additional

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weeks in a post-study continuation (results to be presented as an addendum to this study report). Study visits were conducted weekly during the 8 weeks of treatment and post-study visits were conducted at the investigator's discretion for non-study visits and at the end of the 16 weeks of post-study treatment. Efficacy and safety measures were assessed weekly at every visit.

Number of patients (planned and analyzed):
300 planned, 325 analyzed (159 reboxetine, 166 paroxetine)

Diagnosis and main criteria for inclusion:
Male or female subjects ≥18 and ≤65 years of age who had a diagnosis of major depressive disorder (MDD) (without psychotic features, dysthymic or cyclothymic disorder, bipolar I or bipolar II disorders, substance-related disorders, schizophrenia, other psychotic disorders, or MDD associated with endocrine disorders) as defined by DSM-IV were eligible for the trial. Patients must have a screen and baseline HAM-D total score of ≥22 and ≤35 and an Item 3 score of <3. Patients must not have any medical complication or physical finding that could interfere with study activities or drug absorption, distribution, metabolism or excretion; a history of electroconvulsive therapy within the previous 6 months; hypersensitivity or a lack of response to a previous course of reboxetine or paroxetine; or a positive serum pregnancy test or breast feeding. Patients could not take any psychotropic medications (other than protocol-specified sedatives/hypnotics that could be taken on an as-needed basis for sleep) or any medications that are known to inhibit major drug-metabolizing enzymes (other than cytochrome p450-2D6) or vitamin K-dependent coagulation factors.

Test product, dose and mode of administration, batch number
Reboxetine was supplied as capsules containing PresTabs in strengths of 2 or 4mg. From baseline through week 4 (days 0 to 27) reboxetine was administered in twice-daily doses of 4mg, for a total of 8mg daily. After 4 weeks of treatment (days 28 through 56), an optional increase to 10mg/day was available with patients taking a 4-mg dose in the morning and a 6-mg dose in the late afternoon. The lot numbers for 2-, 4-, and 6-mg capsules are provided in Appendix 6.

Duration of treatment:
Patients were to be treated for a total of 8 weeks unless, in the opinion of the investigator, it was medically necessary or the wish of the patient to withdraw from treatment. A post-study continuation of up to 16 additional weeks of treatment was provided for patients whom it was considered safe and preferable to continue blinded treatment at the same dose as day 56. (Results for the post-study continuation will be provided as an addendum to this report.)

Reference therapy, dose and mode of administration, batch number:
Paroxetine was manufactured by SmithKline Beecham Pharmaceuticals and repackaged as capsules containing PresTabs in strengths of 20 or 40mg. From baseline through week 4 (days 0 to 27), paroxetine was administered in a morning dose of 20mg/day. After 4 weeks of treatment (days 28 through 56), an optional increase to 40mg/day was available with patients taking a 40-mg dose in the morning. Lot numbers for the 20- and 40-mg capsules are provided in Appendix 6.

Placebo capsules consisting of lactose-filled gelatin capsules were administered in the late afternoon to maintain the study blind. Lot numbers for the placebo capsules are also provided in Appendix 6.

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Criteria for evaluation:
Efficacy:
The primary efficacy endpoint was the absolute change from baseline in the 17-Item HAM-D total score.

The secondary efficacy endpoints of this study were the response/remission rates and time to response/remission of the 17-Item HAM-D total, and the CGI scale. A decrease of at least 50% in the HAM-D total score versus baseline was considered the index of response. A HAM-D total score of ≤10 was considered the index of remission. Additional secondary efficacy endpoints included measures of mean change from baseline in the MADRS total score, CGI, 21- and 28-Item HAM-D totals, quality of life (QOL), the SF-36; a scale exploring social functioning, the SASS; and a measure of sexual function using the RSI scale.

Safety:
Adverse events, electrocardiogram (ECG), supine blood pressure and pulse, and laboratory assays were used to monitor patient safety.

Statistical methods:
For the continuous variables (ie, HAM-D total and SASS total), testing for difference between 2 treatment groups was performed using a 2-way analysis of variance (ANOVA) model that included treatment, investigator, age, and baseline terms. Treatment-by-investigator interaction was explored and included if it contributed significantly to the model. The response variables were to be the change from baseline scores at each visit. Treatment-by-investigator interaction was to be tested to evaluate poolability of data. If the interaction effect was significant at the 0.10 level ($p<0.10$), the individual investigator results were to be presented to identify the source of the interactions.

Categorical data (ie, response and remission) were to be analyzed by Cochran-Mantel-Haenszel (CMH) test, stratified by investigator. In addition to p-values, 95% confidence intervals for the difference between 2 treatment groups would also be computed for HAM-D total mean change from baseline, SASS total mean change from baseline, response rate, and remission rate.

Means of individual components of the HAM-D were to be displayed by treatment group and by visit to identify any components that may have major influence on the HAM-D total. This analysis was to be descriptive and would not include statistical hypothesis testing.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:
In the LOCF analysis of the primary endpoint at week 8, although both reboxetine and paroxetine did show improvement in the 17-Item HAM-D total scores, paroxetine displayed better efficacy by demonstrating a statistically significant difference among treatment groups in the mean change from baseline in the 17-Item HAM-D total score (reboxetine mean change, -11.5; paroxetine mean change, -13.2; p=0.0345). The secondary endpoint LOCF analyses at week 8 continued to show a numerically greater mean change in the paroxetine group in all efficacy endpoints studied, however without statistical significance.

The results seen in the OC analysis (a secondary analysis) did not support the findings of the LOCF analysis. In the OC analysis of the primary endpoint at week 8, the mean change from baseline in the 17-Item HAM-D total score was –15.2 in both treatment groups (p=0.9881). The secondary endpoint analyses continued to show a numerically equal or greater mean change in the reboxetine group in all efficacy endpoints studied, except in HAM-D remission. None of these differences was statistically significant.

The results from the secondary measures of quality of life and social and sexual function, (evaluated by the SF-36 survey and SASS and RSI scales [patient rated]) clearly indicate improvement in these areas among both treatment groups during the study, with, in general, more favorable results in the reboxetine group.

SAFETY RESULTS:
The percentage of patients reporting adverse events was approximately equivalent among the paroxetine (75.3%, 125/166) and reboxetine (73.2%, 115/157) treatment groups. The most frequently reported adverse event (reported in at least 5% of reboxetine-treated patients) were dry mouth, constipation, insomnia, headache, diaphoretic, nausea, dizziness, impaired urination, palpitations, chills, and dysuria. The frequency of insomnia was the highest in week 1 (25/157, 15.9%), and the incidence decreased by week 2 (19 patients) and was the lowest in both weeks 7 and 8 (10 patients). In the paroxetine group, the most frequently reported adverse events (reported in at least 5% of paroxetine-treated patients) were headache, nausea, constipation, diarrhea, asthenia, dry mouth, insomnia, tremor, dizziness, somnolence, and , diaploresis. The majority of adverse events reported by patients in both treatment groups were mild to moderate in intensity.

Adverse events that were judged by the investigators to have been caused by the study medication were reported in 63.1% (99/157) of reboxetine-treated patients and 62.7% (104/166) of paroxetine-treated patients. Of the drug-related adverse events that were reported in ≥5% of patients in the reboxetine treatment group, the following events were reported: dry mouth, constipation, insomnia, diaploresis, nausea, headache, dizziness, palpitations, and chills.

No deaths were reported during this study. Serious adverse events were reported in 5.1% (8/157) of reboxetine-treated patients and 1.8% (3/166) of paroxetine-treated patients. In the reboxetine group, the following non-drug-related serious adverse events were each reported in 1 patient: autolysis risk, acute pancreatitis, unilateral epididymec [sic], severe hemorrhage, high blood pressure and heart attack, overreaction to stress, and exacerbation of depression. One event, occurring in patient no. 69302 in the reboxetine group, was judged by the investigator to have been related to the study medication (a peripheral vascular disorder [ie, cold extremities]). The patient recovered from this event 9 days after discontinuing the study (see narrative summary in Section 9.4.2.4). In the paroxetine group, the following non-drug-related serious adverse events were each reported in 1 patient: angina pectoris, suicide attempt, and cholecystectomy.

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Of the patients evaluable for safety analysis, the percentage of patients who discontinued treatment due to adverse events at any time during the treatment period was higher in the reboxetine group (19.7%; 31/157) than in the paroxetine group (8.4%; 14/166), perhaps due to a reboxetine non-titration-starting dose of 8mg/day. Most of the reboxetine patients that discontinued due to adverse events did so in the first week of treatment (6.3%; 10/159). Perhaps the relatively high rate of reboxetine discontinuations in the first week was due to a non-titration-starting dose of 8mg/day.

CONCLUSION:
In conclusion, although both reboxetine and paroxetine did show improvement in the 17-Item HAM-D total scores, paroxetine displayed better efficacy by demonstrating a statistically significant difference among treatment groups in the mean change from baseline in the 17-Item HAM-D total score (reboxetine mean change, -11.5; paroxetine mean change, -13.2; p=0.0345). The adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. No new safety concerns associated with the use of reboxetine were identified.

Date of the report:
03 December 2001

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4 ABBREVIATIONS AND DEFINITION OF TERMS

ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
CGI	Clinical Global Impression
CI	Confidence Interval
COSTART	Coding Symbols and Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECG	Electrocardiogram
HAM-D	Hamilton Rating Scale for Depression
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
SF-36	Medical Outcomes Study Short-Form Health Survey (36 items)
OC	Observed Cases
QOL	Quality of Life
RSI	Rush Sexual Inventory Scale
SASS	Social Adaptation Self-evaluation Scale
SSRI	Selective Serotonin Reuptake Inhibitors
T_4	Thyroxine
TCA	Tricyclic Antidepressants
TES	Treatment-Emergent Symptoms
TSH	Thyroid-Stimulating Hormone

5 ETHICS

5.1 Independent Ethics Committee (IEC)

The protocol and all amendments for this trial were reviewed by Independent Ethics Committees (IEC)/Institutional Review Boards (IRB). Appendix 3 contains a copy of the protocol and its amendments*, Appendix 4 contains copies of the unique pages of the case report forms (CRF), and Appendix 5 lists the IECs/IRBs that were consulted.

5.2 Ethical Conduct of the Study

Monitoring and auditing 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. Section 9.1.2 lists the protocol deviations that occurred during this study.

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 3 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 similar 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

* Amendments 1 and 2 were made to the protocol before the study was initiated, therefore, a “working protocol” that incorporates these amendments was given to the investigators and sent to their IEC/IRB for approval. Because of the extensive changes that were made to the protocol (as detailed in Amendments 1-4), a second “working protocol,” which incorporates Amendments 1 through 4, was provided to the investigators as a convenience and was not sent to IEC/IRB for approval since the sites had already separately submitted Amendments 3 and 4 for approval.

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, one third partial responses, 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, therefore, 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 indicate that reboxetine is effective in the treatment of patients with symptoms secondary to major depression.

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 may indicate a better quality of remission for social adaptation in the reboxetine-treated patients.

In terms of safety 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.

7 OBJECTIVES

7.1 Primary Objective

To assess efficacy and tolerability of reboxetine in comparison with paroxetine in patients suffering from Major Depressive Disorder (MDD) as determined by the HAM-D scale.

7.1.1 Primary Endpoint

The primary efficacy measure was the absolute change from baseline of the 17-Item HAM-D total score.

7.2 Secondary Objective

To assess efficacy of reboxetine in comparison with paroxetine in patients suffering from MDD as determined by the Montgomery-Asberg Depression Rating Scale (MADRS), Medical Outcomes Study Short-Form Health Survey (36 items) (SF-36), Clinical Global Impression (CGI), and SASS scales.

7.2.1 Secondary Endpoint(s)

The secondary efficacy measures were mean change from baseline in the CGI, MADRS total score, and the 21- and 28-Item HAM-D total scores, as well as response/remission rates, and time to response/remission. A decrease of at least 50% in the HAM-D total score versus baseline was considered the index of response whereas a HAM-D total score of 10 or less was considered index of remission. Additional secondary efficacy measures included measures of quality of life (QOL) using the SF-36, and a scale exploring social functioning, the SASS. Another secondary endpoint was a measure of sexual function using the Rush Sexual Inventory (RSI) scale.

8 METHODS

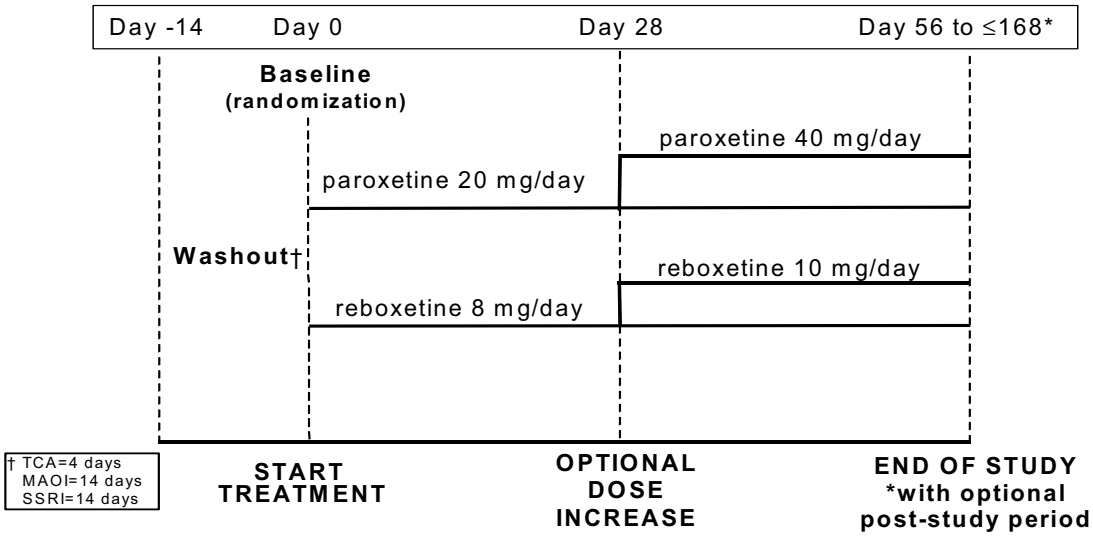
8.1 Overall Study Design and Plan

This phase III, multicenter, randomized, double-blind, 2 arm active-controlled, parallel-group study was conducted in 325 patients (randomized population) aged 18 to 68 years who suffered from MDD without psychotic features, as diagnosed using criteria defined by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) [2]. Written informed consent was obtained for each patient prior to entry into the study. Patients were required to have a screening total score of ≥22 and ≤35 on the 17-Item HAM-D that was confirmed at the baseline visit after an appropriate washout period based on the type of previously used psychoactive medication(s). Eligible patients were randomized to receive 8 weeks of treatment with reboxetine (8mg/day, days 0-27; 8-10mg/day, days 28-56) or paroxetine (20mg/day, days 0-27; 20-40mg/day, days 28-56). The optional dose increase to 10mg/day of reboxetine or 40mg/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.

If the investigator considered it safe and preferable, patients were given the option to continue on blinded treatment (at the same dose as day 56) for up to 16 additional weeks in a post-study continuation (results to be presented as an addendum to this study report). Study visits were conducted weekly during the 8 weeks of treatment and post-study visits were conducted at the investigator's discretion for non-study visits and at the end of the 16 weeks of post-study treatment. Efficacy and safety measures were assessed weekly at every visit.

The study design is presented in Figure 1

Figure 2. 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 chosen because it is one of the most commonly prescribed SSRIs and because its efficacy and safety have been demonstrated and documented in several placebo- and active-controlled trials.

HAM-D was chosen as the primary efficacy measure in this study because its use in a wide variety of populations has proven its validity and reliability and has, therefore, become accepted internationally as a standard measure of the severity of depression in psychiatric research. The MADRS, SF-36, CGI, and SASS scales were chosen as the secondary efficacy measure in this study. The MADRS, a newer rating scale than the HAM-D, has also been used successfully to assess the severity of depression, and has been shown to be sensitive to changes in patient symptoms. The SF-36 is a quality-of-life scale that has been used extensively in patients with clinical depression. The CGI has been routinely used as an outcome measure in therapeutic trials. The SASS is an easy-to-handle self-rating scale that provides a means of collecting patient perception of his/her level of social motivation and functioning.

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 oral contraceptive, implantable or injectable contraceptive, intrauterine device, or barrier method, or have been surgically sterilized
- Total score of ≥22 and ≤35 on the 21-Item HAM-D at screen and confirmed at baseline.
- 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, dysthymic or cyclothymic disorder, bipolar I or bipolar II disorders, substance-related disorders, schizophrenia, or other psychotic disorders.
- A lack of response to a previous course of either reboxetine or paroxetine.
- History of MDD associated with endocrine disorders: hypo- or hyper-thyroidism tested by thyroid-stimulating hormone and thyroxine, adrenal insufficiency, or Cushing's syndrome, etc.
- Positive serum pregnancy test for females of childbearing potential.
- Breast-feeding female patients.
- Participation in a clinical study with an investigational compound in the 4 weeks preceding the study.
- 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.
- 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 known to inhibit major drug-metabolizing enzymes other than cytochrome p450-2D6: azole antifungals, macrolide antibiotics (such as erythromycin), or fluvoxamine.
- 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. Termination of study medication prior to study completion was considered in cases of adverse events, pregnancy, increased risk of suicide, clinical deterioration, and switch to mania. The reasons for the withdrawal of 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.

8.4 Treatments

8.4.1 Trial Products

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

From baseline through week 4 (days 0-27), reboxetine was administered in twice-daily doses of 4mg, for a total daily dose of 8mg of reboxetine. After 4 weeks of treatment, the reboxetine dose was increased to 10mg/day (administered as a 4-mg dose in the morning and a 6-mg dose 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 20mg of paroxetine. After 4 weeks of treatment, the paroxetine dose was increased to 40mg/day (administered as a morning dose of 40mg 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.

After 8 weeks of treatment, if the investigator considered it safe and preferable, patients were given the option to continue blinded treatment (at the same dose as day 56) for up to 16 additional weeks in a post-study continuation.

8.4.2 Identity of Investigational Products

Study medications for the randomized treatments consisted of identically appearing capsules that contained PresTabs of 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 obtained commercially 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, Manufacturers, and Batch Numbers

Study Medication	Capsule Strength	Manufacturer	Lot Numbers*
Reboxetine	2mg (one 2-mg PresTab)	P&U	Provided in Appendix 6
Reboxetine	4mg (one 4-mg PresTab)	P&U	
Reboxetine	6mg (one 2-mg PresTab and one 4-mg PresTab)	P&U	
Paroxetine	20mg (one 20-mg PresTab)	SmithKline Beecham, (repackaged by P&U)†	
Paroxetine	40mg (one 40-mg PresTab)	SmithKline Beecham, (repackaged by P&U)†	
Placebo	Not applicable	P&U	

* Appendix 6 lists the patient numbers according to the lot number of study medication that each patient received.

† Paxil tablets, manufactured by SmithKline Beecham Pharmaceuticals, were inserted into gelatin capsules by Pharmacia & Upjohn

The study medications were provided in product packages that were labeled (in the appropriate language) with the protocol number, the patient number, the study week (1 through 8), and the dose level (I or II). Each product package labeled as dose level I contained 2 bottles that provided the study medication for the first 4 weeks; 1 bottle contained capsules for the morning dose, and 1 bottle contained capsules for the late afternoon dose. Two extra capsules (total of 9 capsules) were included in each bottle, to allow for possible loss or extra days between visits.

To allow for the optional dose increase after week 4 (day 28), an additional package was provided and labeled as dose level II. The product packages that contained the regular dose (8mg/day of reboxetine, 20mg/day of paroxetine with placebo) were marked as dose level I and patients were to continue taking medication from these bottles. The packages that were issued for patients taking the escalated dose were marked as dose level II. Patients were to take 1 capsule from each dose level I and II bottles in the morning and 1 capsule from each dose level I and II bottles in the evening. The dose level II bottles contained placebo capsules for the morning dose and 2mg reboxetine capsules for the late afternoon dose. Therefore, the dose for these patients from weeks 4 through 8 was 4mg reboxetine each morning and 6mg reboxetine each afternoon (10mg reboxetine daily). The 2 bottles labeled as dose level II for patients randomized to paroxetine contained 20mg paroxetine capsules in the morning bottle and placebo capsules in the late afternoon bottle. Therefore the dose for these patients from weeks 4 through 8 was 40mg paroxetine each morning and placebo each afternoon (40mg paroxetine daily).

After 8 weeks of treatment, if the investigator considered it safe and preferable, patients were given the option to continue on blinded treatment (at the same dose as day 56) for up to 16 additional weeks in a post-study continuation.

Medications were dispensed to patients at each visit during the 8-week treatment period. At the same visit, the patients were to return the bottles that had been dispensed at the previous visit. All unused medications and empty bottles were to be 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 6 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 patient assignment to 1 of the 2 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 7 contains the randomization code. The study blind was broken based on the status of the database when all patients had completed the 8-week treatment period, regardless of whether those patients were still in the 16-week continuation period.

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 starting dose of paroxetine that was administered in this study (20mg/day) has been shown to be the minimally effective and optimal dose for most patients. The optional dose increase to 40mg/day of paroxetine is consistent with the recommended increase in patients who do not respond to treatment with 20mg/day [19].

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).

Reboxetine was administered at a dose of 8mg/day during the first 4 weeks of treatment. Paroxetine was administered at a dose of 20mg/day during the first 4 weeks of treatment.

An optional dose increase (to 10mg/day of reboxetine or 40mg/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 tolerating the initial dosage 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 decreased the dose back to the initial dosing regimen (used from baseline through week 4).

After 8 weeks of treatment, if the investigator considered it safe and preferable, patients were given the option to continue on blinded treatment (at the same dose as day 56) for up to 16 additional weeks in a post-study continuation.

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 or paroxetine with placebo. The capsules were provided in clinical supply packages that were labeled (in the appropriate language) with the protocol number, patient number, treatment period, dose level (I or II), dosing directions, and storage conditions.

Investigators were given sealed drug-disclosure sheets containing information that revealed each patient's treatment assignment. These sheets were opened only in case of emergency, when knowledge of the treatment was necessary for proper management of the patient. If the drug-disclosure sheet 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 to be 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 lorazepam, zolpidem, or chloral hydrate, 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 leading to the exclusion of the patient from the study. Use of St. John's Wort was also not allowed during the study.

Other therapy that was considered necessary for the patient's welfare was permitted at the investigator's discretion. All such therapy was recorded on the Non-Investigational Medication CRF.

No other investigational drug or drug mentioned in the exclusion criteria was permitted 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 Non-Investigational 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 the number of capsules dispensed and returned were recorded.

Acceptable patient compliance during or following treatment was defined as an overall drug intake of at least 80% of the prescribed amount (for analysis purposes, 80% compliance was used in this report instead of 90%, as originally proposed in the protocol) to comply with current protocol standards. Treatment compliance was monitored by the investigators and was recorded on the appropriate CRF at each visit.

8.4.9 Continuation of Treatment

After completion of the 8 weeks of study treatment, the patients were given the opportunity to continue on the same (blinded) treatment for an additional 16 weeks. Post study continuation was offered only if it was considered by the investigator to be safe and preferable compared to other available treatment options for depression. The frequency of patient office visits was according to the investigator's discretion for these non-study visits. However, at the end of the post-study period (ie, 16 weeks or study discontinuation prior to that), the patient was seen by the investigator for an evaluation of depressive symptoms (including HAM-D, MADRS, CGI, SF-36, SASS, and RSI) as well as reporting of any adverse events. Findings of the post-study continuation will be reported in an addendum to this report.

8.5 Efficacy and Safety Variables

8.5.1 Study Schedule

The schedule of study activities is summarized in Table 2.

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Table 2. Schedule of Activities

Study Activity	Study Week										
	Screening -2	Baseline 0	1	2	3	4	5	6	7	8	F-U* 24
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	X	X	X
ECG	X					X				X	
Laboratory Assays	X					X				X	
Pregnancy test (serum)	X									X	
Urine drug screen	X									X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X
17-Item HAM-D	X	X	X	X	X	X	X	X	X	X	X
MADRS		X	X	X	X	X	X	X	X	X	X
CGI		X	X	X	X	X	X	X	X	X	X
SASS		X	X	X	X	X	X	X	X	X	X
SF-36		X	X	X	X	X	X	X	X	X	X
RSI		X				X				X	X
Non-Investigational Medication	X	X	X	X	X	X	X	X	X	X	
Compliance			X	X	X	X	X	X	X	X	X
Adverse Events Query		X	X	X	X	X	X	X	X	X	X

* Post-study, follow-up visit after continued treatment for up to 16 additional weeks.

Abbreviations: CGI = Clinical Global Impression, ECG = electrocardiogram, F-U = follow-up, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, RSI = Rush Sexual Inventory scale, 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 week (weeks 0, 1, 2, 3, 4, 5, 6, 7, and 8) and at the post-study continuation (week 24), if applicable, using the results of both clinician- and patient-rated assessment instruments Table 3..

Table 3. Efficacy Measures

Domain	Assessment Instrument	Endpoint	Rater
Depression	17-Item HAM-D	Primary	Clinician
	MADRS	Secondary	Clinician
	CGI	Secondary	Clinician
Quality of Life	SF-36	Secondary	Patient
Social Function	SASS	Secondary	Patient
Sexual Function	RSI	Secondary	Patient

Abbreviations: CGI = Clinical Global Impression, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, RSI = Rush Sexual Inventory scale, 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 absolute change from baseline in the Hamilton Depression Rating Scale (17-Item HAM-D) total score. A decrease of at least 50% in the HAM-D total score versus baseline was considered the index of response. A HAM-D total score of ≤10 was considered the index of remission.

8.5.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study were the response/remission rates and time to response/remission of the MADRS Total, and the CGI scale. Additional secondary efficacy endpoints included measures of QOL, the SF-36; a scale exploring social functioning, the SASS; and a measure of sexual function using the RSI scale.

8.5.2.3 Description of Efficacy Scales

All clinical efficacy assessments were to be done by the investigator/co-investigator or personnel suitably trained and delegated by the primary investigator. All psychiatric evaluations and ratings were to be carried out by the same observer for a given patient, preferably in the same setting and at the same time of day.

8.5.2.3.1 Hamilton Depression Rating Scale

The 17-, 21-, and 28-Item HAM-D [20] are observer-rated scales that are 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 higher the score, the greater the severity). Total scores on the 17-Item HAM-D 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.

8.5.2.3.2 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 [22]. The ability of the MADRS to differentiate between antidepressant treatment responders and non-responders, and to distinguish between subjects who are likely and less likely to experience somatic adverse events from treatment, has been demonstrated in several studies [21, 23, 24, 25]. The MADRS consists of 10 items, each of which is scored on a 7-point scale on which 0 corresponds to the absence of the symptom and 6 corresponds to the most extreme form of the symptom. The MADRS total score ranges from 0 to 60. Remission is defined as a MADRS total score of ≤12. Response to study medication is defined as a decrease of ≥50% from baseline in the MADRS total score at the postbaseline assessment.

8.5.2.3.3 Clinical Global Impression

The CGI [26] consists of the following 3 parts: Severity of Illness, Global Improvement, and Efficacy Index. A mean decrease from baseline on the CGI Severity of Illness score represents patient improvement. The Severity of Illness and Global Improvement parts are 7-point measures, with lower scores indicating better health. The Efficacy Index calls for an estimation of therapeutic effect in relation to severity of side effects based on a 4-by-4 grid. 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 it emphasizes a domain that is different from other scales of

depression and might provide information about drug sensitivity in those specific areas of functioning.

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

The SF-36 [27, 28] 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. The reliability and validity of the 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.

8.5.2.3.6 Rush Sexual Inventory (RSI) Scale

The RSI scale 29 is a comprehensive, succinct, self-rated patient inventory created to assess changes in sexual function over time. Each inventory consists of 5 visual analog items and individual "yes/no" gender-separated items. The scale includes queries for premorbid as well as current functioning and may be administered at any chosen interval. Completion time for the patient averages 7 minutes.

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 screen and each visit in the supine position (after 5 minutes supine).
- Adverse events recorded at each visit.
- ECG obtained at screen, week 4, and week 8 (end of treatment). Abnormal ECG patterns were assessed and the heart rate, PR, QRS, QT and QTc intervals were measured.
- Laboratory assays: hematology and serum chemistries were performed at screen and on weeks 4 and 8, serum pregnancy tests for females of childbearing potential were performed at screen and week 8, and thyroid-function tests and a urine drug test were performed at screen. Laboratory tests were performed at SmithKline Beecham Clinical Laboratories (Middlesex, England and Van Nuys, CA for the drug/alcohol screen), that later changed its name to Quest Diagnostics. The specific tests that were evaluated are summarized in Table 4 4..

Table 4. Laboratory Assays

Category	Assay
Hematology	Hematocrit Hemoglobin White blood cell count Differential Total neutrophils Lymphocytes Monocytes Eosinophils Basophils Platelet count Red blood cell count Mean corpuscular volume Reticulocyte 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 week 8
Urinalysis	Drug screen (including benzodiazepine assay) with alcohol screen (screen and week 8)

8.5.3.2 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 the first dose of investigational medication until 1 week after 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 overdose, 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 non-invasive and invasive 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.

8.5.3.2.1 Eliciting Adverse Event Information

Investigators reported all directly observed adverse events and all adverse events that were spontaneously reported by the patients and not present at baseline. In addition, each patient was questioned about adverse events at each clinic visit, in an open-ended manner: "Since your last clinic visit," (or "Since you began taking the investigational medication,") "have you had any health problems?"

8.5.3.2.2 Adverse Events Reporting Period

The adverse event reporting period began with the administration of the first dose of study medication (at the baseline visit) and ended 1 week after the final clinic visit (week 8 or up to week 24 if participating in the post-study continuation). 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.

8.5.3.2.3 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 resulted in permanent impairment of function or permanent damage to a body structure or if medical or surgical intervention was required to prevent permanent impairment or damage. 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.)

8.5.3.2.4 Assessment of Drug-Relatedness

Investigators assessed the possible relationship between the adverse event and the study medication as well as any concomitant medications.

8.5.3.2.5 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."

8.5.3.2.6 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. If the pregnancy ended for any reason prior to the anticipated date provided, the investigator was to notify the monitor. 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.
- 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, Middlesex, England and Van Nuys, CA (for drug/urine screen), a central laboratory that is certified by the Clinical Laboratory Improvement Act and the College of American Pathologists. (Documentation is provided in Appendix 11.) SmithKline Beecham Clinical Laboratories changed its name to Quest Diagnostics part way through the study.
- Laboratory data were entered at SmithKline Beecham Clinical Laboratories, which became Quest Diagnostics, and were transmitted electronically to P&U for analysis.
- Data (ie, HAM-D scores, MADRS scores, and adverse events) in the clinical database were reviewed to verify their agreement with the data on the patient CRFs.
- The International Conference on Harmonisation Good Clinical Practice Guidelines and Practices and all applicable laws in the country in which the study was conducted were followed.
- P&U's Standard Operating Procedures were followed in the conduct and analysis of the study.

Pharmacia & Upjohn is responsible for independent quality assurance audits of the clinical trial processes at company sites worldwide. Audits of selected clinical investigator sites are also conducted to assess and help assure compliance with Good Clinical Practice and applicable regulatory requirements.

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 Recording

Data from subjects in this study were recorded on CRFs for subsequent compilation and analysis. Instructions for completion and submission of these forms were included in the Study Administrative Manual. All information relevant to subject safety or study endpoints was to be recorded. However, to ensure that it would receive appropriate and timely attention, information was to be recorded on the CRFs only in the appropriate response fields or Comments boxes. Nothing was to be entered in the margins or shaded areas of the form.

8.7.1.2 Analysis of Data

8.7.1.2.1 Baseline and Demographic Measures

The following case report forms contained data that would permit pre-study comparisons of patients randomized into the two treatment groups:

a. Medical History

b. Physical Examination

c. History of Mental Disorder

c. Baseline Efficacy Forms

The number and proportion of patients for categorical variables and the number of patients, mean, standard deviation, minimum, and maximum for continuous variables were to be presented. The comparability between treatment groups was to be assessed using one-way analysis of variance with treatment and investigator as factors for the continuous variables and by the Chi-square for the categorical variables.

8.7.1.2.2 Efficacy Measures

The primary efficacy measure was to be the change from baseline on the HAM-D total score. The secondary efficacy measures were to be: CGI, MADRS, SF-36, RSI, SASS total score, as well as response/remission rates and time to response/remission. A decrease of at least 50% in the total HAM-D score versus baseline was to be considered index of response, whereas total HAM-D score of 10 or less was to be considered index of remission.

8.7.1.2.3 Data Sets Analyzed

The intent-to-treat (ITT) data set, which includes all patients randomized into the trial who had received at least 1 treatment dose with at least 1 post-baseline efficacy follow-up evaluation, was to be used for the analysis.

No windowing was to be used to assign the visit or week number; all analyses would be based on the pre-printed visit numbers on the case report form.

Two types of analyses were to be performed for the primary variables: "last observation carried forward" (LOCF) and "observed cases" (OC). The LOCF analyses uses the last valid assessment as an estimate for all subsequent missing values. The OC analysis does not replace missing data. The intent-to-treat data set using the LOCF technique was to be the primary analysis and the OC analysis was to be included as a secondary analysis. Data from investigators with a small number of patients were to be pooled and considered as a single investigator for purposes of statistical testing.

8.7.1.2.4 Subset Analyses

Subset analyses were to be conducted using 2 covariates: (1) severity of illness at baseline (patients scoring 5 to 7 on the CGI Severity of Illness scale at baseline would be defined as "severely ill patients" and others as "non-severe patients"), and (2) gender.

8.7.1.3 Statistical Methods

Appendix 8 contains further documentation of the statistical methods.

8.7.1.3.1 Continuous Endpoints

For the continuous variables (eg, HAM-D total and SASS total), testing for difference between 2 treatment groups was performed using a 2-way analysis of variance (ANOVA) model that included treatment, investigator, age, and baseline terms. Treatment-by-investigator interaction was explored and included if it contributed significantly to the model. The response variables were to be the change from baseline scores at each visit. Treatment-by-investigator interaction was to be tested to evaluate poolability of data. If the interaction effect was significant at the 0.10 level ($p<0.10$), the individual investigator results were to be presented to identify the source of the interactions. Tests of main effects would not be dependent on significance of the interaction term. In addition to p-values, 95% confidence intervals for the difference between 2 treatment groups would also be computed for HAM-D total mean change from baseline and SASS total mean change from baseline.

8.7.1.3.2 Categorical Endpoints

Categorical data (eg, response and remission) were to be analyzed by Cochran-Mantel-Haenszel (CMH) test, stratified by investigator. In addition to p-values, 95% confidence intervals for the difference between 2 treatment groups would also be computed for HAM-D response rate and remission rate.

Means of individual components of the HAM-D were to be displayed by treatment group and by visit to identify any components that may have major influence on the HAM-D total. This analysis was to be descriptive and would not include statistical hypothesis testing.

8.7.1.4 Safety Data

All patients who were randomized and received at least 1 dose of the study drug were to be included in all safety analyses.

The original terms that were used by investigators to identify adverse events on the CRFs were to be translated according to the World Health Organization Adverse Reaction Terms

(WHOART). The adverse events would then be grouped according to body system and preferred terms.

Each adverse event was to be 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 to be considered a pre-treatment event and would not be counted in the adverse event incidence tables. If the onset was prior to the first dose of study medication and the severity increased after baseline, then the event was to be considered an adverse event and was to be counted as an adverse event. This rule is consistent with the treatment-emergent symptoms (TES, hereafter referred to as adverse events) convention for counting adverse events.

The adverse event incidence was to be summarized as follows: (1) by body system and preferred term; (2) by maximum severity; (3) by relationship to study medication; (4) by gender; and (5) by age. The relationship of an adverse event to study medication was based on the investigator's judgment. A summary of adverse events causing termination of study medication would also be presented. Serious adverse events and dropouts due to adverse events were to be summarized and the corresponding patient data listing would also be provided.

For each vital sign, lab test, and ECG variable, the paired t-test was to be performed at each visit to determine if the mean change of the responses on that visit was significantly ($p<0.05$) different from baseline. Between groups, comparisons would also be done on the change from baseline at each visit by using ANOVA model.

A list of patients with any abnormal safety results was to be presented.

Appendix 9 includes documentation of inter-laboratory standardization methods.

8.7.2 Determination of Sample Size

The adequacy of the sample size was investigated by looking at the power of the parametric test and the 95% confidence interval on the difference between reboxetine and paroxetine patients on the change from baseline of 21-item HAM-D total score. Power calculation was based on the results of previously conducted reboxetine studies and the placebo-controlled trials in the paroxetine NDA trials. In previously conducted placebo controlled reboxetine studies, the HAM-D total score reduction from baseline in the reboxetine group ranged from 13 to 16 with average standard deviation of 7. In the paroxetine trials, the HAM-D total score reduction from baseline in the paroxetine group ranged from 8 to 13.

Assuming the difference between paroxetine and the reboxetine groups in the change from baseline of 21-item HAM-D total score was 3 with the standard deviation of 10, one hundred and fifty patients per group would provide the test with a power of 0.74 to claim that reboxetine was better than paroxetine with alpha=0.05 (two-sided). If both treatments have the same effect size then the chance to have the lower bound of 95% confidence interval of the difference greater than -2.5 would be 86%. This means, with 150 patients per arm and the assumption that a difference of 2.5 or less can be considered clinically equivalent, we would have 86% chance to claim that reboxetine was not worse than paroxetine.

It was estimated that 350-400 patients needed to be enrolled in order to obtain data from 300 patients who would complete the 8-week study.

8.8 Changes in the Conduct of the Study or Planned Analyses

8.8.1 Protocol Amendments

The original protocol (dated 12 June 1998) was amended 4 times* (see Appendix 3 for a copy of the protocol and its amendments). Amendments 1 and 2 were implemented before any patients were enrolled in the study. The protocol amendments, along with the reasons for each, are briefly summarized below.

8.8.1.1 Amendment #1 (20 July 1998)

This amendment incorporated several small changes to the protocol for further clarification along with 2 additional criteria for exclusion, as outlined below:

- All investigators were to be qualified to conduct the trial and the results were to be pooled for the multinational analysis.
- Two additional exclusion criteria were added for those patients with any known or suspected allergy to reboxetine or paroxetine and those taking drugs known to inhibit other major drug metabolizing enzymes other than CYP2D6 (ie, antifungal agents, macrolide antibiotics [erythromycin], fluvoxamine, or oral anticoagulants [warfarin]) were to be excluded from the study.
- Case report forms were to be submitted using the Pharmacia & Upjohn data flow process.
- The reason for beginning study treatment prior to the optimal washout period was to be recorded on the medication record CRF.
- Temazepam. Lorazepam, zolpidem or oxazepam when taken as a sleep inducer or on an as needed basis were allowed during the study.
- A sentence was changed by adding the word ‘antidepressant’ in order to specify that additional data comparing reboxetine to other antidepressant medications was needed.
- A paragraph outlining instructions for patient diaries was deleted from the protocol because no patient diaries were used in this study.
- A paragraph was added stating that all investigators were to conduct the study in accordance with ICH GCP Guidelines and Practices and all applicable laws of the country in which the study was being conducted.

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

- An FDA 1572 form was necessary only for participating centers located in the United States.

8.8.1.2 Amendment #2 (19 February 1999)

Amendment 2 covered the transfer of responsibility from Pharmacia & Upjohn Clinical Research and Development to Pharmacia & Upjohn Global Medical Affairs due to the post-registration nature of this study. Substantial changes were also made in the protocol to more adequately reflect antidepressant use in clinical practice, to obtain more data regarding patient energy levels and drive, and to add blood sampling for future genotyping. It was also decided that this protocol would not be done in the United States due to pending FDA approval for reboxetine. The following specific changes were made:

- The protocol summary was amended to: (1) include a 4mg dosage form of reboxetine, (2) change paroxetine 20-40mg/day dose regimen from twice a day divided doses to once daily dosing, (3) add information regarding a 16 week post-study continuation in order to comply with international guidelines for length of antidepressant treatment, and (4) increase the maximum number of patients and number of study centers from 350 patients and 15-30 centers to 400 patients and 25-35 centers due to results from recent reboxetine studies indicating a 20%-30% dropout rate.
- The version of HAM-D was changed from 21 Items to 25 Items in order toinclude items on patient energy and drive related symptoms.
- In order to more adequately mimic the use of antidepressants in the clinical setting, the washout period for fluoxetine was shortened from 4 to 2 weeks.
- Exclusion criteria were altered to permit study entry of patients who may have been resistant to antidepressant treatment (lack of response to at least 2 consecutive courses of previous antidepressants given at full doses for >1 month) and/or had a major risk of suicide in the judgement of the investigator, by HAM-D Item 3 score of ≥3, or history of a suicide attempt during the current depressive episode.
- In order to maintain the blind in patients who were given increased doses at week 4, the labeling of additional bottles was changed to Level II, AM and PM.
- For patients completing a post-study continuation period, an additional visit was added to allow investigator evaluation of depressive symptoms (including HAM-D, MADRS, CGI, SF-36, SASS, and RSI) and any adverse events.
- Study blinding was to be broken based on the status of the database when all patients had completed 8 weeks of the study, regardless of whether the patient was still in the 16-week post-study continuation period.
- A new section of the protocol was added that gave patients the option of entering a separate reboxetine pharmacogenomics study (protocol # 950ECNS0323-001). Participating patients were to sign a separate consent form allowing a 20mL blood sample to be collected for future genomic analysis. Lack of participation in the

pharmacogenomics study did not exclude patients from being eligible for this protocol (97-CRBX-052).

8.8.1.3 Amendment #3 (1 July 1999)

In response to feedback from study investigators and Ethics Committees, additional changes to the protocol were made for safety reasons. The following specific changes were made:

- This study was declared as no longer operating under US IND.
- The duration of subject participation in the study was corrected to 10 weeks (up to 2 weeks washout and 8 weeks treatment) plus a 16-week post-study continuation
- At the suggestion of study investigators, an exclusion criterion was deleted and patients with an Axis IV history of psychosocial or environmental problems in the year preceding the trial, or prior to the previous year if judged relevant by the investigator, were allowed to participate.
- At the suggestion of Ethics Committees, an exclusion criterion was added back into the protocol (Amendment #2 had deleted it) making patients with a major risk of suicide (in the judgement of the investigator, by HAM-D Item 3 score of ≥3, or history of a suicide attempt during the current depressive episode) ineligible for participation in the study.
- Patients who had been on MAOIs were not allowed to be randomized without completing the full 2-week washout since treatment with an SSRI within 2 weeks of discontinuation of an MAOI could potentially induce the symptoms of serotonin syndrome.
- In order to allow concomitant treatment with only the most commonly used sleep inducers, only loraxepam, zolpidem, and chloral hydrate as sleep inducers on an as needed basis were allowed during the study (temazepam and oxazepam were no longer permitted).
- A clarification was made that no other drug under investigation or that was mentioned in the exclusion criteria was allowed to be used concomitantly with the study drug.

8.8.1.4 Amendment #4 (5 April 2000)

The primary measure was changed to the 17-item HAM-D since this is the standard used in the majority of clinical trials. This change allows comparison of data between studies and among countries. Other changes were made for clarification. The following specific changes were made:

- In order to allow comparison of data with the majority of clinical trials, HAM-D (17-item) total score of 10 or less will be considered index of remission. The 21- and 28-Item HAM-D scores will be considered secondary measurements of efficacy.
- A change was made in the trial products section of the protocol in order to clarify that the 4mg reboxetine marketed product is in the form of PresTabs that are contained inside the gelatin capsules, that this was the formulation used for the study, and to correct the configuration in order to concur with capsules used for the study.

- Clarification of the treatment schedule was made for patients who had their dose increased during the 8-week treatment period. This change stated: (1) that each patient who had their dose increased would be given 2 additional bottles labeled Level II AM and Level II PM, (2) what was contained in each bottle depending upon which treatment patients had been randomized, and (3) that patients would take 1 capsule from each bottle labeled Level I AM and Level II AM in the morning, and from each bottle labeled Level I PM and Level II PM in the evening in order to ingest a total of either 10mg reboxetine or 40mg paroxetine daily.
- The description of the HAM-D scale was changed in the clinical efficacy assessment section in order to include all versions of the HAM-D that were used, ie, 17-, 21-, and 28-Item HAM-D. The reference that was added in Amendment #2 that supported the 25-Item HAM-D was deleted.
- The adverse event-reporting period for this trial was increased to include 1 week after the final clinic visit. A post-study phone call was added in order to collect this adverse event information.

8.8.2 Changes in Planned Analyses

In addition to the amendments, the following changes were made:

- For the purpose of statistical testing, data from investigators was pooled within country (instead of investigator). This was because there were many investigators with a small number of patients (more than half of the sites enrolled 5 or fewer patients).
- During the analysis of the efficacy parameters, the interaction term was removed from the ANOVA model if it was not significant in order to increase the degrees of freedom. The baseline value of the parameter being analyzed was added as a covariate to reduce the variation. Age was also added to the model as a covariate because there was a statistically significant difference between the two groups at baseline.
- Windowing was used to assign the visit or week number for the Rush Sexual Inventory (RSI) and ECG. See Section 9.3.1 for details.
- For the analysis of safety endpoints, the original terms used by investigators to identify adverse events in the CRFs were translated into COSTART terms (instead of WHOART terms).
- For ECG, the PQ interval was measured instead of PR, as this is the usual measurement done in Europe. The few sites that measured PR left this field blank.
- For analysis purposes, 80% compliance was used in this report instead of 90%, as originally proposed in the protocol, to comply with current protocol standards.

9 RESULTS

Important 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. Findings of the post-study continuation portion of this protocol will be presented in an addendum to this report.

9.1 Study Patients

9.1.1 Disposition of Patients

A total of 325 patients were enrolled in the study and were randomized to receive treatment with reboxetine (159 patients) or paroxetine (166 patients). The study was conducted at 41 study centers, including 9 centers in the United Kingdom, 7 in Germany, 5 in Italy, 6 in Belgium, 4 in Spain, 4 in Portugal, 2 in Sweden, 2 in Denmark, and 2 centers in Austria.

Several investigators enrolled a small number of patients (more than half of the sites enrolled 5 or fewer patients), which could effect study outcomes; therefore, for the purpose of statistical testing, data from investigators was pooled within country (instead of investigator).

A total of 323 patients were included in the safety analysis (157 reboxetine patients and 166 paroxetine patients). The ITT population, which includes all patients who received at least one dose of study medication with at least 1 post-baseline efficacy follow-up evaluation, includes 154 reboxetine-treated patients and 164 paroxetine-treated patients.

The percentage of patients who completed the 8-week treatment period was larger in the paroxetine group (80.1%, 133/166) than in the reboxetine group (66.7%, 106/159). The reasons for study discontinuation are summarized in Table 5..

Table 5. Patient Disposition

	Reboxetine		Paroxetine	
	n	%*	n	%*
Number of patients				
Randomized	159	100.0	166	100.0
Safety population	157	98.7	166	100.0
Intent-to-treat†	154	96.9	164	98.8
Completed 8-week study	106	66.7	133	80.1
Discontinued study	53	33.3	33	19.9
Reason for discontinuation				
Adverse event	31	19.5	10	6.0
Lack of efficacy	8	5.0	10	6.0
Consent withdrawn	7	4.4	6	3.6
Protocol non-compliance‡	3	1.9	1	0.6
Lost to follow-up	2	1.3	3	1.8
Other	2	1.3	1	0.6
Protocol entry violation	0	-	2	1.2

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

† The intent-to-treat population includes all patients who received at least one dose of study medication with at least 1 post-baseline efficacy follow-up evaluation.

‡ For reasons other than entry criteria.

Source: Section 13, Table 1.3

The most common reason for discontinuation of study medication was due to adverse events, which occurred in a higher percentage of reboxetine-treated patients (19.5%; 31/159) than paroxetine-treated patients (6.0%; 10/166) Table 5. Discontinuations due to adverse events are discussed in Section 9.4.2.3.

Lack of efficacy led to the discontinuation of treatment in a comparable number of patients in each treatment group: 5.0% (8/159) of the reboxetine-treated patients and 6.0% (10/166) of the paroxetine-treated patients.

Withdrawal of patient consent (unrelated to an adverse event or any other listed reason) occurred in a comparable number of patients in each treatment group: 4.4% (7/159) of the reboxetine-treated patients and 3.6% (6/166) of the paroxetine-treated patients. All other reasons for discontinuation were generally comparable between the 2 treatment groups.

Section 13, Table 1.1, summarizes patient enrollment by investigator. The patients who prematurely discontinued from the study are listed in Appendix 10. The 7 patients who were randomized for treatment but were not included in the ITT group are listed in Appendix 12.

9.1.2 Protocol Deviations

Most deviations were considered minor, including violations of inclusion and exclusion criteria, and did not effect the results of this study. The most common deviation in both treatment groups was regarding study medication doses that were less than the prescribed amount (Table 6). In the reboxetine group, 4.5% (7/157) of patients took less than the

prescribed amount of medication (<80% compliant) and in the paroxetine group, 5.4% (9/166) took less than the prescribed amount of medication (<80% compliant).

The next most common deviation in both treatment groups involved insufficient washout of previous medications taken for depression (reboxetine, 5/159 [3.1%]; paroxetine, 8/166 [4.8%]). Most of the cases involved patients whose conditions worsened so severely during the required medication-free period that, ethically, treatment could be withheld no longer. Consequently, these patients were allowed study entry prior to completing the protocol-specified length of washout. The CRFs of 4 patients (Nos. 2174, 12324, 91095, and 91550) incorrectly reported that washout requirements had not been met; however, these patients were not taking any medications requiring washout and therefore, were not included in this category.

The next most frequent deviation in both treatment groups was for patients scoring a 3 on Item 3 of the HAM-D (reboxetine, 3/159 [1.9%]; paroxetine, 5/166 [3.0%]). Amendment #2 had allowed entry of patients with a score of 3 on Item 3, but Amendment #3 reversed this decision.

The following less frequent deviations were also reported: total HAM-D score outside range (22-35), Axis IV history of psychosocial/environmental problems in the past year, only 1 HAM-D evaluation done prior to randomization, age outside range (18-65), and electroconvulsive therapy (ECT) in the previous 6 months.

Table 6. Protocol Deviations

	RBX (N=159*)	PAR (N=166)
	n (%)	n (%)
Patients <80% compliant during the 8-week study period	7 (4.5)	9 (5.4)
Washout requirements not met	5 (3.1)	8 (4.8)
HAM-D Item 3 score of 3	3 (1.9)	5 (3.0)
Total HAM-D score outside of range (22-35)	1 (0.6)	3 (1.8)
Axis IV history of psychosocial/ environmental problems within the past year	1 (0.6)	2 (1.2)
Only 1 HAM-D done prior to randomization	1 (0.6)	1 (0.6)
Patient age >65 years	1 (0.6)†	0
ECT within previous 6 months	1 (0.6)	0

* For compliance, N=157.

† This patient (No. 33233) was 68 years of age.

Abbreviations: ECT = electroconvulsive therapy, PAR = paroxetine, RBX = reboxetine

Source: Appendix 11 and Section 13, Table 19.1

9.1.3 Data Sets Analyzed

The efficacy analyses were based on the intent-to-treat population, which includes all patients randomized into the trial who received at least one treatment dose with at least one post-baseline efficacy follow-up. Of the 325 patients randomized, 318 (154 in the reboxetine group and 164 in the paroxetine group) were included in the intent-to-treat efficacy analysis (Section 13, Table 1.3).

All patients who were randomized and received at least 1 dose of the study drug were included in all safety analyses. Of the 325 patients who were randomized into the study, 323 patients (157 reboxetine-treated and 166 paroxetine-treated patients) satisfied this criterion and were, therefore, included in all safety analyses.

9.1.4 Demographic and Other Baseline Characteristics

9.1.4.1 Demographic Characteristics

A difference among the treatment groups at screen was noted in the mean age of patients, which was lower in the reboxetine group (42.4 years) than in the paroxetine group (45.1 years). Although this difference was statistically significant, it is generally small and is unlikely to be clinically relevant.

Overall, the patient population in this study was reflective of the general population of patients with depression [30]. The patients in the study ranged in age from 18 to 68 years, and the majority of the patients were female and white. Selected demographic characteristics are compared by treatment group in Table 7.

Table 7. Patient Demographics at Screen; Randomized Population

Variable		RBX N=159	PAR N=166	P Value†
Age, years	Mean ± SD	42.4 ± 12.1	45.1 ± 11.0	0.0355*
	Range	18-68	18-64	
Sex: n (%)	Male	59 (37.1%)	63 (38.0%)	0.8750
	Female	100 (62.9%)	103 (62.0%)	
Race: n (%)	White	154 (96.8%)	164 (98.8%)	0.5224
	Black	2 (1.3%)	0	
	Asian	2 (1.3%)	1 (0.6%)	
	Other	1 (0.6%)	1 (0.6%)	

* $p \leq 0.05$

† 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, RBX = reboxetine

Source: Section 13, Tables 1.5, 1.6

Of the other continuous demographic characteristics that were assessed at screen (eg, weight, height, supine systolic and diastolic blood pressure, and supine pulse), the only statistically significant differences noted among the treatment groups occurred in supine systolic and diastolic blood pressure (Section 13, Table 1.7). The mean systolic/diastolic blood pressures

were 123/77 for the reboxetine-treated patients and 128/81 for the paroxetine-treated patients; the difference between the groups is small and unlikely to be clinically relevant.

On physical examination, the only statistically significant difference between treatment groups was noted in the proportion of patients with a back/spine abnormality (3.1% of reboxetine-treated patients and 9.0% of paroxetine-treated patients; p=0.0272); however, this difference is not felt to be clinically relevant (Section 13, Table 1.9). No statistically significant differences in the medical history findings were noted among the treatment groups (Section 13, Table 1.8).

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 number of previous hospitalizations for depression, or in the number of patients who were ever treated with psychotropic medications (other than antidepressants) Table 8. Nearing statistical significance, the mean approximate duration of the last depressive episode was 34 weeks in the reboxetine group and 28 weeks in the paroxetine group (p=0.0568). Patients in each treatment group tended to have been in their mid-thirties at the time of onset of their illness and of those who had previous episodes, the mean was 3. Slightly more of the patients in the reboxetine-treated group (28%) than those in the paroxetine-treated group (21%) were previously hospitalized for depression. The number of patients who had ever been treated with psychotropic medication (other than antidepressants) was about the same in each treatment group (reboxetine, 65%; paroxetine, 64%).

Table 8. Previous History of Depression

Variable	RBX N=159	PAR N=166	P Value*
Age (years) at onset of first major depressive episode			
Mean ± SD	35.4 ± 12.5	36.4 ± 11.4	0.4587
Range	4 - 63	12 - 64	
Number of patients reporting	159	165	
Number of previous episodes			
Mean ± SD	3.4 ± 4.0	3.2 ± 2.3	0.6685
Range	1 - 28	1 - 11	
Number of patients reporting	103	120	
Approximate duration of last episode (weeks)			
Mean ± SD	33.6 ± 33.3	28.0 ± 36.0	0.0568
Range	4 - 157	2 - 209	
Number of patients reporting	103	121	
Previous hospitalization for depression			
Number (%)	44 (27.7%)	35 (21.1%)	0.1663
Previous treatment			
Number (%) of patients who ever received psychotropic medications (other than antidepressants)	104 (65.4%)	106 (63.9%)	0.7697

* 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, RBX = reboxetine

Source: Section 13, Table 1.10, 1.11

9.1.4.2.2 Characteristics of the Present Depressive Episode

In the reboxetine-treated group, over half of the patients (54%) were in no treatment, 34% were in outpatient treatment, 13% were in inpatient treatment, and none were in day (partial hospitalization) treatment prior to the screening visit for this trial. In the paroxetine-treated group, 46% were in outpatient treatment, 43% of the patients were in no treatment, 10% were in inpatient treatment, and <1% were in day (partial hospitalization) treatment prior to the screening visit for this trial Table 9.

Among the treatment groups at screen, no statistically significant differences were noted in the characteristics of the present depressive episode. The mean approximate duration of the current depressive episode at study start was 21 weeks in the reboxetine group and 26 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 (66% in the reboxetine group and 73% in the paroxetine group). Just over half of the patients (56% in the reboxetine group and 52% in the paroxetine group) in each group had precipitating stress associated with their present episode.

Table 9. Characteristics of the Present Depressive Episode

Variable	RBX N=159	PAR N=166	P Value*
No. (%) of patients by treatment status prior to screen			
No treatment	85 (53.5%)	71 (42.8%)	0.0683
Outpatient treatment only	54 (34.0%)	77 (46.4%)	
Partial hospitalization (day treatment)	0	1 (0.6%)	
Inpatient	20 (12.6%)	17 (10.2%)	
Approximate duration of present episode at study start (weeks)			
Mean ± SD	20.6 ± 20.8	26.2 ± 49.5	0.5537
Range	0 - 157	2 - 470	
No. (%) of patients whose present episode was diagnosed as:			
Single episode	54 (34.0%)	45 (27.1%)	0.1796
Recurrent episode	105 (66.0%)	121 (72.9%)	
No. (%) of patients whose present episode was best characterized as:			
Exacerbation of chronic condition	13 (8.2%)	15 (9.0%)	0.3922
Recurrence of similar previous conditions	88 (55.3%)	105 (63.3)	
Significantly different from previous conditions	11 (6.9%)	10 (6.0%)	
First occurrence, no previous psychiatric diagnosis	47 (29.6%)	36 (21.7%)	
No. (%) of patients for whom precipitating external stress was:			
Absent	70 (44.0%)	80 (48.2%)	0.7158
Probably present	58 (36.5%)	58 (34.9)	
Definitely present	31 (19.5%)	28 (16.9%)	

* 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, RBX = reboxetine

Source: Section 13, Tables 1.10, 1.11, 1.12

9.1.4.2.3 Severity of Depression at Baseline

No statistically significant differences were noted among the treatment groups in the severity of depression at baseline in randomized patients, as judged by the mean total scores for the HAM-D, MADRS, CGI Severity of Illness, or SASS Table 10.

Table 10. Severity of Depression at Baseline; Randomized Patients

Variable	RBX N=159	PAR N=166	P Value*
17-Item HAM-D total score			
No. of patients	159	166	0.8519
Mean ± SD	24.2 ± 3.6	24.1 ± 3.4	
Range	18 - 33	15 - 32	
MADRS total score			
No. of patients	159	166	0.9516
Mean ± SD	30.9 ± 6.7	30.8 ± 6.2	
Range	14 - 50	14 - 49	
CGI Severity of Illness score			
No. of patients	159	166	0.6702
Mean ± SD	4.7 ± 0.8	4.7 ± 0.7	
Range	3 - 6	3 - 6	
SASS total score			
No. of patients	146	154	0.2499
Mean ± SD	28.8 ± 7.7	27.8 ± 7.5	
Range	9 - 46	4 - 43	

* 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, RBX = reboxetine, SASS = Social Adaptation Self-evaluation Scale

Source: Section 13, Table 1.13

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: 61.8% (97/157) of patients in the reboxetine group, 60.8% (101/166) of patients in the paroxetine group (Section 13, Table 2.2A). The therapeutic classes of medications that were taken most frequently (≥5% in any treatment group) included the following: antianxiety agents (primarily lorazepam or lorazepam-containing agents), nonbarbiturate sedatives and hypnotics (primarily zolpidem tartrate or zolpidem tartrate-containing agents), estrogens, nonsteroidal anti-inflammatory agents, and beta-adrenergic blocking agents (Section 13, Table 2.2C).

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: 72.0% (113/157) of patients in the reboxetine group, 76.5% (127/166) of patients in the paroxetine group (Section 13, Table 2.2B). 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: nonbarbiturate sedatives and hypnotics (primarily chloral hydrate , zolpidem tartrate, or zolpidem tartrate-containing agents), antianxiety agents (primarily lorazepam or lorazepam-containing agents), acetaminophen (primarily paracetamol), nonsteroidal anti-inflammatory agents, unknown and/or combinations (primarily unrecognizable drugs), salicylates, estrogens, GI stimulants (primarily metoclopramide), and beta-adrenergic blocking agents (Section 13, Table 2.2D).

9.2 Dosage Information

9.2.1 Extent of Exposure

The mean daily dose of study medications are presented by visit in Table 11. These mean-dosing data suggest that most patients complied with the dosing regimens that were specified in the protocol for the reboxetine group (8mg/day, days 0-27; 8-10mg/day, days 28-56) and for the paroxetine group (20mg/day, days 0-27; 20-40mg/day, days 28-56).

Table 11. Mean Daily Dose by Week; Safety Population

Visit	Reboxetine (N=157)			Paroxetine (N=166)		
	n*	Mean Dose† (mg/day)	Compliance (%)	n*	Mean Dose† (mg/day)	Compliance (%)
1	152	7.9	98.8	162	19.8	99.0
2	137	7.9	99.1	158	19.9	99.4
3	134	7.8	97.0	148	19.9	99.4
4	128	7.9	98.7	143	19.7	98.7
5	123	8.4	97.2	141	25.6	97.3
6	110	8.6	97.5	140	26.5	97.0
7	108	8.8	98.2	132	27.4	97.9
8	103	8.7	97.3	130	27.4	97.9

* Number of patients for whom data were recorded for the particular visit.

† Mean daily dose was based on the average dose for all patients who took the study medication during the corresponding week.

Source: Section 13, Table 2.1

9.2.2 Treatment Compliance

Acceptable treatment compliance during treatment was defined in the protocol as an overall drug intake of at least 90% of the prescribed amount, however to conform with current protocol standards, patients with an overall drug intake of at least 80% are considered compliant in this report.

Data from the medication record CRFs of all randomized patients indicate that the majority of patients in each treatment group were at least 80% compliant throughout the study (reboxetine, 146/157, 93.0%; paroxetine, 155/166, 93.4%) (Table 12). The frequency of patients who took less than 80% of the prescribed amount of study medication was similar for each treatment group (reboxetine, 7/157, 4.5%; paroxetine, 9/166, 5.4%).

Table 12. Treatment Compliance*; Safety Population

Compliance (%)	Reboxetine N=157		Paroxetine N=166	
	n	%	n	%
>100%	11	7.0	20	12.0
80% to 100%	135	86.0	135	81.3
<80%	7	4.5	9	5.4
Not Applicable	4	2.5	2	1.2

* Compliance is calculated as the total number of capsules taken divided by the total number of capsules prescribed per day.

Source: Section 13, Table 19.1

9.3 Efficacy Results

9.3.1 Statistical and/or Analytical Issues

Patient 67299 returned two months after she withdrew from the study prematurely at week 3, and all forms for week 8 were completed. All data from the week 8 visit were excluded from all analyses, as they fell outside the 8-week scope of the trial.

All statistical tests for efficacy endpoints and safety endpoints were two-sided using an alpha level of 0.05 unless otherwise specified. Only the primary comparison was considered to be confirmatory. All others were considered to be exploratory and used as a measure of difference.

No windowing was used to assign the visit or week number and all analyses were based on the pre-printed visit numbers on the case report form, except for RSI, ECG and Lab, which were administered at baseline/screen, week 4 and study termination, only. If a patient completed the RSI at week 3 or 5 instead of week 4, this week was reclassified as week 4. If a patient withdrew before week 4, then the RSI completed at termination was analyzed with the week 4 data. If a patient withdrew after week 4, then the RSI completed at termination was analyzed with the week 8 data.

9.3.2 Primary Efficacy Endpoint

9.3.2.1 Primary Analysis

In the LOCF analysis, both of the treatment groups showed decreases from baseline in the mean 17-Item HAM-D total score throughout the entire 8 weeks of treatment (Table 13). The largest mean change from baseline HAM-D total scores for both treatment groups occurred at week 8 (reboxetine mean change, -11.5; paroxetine mean change, -13.2;

p=0.0345). The mean changes in HAM-D total scores were numerically greater in the paroxetine group than those in the reboxetine group at every week. The differences between treatment groups in mean change from baseline in HAM-D total scores were statistically significant at most of the weekly evaluations (excluding weeks 2 and 5). The LOCF analyses of the mean scores of the individual HAM-D items by visit are provided in Section 13, Table 3.3A.

Table 13. Mean Change From Baseline in the 17-Item HAM-D Total Score

Visit	LOCF					Observed Cases				
	Mean Change from Baseline				P Values*	Mean Change from Baseline				P Values*
	RBX		PAR		RBX vs PAR	RBX		PAR		RBX vs PAR
	n	X†	n	X†		n	X†	n	X†	
Baseline	152	24.2	164	24.1	-	152	24.2	164	24.1	-
Week 1	152	-1.8	164	-2.8	0.0173‡	152	-1.8	164	-2.8	0.0173‡
Week 2	152	-4.4	164	-5.5	0.0702	137	-5.0	158	-5.6	0.2336
Week 3	152	-6.0	164	-8.2	0.0014‡	134	-6.8	150	-8.7	0.0073‡
Week 4	152	-7.6	164	-9.4	0.0120‡	127	-8.9	148	-10.0	0.1147
Week 5	152	-8.7	164	-10.0	0.0649	122	-10.6	144	-10.9	0.7239
Week 6	152	-9.6	164	-11.4	0.0360‡	111	-12.3	140	-12.5	0.7773
Week 7	152	-10.1	164	-12.1	0.0181‡	106	-13.2	136	-13.5	0.6619
Week 8	152	-11.5	164	-13.2	0.0345‡	105	-15.2	133	-15.2	0.9881

* P values are based on ANCOVA with treatment and country as the main effect, and age and baseline 17-Item HAM-D score as covariates.
† Mean at the baseline visit, mean change from baseline value for all other visits
‡ $p \leq 0.05$
Abbreviations: ANCOVA = analysis of covariance, BL = baseline, HAM-D = Hamilton Depression Rating Scale, LOCF = last observation carried forward, PAR = paroxetine, RBX = reboxetine
Source: Section 13, Tables 3.1A, 3.1B

9.3.2.2 Secondary Analyses of the Primary Endpoint

9.3.2.2.1 Observed Case Analysis

As in the LOCF analysis, the OC analysis shows that both of the treatment groups had decreases from baseline in the mean HAM-D total score throughout the entire 8 weeks of treatment. The largest mean change from baseline HAM-D total scores for both treatment groups occurred at Week 8 (reboxetine mean change, -15.2; paroxetine mean change, -15.2; p=0.9881). The mean changes in HAM-D total scores were numerically greater in the paroxetine group than those in the reboxetine group at almost every week in the OC analysis (excluding week 8) (Table 13). The differences in mean change in HAM-D total scores among the treatment groups were statistically significant at weeks 1 and 3. The OC analyses of the mean scores of the individual HAM-D items by visit are provided in Section 13, Table 3.3B.

9.3.2.2.2 21-Item HAM-D Total Score

As in the 17-Item HAM-D LOCF analysis results, both of the treatment groups showed decreases from baseline in the mean 21-Item HAM-D total score throughout the entire 8 weeks of treatment Table 14. The largest mean change from baseline scores for both treatment groups occurred at week 8 (reboxetine mean change, -13.0; paroxetine mean change, -14.7; p=0.0604). The mean changes in 21-Item HAM-D total scores were numerically greater in the paroxetine group than in the reboxetine group at every week in the LOCF analysis. The mean change between the treatment groups was statistically significant at weeks 3, 4, and 7. Section 13, Tables 4.3A and 4.3B present the mean of HAM-D individual items 18 through 21 in LOCF and OC analyses.

In the OC analysis the mean change from baseline in the 21-Item HAM-D total score was numerically greater in the reboxetine group or equal to the mean change in the paroxetine group at weeks 5, 6, and 8, although these results were not statistically significant (Table 14). At week 3, the mean change was numerically greater in the paroxetine group (-9.5) than in the reboxetine group (-7.8) and these values were statistically significant (p=0.0274).

Table 14. Mean Change From Baseline in the 21-Item HAM-D Total Score

Visit	LOCF					Observed Cases				
	Mean Change from Baseline				P Values*	Mean Change from Baseline				P Values*
	RBX		PAR		RBX vs PAR	RBX		PAR		RBX vs PAR
	n	X†	n	X†		n	X†	n	X†	
Baseline	152	26.8	164	26.6	-	152	26.8	164	26.6	-
Week 1	152	-2.3	164	-3.1	0.0586	152	-2.3	164	-3.1	0.0586
Week 2	152	-5.1	164	-6.0	0.1429	137	-5.7	158	-6.2	0.3500
Week 3	152	-7.0	164	-9.0	0.0070‡	134	-7.8	150	-9.5	0.0274‡
Week 4	152	-8.7	164	-10.3	0.0408‡	127	-10.1	148	-11.0	0.2364
Week 5	152	-10.0	164	-11.1	0.1487	122	-12.0	144	-12.0	0.9997
Week 6	152	-11.0	164	-12.6	0.0830	111	-13.8	140	-13.8	0.9896
Week 7	152	-11.5	164	-13.3	0.0440‡	106	-14.8	136	-14.9	0.8530
Week 8	152	-13.0	164	-14.7	0.0604	105	-17.0	133	-16.8	0.8261

* P values are based on ANCOVA with treatment and country as the main effect, and age and baseline 21-Item HAM-D score as covariates.

† Mean at the baseline visit, mean change from baseline value for all other visits

‡ $p \leq 0.05$

Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, HAM-D = Hamilton Depression Rating Scale, PAR = paroxetine, RBX = reboxetine

Source: Section 13, Tables 4.1A, 4.1B

9.3.2.2.3 28-Item HAM-D Total Score

In the LOCF analysis, the paroxetine treatment group demonstrated a mean change from baseline in the 28-Item HAM-D total score that was numerically greater than the mean change that was observed in the reboxetine group at every week (Table 15). The mean changes between the treatment groups were not statistically significant. Section 13, Tables 5.3A and 5.3B present the mean of HAM-D individual items 22 through 28 in LOCF and OC analyses.

In the OC analysis the mean change from baseline in the 28-Item HAM-D total score was numerically greater in the reboxetine group or equal to the mean change in the paroxetine group at weeks 2, 5, 6, 7, and 8, although these results were not statistically significant (Table 15).

Table 15. Mean Change From Baseline in the 28-Item HAM-D Total Score

Visit	LOCF					Observed Cases				
	Mean Change from Baseline				P Values*	Mean Change from Baseline				P Values*
	RBX		PAR		RBX vs PAR	RBX		PAR		RBX vs PAR
	n	X†	n	X†		n	X†	n	X†	
Baseline	152	30.5	163	30.1	-	152	30.5	163	30.1	-
Week 1	152	-3.1	163	-3.5	0.2811	152	-3.1	163	-3.5	0.2811
Week 2	152	-6.3	164	-6.7	0.4322	137	-6.9	158	-6.9	0.7882
Week 3	152	-8.5	164	-9.9	0.0594	134	-9.3	150	-10.4	0.1582
Week 4	152	-10.5	164	-11.5	0.1530	127	-11.9	148	-12.3	0.5323
Week 5	152	-12.0	164	-12.4	0.4680	122	-14.1	144	-13.4	0.5120
Week 6	152	-13.2	164	-14.0	0.3004	111	-16.0	140	-15.4	0.5958
Week 7	152	-13.7	164	-14.9	0.1543	106	-17.0	136	-16.6	0.8477
Week 8	152	-15.2	164	-16.4	0.1688	104	-19.1	133	-18.7	0.6980

* P values are based on ANCOVA with treatment and country as the main effect, and age and baseline 28-Item HAM-D score as covariates.

† Mean at the baseline visit, mean change from baseline value for all other visits

Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, HAM-D = Hamilton Depression Rating Scale, PAR = paroxetine, RBX = reboxetine

Source: Section 13, Tables 5.1A, 5.1B

9.3.2.2.4 HAM-D Response Rate

No statistically significant differences were observed among treatment groups in the HAM-D response rate during the 8-week trial in either the LOCF or OC analyses; however, the paroxetine group exhibited a greater response rate throughout the duration of the trial (Table 16).

Table 16. HAM-D Response Rate; ITT Patients

Visit	LOCF					Observed Cases				
	Response Rate*				P Values†	Response Rate*				P Values†
	RBX		PAR			RBX		PAR		
	n/N	%	n/N	%		n/N	%	n/N	%	
Week 1	2/152	1.3	7/164	4.3	0.0963	2/152	1.3	7/164	4.3	0.0963
Week 2	17/152	11.2	24/164	14.6	0.3517	17/137	12.4	24/158	15.2	0.4674
Week 3	35/152	23.0	48/164	29.3	0.1929	34/134	25.4	48/150	32.0	0.1983
Week 4	44/152	28.9	59/164	36.0	0.1778	43/127	33.9	57/148	38.5	0.4400
Week 5	56/152	36.8	70/164	42.7	0.3163	55/122	45.1	67/144	46.5	0.8850
Week 6	64/152	42.1	81/164	49.4	0.2490	60/111	54.1	77/140	55.0	0.9339
Week 7	65/152	42.8	89/164	54.3	0.0506	60/106	56.6	85/136	62.5	0.2815
Week 8	80/152	52.6	100/164	61.0	0.1644	75/105	71.4	95/133	71.4	0.9742

* Response was defined as a decrease of ≥50% in the 17-Item HAM-D total score versus baseline

† P values are based on Cochran-Mantel-Haenszel test (after controlling for country)

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

Source: Section 13, Tables 3.4A, 3.4B

9.3.2.2.5 HAM-D Remission Rate

No statistically significant differences were observed among the treatment groups in the HAM-D remission rate during the 8-week trial in either the LOCF or OC analyses; however, the paroxetine group exhibited a greater remission rate throughout the duration of the trial (Table 14).

Table 17. HAM-D Remission Rate; ITT Patients

Visit	LOCF					Observed Cases				
	Response Rate*				P Values†	Response Rate*				P Values†
	RBX		PAR			RBX		PAR		
	n	%	n	%		n	%	n	%	
Week 1	3/152	2.0	5/164	3.0	0.5033	3/152	2.0	5/164	3.0	0.5033
Week 2	15/152	9.9	22/164	13.4	0.2927	15/137	10.9	22/158	13.9	0.3793
Week 3	31/152	20.4	38/164	23.2	0.5155	30/134	22.4	37/150	24.7	0.6295
Week 4	36/152	23.7	45/164	27.4	0.4653	35/127	27.6	43/148	29.1	0.8189
Week 5	42/152	27.6	55/164	33.5	0.2770	41/122	33.6	53/144	36.8	0.6270
Week 6	53/152	34.9	67/164	40.9	0.3401	49/111	44.1	65/140	46.4	0.7654
Week 7	59/152	38.8	77/164	47.0	0.1968	54/106	50.9	74/136	54.4	0.5148
Week 8	69/152	45.4	89/164	54.3	0.1505	64/105	61.0	85/133	63.9	0.6186

* Remission was defined as a total score of ≤10 on the 17-Item HAM-D

† P values are based on Cochran-Mantel-Haenszel test (after controlling for country)

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

Source: Section 13, Tables 3.6A, 3.6B

9.3.2.2.6 Analysis of Covariance

9.3.2.2.6.1 Severity of Illness

When the results of the mean change from baseline in the 17-item HAM-D total score were analyzed by baseline severity, the difference between the reboxetine and paroxetine groups was only statistically significant in the severely ill patients at week 3 in the LOCF analysis (p=0.0277 in the LOCF analysis) (Section 13, Table 7.1A). In severely ill patients, the mean change from baseline in the HAM-D total score was numerically greater in the paroxetine group than the reboxetine group at every visit in the LOCF analysis.

In the OC analysis, the difference between the reboxetine and paroxetine groups was not statistically significant at any of the visits (Section 13, Table 7.1B). In severely ill patients, the mean change from baseline in the HAM-D total score was numerically greater in the paroxetine group than the reboxetine group at most visits, except weeks 2, 6, and 8 in the OC analysis.

9.3.2.2.6.2 Gender

When the results of the mean change from baseline in the 17-item HAM-D total score were analyzed by gender, the difference between the reboxetine and paroxetine groups was statistically significant in females at weeks 1, 2, and 3 and in males at weeks 3 through 8 in the LOCF analysis (Section 13, Table 7.2A). In both males and females, the mean change from baseline in the HAM-D total score was numerically greater in the paroxetine group than the reboxetine group at every visit in the LOCF analysis.

In the OC analysis, the difference between the reboxetine and paroxetine groups was only statistically significant in females at weeks 1 and 3 (Section 13, Table 7.2B). The mean change from baseline in the HAM-D total score was numerically greater in the reboxetine group than the paroxetine group in half of the visits (weeks 2, 6, 7, and 8).

9.3.2.2.7 Last Assessment for Patients Who Discontinued Early

As shown in Table 18, patients in the reboxetine group who discontinued early from the study were experiencing some improvement in their symptoms when they discontinued treatment, as demonstrated by the mean decrease in the HAM-D total score at last assessment. Patients in the paroxetine group who discontinued early also were experiencing an improvement in their symptoms when they discontinued treatment. The largest mean change in both treatment groups occurred among patients who discontinued treatment during weeks 4 and 5 (reboxetine mean change, -8.4; paroxetine mean change, -9.4). These values were comparable to the mean change from baseline in the total ITT patient population in the LOCF and OC analyses at the week-4 assessment.

Table 18. Mean Change From Baseline in the HAM-D Total Score at Last Assessment for Patients Who Discontinued Early

Day of Last Dose*	RBX N=154		PAR N=164	
	n	Mean Change	n	Mean Change
< Week 2	14†	-0.9	9	-2.3
Week 2-3	10	-6.6	5‡	-5.2
Week 4-5	14	-8.4	9	-9.4
Week 6-8	8	-6.0	7	-9.1
Total number of discontinuations	46		30	

* Patients are included only in the row that represents the day of their last dose-

† Two patients were not included because there were no HAM-D scores at the last visit.

‡ One patient was not included because there was no HAM-D score at the last visit.

Abbreviations: HAM-D = Hamilton Depression Rating Scale, PAR = paroxetine, RBX = reboxetine

Source: Section 13, Table 1.4

9.3.2.2.8 HAM-D Cluster Analyses

9.3.2.2.8.1 HAM-D Item-1 Score

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. The mean decrease from baseline in the HAM-D Item 1 score was equal or numerically greater in the paroxetine group than in the reboxetine group at every visit in the LOCF analysis. In the OC analysis, the mean decrease from the baseline HAM-D Item 1 score was equal or numerically greater in the paroxetine group than in the reboxetine group at weeks 1, 2, 3, 4, and 6. The mean change between treatment groups was statistically significant at week 3 in both the LOCF (paroxetine, -1.0; reboxetine, -0.8; p=0.0137) and the OC (paroxetine, -1.1; reboxetine, -0.9; p=0.0321) analyses Table 19.

Table 19. Mean Change From Baseline in the HAM-D Item 1 Score

Visit	LOCF					Observed Cases				
	Mean Change from Baseline				P Values*	Mean Change from Baseline				P Values*
	RBX		PAR		RBX vs PAR	RBX		PAR		RBX vs PAR
	n	X†	n	X†		n	X†	n	X†	
Baseline	153	2.9	164	2.8	-	153	2.9	164	2.8	-
Week 1	153	-0.3	164	-0.3	0.3195	153	-0.3	164	-0.3	0.3195
Week 2	153	-0.5	164	-0.7	0.0870	138	-0.5	158	-0.7	0.1441
Week 3	153	-0.8	164	-1.0	0.0137‡	134	-0.9	151	-1.1	0.0321‡
Week 4	153	-1.0	164	-1.2	0.0866	128	-1.1	148	-1.2	0.3004
Week 5	153	-1.2	164	-1.2	0.5704	122	-1.4	144	-1.3	0.5679
Week 6	153	-1.3	164	-1.4	0.1641	111	-1.6	140	-1.6	0.9038
Week 7	153	-1.4	164	-1.5	0.3053	106	-1.8	136	-1.6	0.5531
Week 8	153	-1.6	164	-1.7	0.2890	107	-2.0	133	-1.9	0.4971

* P values are based on ANCOVA with treatment and country as the main effect, and age and baseline HAM-D score as covariates.

† Mean at the baseline visit, mean change from baseline value for all other visits

‡ $p \leq 0.05$

Abbreviations: ANCOVA = analysis of covariance, BL = baseline, HAM-D = Hamilton Depression Rating Scale, LOCF = last observation carried forward, PAR = paroxetine, RBX = reboxetine

Source: Section 13, Tables 6.1A, 6.1B

9.3.2.2.8.2 HAM-D Retardation Cluster Score

The HAM-D Retardation Cluster (Items 1, 7, 8, and 14 [20, 26]) represents a symptom cluster that is primarily focussed on the depressed mood and the associated psychomotor effects of depression. The mean decrease from baseline in the HAM-D Retardation Cluster score was numerically greater in the paroxetine group than in the reboxetine group at every visit in the LOCF analysis (Table 20). When comparing the mean change between treatment groups, the values were statistically significant at week 3 (paroxetine, -2.5; reboxetine, -2.0; p=0.0168). In the OC analysis, the mean decrease from baseline in the HAM-D Retardation Cluster score was numerically greater in the reboxetine group than in the paroxetine group at weeks 5, 7, and 8. When comparing the mean change between treatment groups, the values neared statistical significance at week 3 (paroxetine mean change -2.6; reboxetine mean change, -2.1; p=0.0512).

Table 20. Mean Change From Baseline in the HAM-D Retardation Cluster Score

Visit	LOCF					Observed Cases				
	Mean Change from Baseline				P Values*	Mean Change from Baseline				P Values*
	RBX		PAR		RBX vs PAR	RBX		PAR		RBX vs PAR
	n	X†	n	X†		n	X†	n	X†	
Baseline	152	8.4	164	8.4	-	152	8.4	164	8.4	-
Week 1	152	-0.7	164	-0.7	0.6381	152	-0.7	164	-0.7	0.6381
Week 2	152	-1.4	164	-1.6	0.3186	138	-1.5	158	-1.6	0.6084
Week 3	152	-2.0	164	-2.5	0.0168‡	134	-2.1	150	-2.6	0.0512
Week 4	152	-2.6	164	-2.8	0.2111	127	-2.9	148	-3.0	0.6502
Week 5	152	-3.0	164	-3.2	0.4254	122	-3.5	144	-3.4	0.6031
Week 6	152	-3.4	164	-3.8	0.1984	111	-4.1	140	-4.1	0.8531
Week 7	152	-3.6	164	-4.0	0.1273	106	-4.6	136	-4.4	0.8184
Week 8	152	-4.2	164	-4.4	0.3621	107	-5.3	133	-5.0	0.3240

* P values are based on ANCOVA with treatment and country as the main effect, and age and baseline HAM-D score as covariates.

† Mean at the baseline visit, mean change from baseline value for all other visits

‡ $p \leq 0.05$

Abbreviations: ANCOVA = analysis of covariance, BL = baseline, HAM-D = Hamilton Depression Rating Scale, LOCF = last observation carried forward, PAR = paroxetine, RBX = reboxetine

Source: Section 13, Tables 6.4A, 6.4B

9.3.2.2.9 Additional HAM-D Items from the 25-Item Version

Data from items in the 25-Item version that were not in the 28-Item version were also collected. These were summarized descriptively. See Section 13, Tables 5.4a and 5.4b.

9.3.3 Continuous Secondary Measures of Antidepressant Efficacy

9.3.3.1 MADRS Total Score

In the LOCF analysis, the paroxetine treatment group demonstrated a mean change from baseline in the MADRS total score that was numerically greater than the mean change that was observed in the reboxetine group at every week (Table 21). The mean changes between the treatment groups were statistically significant at weeks 3 and 4.

In the OC analysis the mean change from baseline in the MADRS total score was numerically greater in the reboxetine group or equal to the mean change in the paroxetine group at weeks 2, 5, 6, 7, and 8, although these results were not statistically significant Table 21.

Table 21. Mean Change From Baseline in the MADRS Total Score

Visit	LOCF					Observed Cases				
	Mean Change from Baseline				P Values*	Mean Change from Baseline				P Values*
	RBX		PAR		RBX vs PAR	RBX		PAR		RBX vs PAR
	n	X†	n	X†		n	X†	n	X†	
Baseline	153	30.9	164	30.9	-	153	30.9	164	30.9	-
Week 1	153	-2.6	164	-2.9	0.4931	153	-2.6	164	-2.9	0.4931
Week 2	153	-5.4	164	-5.8	0.5174	138	-6.1	158	-6.1	0.9559
Week 3	153	-7.3	164	-9.4	0.0174‡	134	-8.1	151	-10.1	0.0521
Week 4	153	-9.4	164	-11.3	0.0471‡	128	-10.9	147	-12.3	0.2136
Week 5	153	-11.4	164	-12.2	0.4150	122	-13.9	144	-13.3	0.5505
Week 6	153	-12.6	164	-14.0	0.2560	111	-16.2	140	-15.6	0.5816
Week 7	153	-13.3	164	-15.2	0.1154	106	-17.3	136	-17.3	0.9190
Week 8	153	-15.1	164	-17.0	0.0907	106	-20.1	133	-19.8	0.9577

* P values are based on ANCOVA with treatment and country as the main effect, and age and baseline MADRS score as covariates.
† Mean at the baseline visit, mean change from baseline value for all other visits
‡ $p \leq 0.05$
Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, MADRS = Montgomery Asberg Depression Rating Scale, PAR = paroxetine, RBX = reboxetine
Source: Section 13, Tables 8.1A, 8.1B

9.3.3.2 CGI Severity of Illness

The mean decrease from baseline in the CGI Severity of Illness score was numerically greater in the paroxetine group or equal to the mean decrease in the reboxetine group at all the visits in both the LOCF and OC analyses (Table 22). However, none of these differences were statistically significant.

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 9.2.

Table 22. Mean Change From Baseline in the CGI Severity of Illness Score

Visit	LOCF					Observed Cases				
	Mean Change from Baseline				P Values*	Mean Change from Baseline				P Values*
	RBX		PAR		RBX vs PAR	RBX		PAR		RBX vs PAR
	n	X†	n	X†		n	X†	n	X†	
Baseline	153	4.7	164	4.7	-	153	4.7	164	4.7	-
Week 1	153	-0.2	164	-0.2	0.9135	153	-0.2	164	-0.2	0.9135
Week 2	153	-0.5	164	-0.5	0.5382	138	-0.5	158	-0.5	0.9660
Week 3	153	-0.7	164	-0.9	0.0744	134	-0.8	151	-1.0	0.1282
Week 4	153	-1.0	164	-1.2	0.2293	127	-1.1	148	-1.2	0.7362
Week 5	153	-1.2	164	-1.3	0.7184	122	-1.4	144	-1.4	0.4672
Week 6	153	-1.3	164	-1.6	0.1234	109	-1.6	140	-1.8	0.6634
Week 7	153	-1.4	164	-1.7	0.2763	106	-1.8	136	-1.9	0.9959
Week 8	153	-1.7	164	-2.0	0.1457	107	-2.3	133	-2.3	0.7412

* P values are based on ANCOVA with treatment and country as the main effect, and age and baseline CGI severity of illness score as covariates.

† Mean at the baseline visit, mean change from baseline value for all other visits

Abbreviations: ANCOVA = analysis of covariance, CGI = Clinical Global Impression, LOCF = last observation carried forward, , PAR = paroxetine, RBX = reboxetine

Source: Section 13, Tables 9.1A, 9.1B

9.3.4 Categorical Secondary Measures of Antidepressant Efficacy

9.3.4.1 CGI Global Improvement Response Rate

No statistically significant differences were observed among treatment groups in the CGI Global Improvement scale response rate during the 8-week trial in either the LOCF or OC analyses. However, the paroxetine group exhibited a greater response rate throughout the duration of the trial, except in the OC analysis at weeks 7 and 8 (Table 23).

Table 23. CGI Global Improvement Response Rate; ITT Patients

Visit	LOCF					Observed Cases				
	Response Rate*				P Values†	Response Rate*				P Values†
	RBX		PAR			RBX		PAR		
	n	%	n	%		n	%	n	%	
Week 1	10	6.5	13	7.9	0.5647	10	6.5	13	7.9	0.5647
Total	153	100.0	164	100.0		153	100.0	164	100.0	
Week 2	27	17.6	31	18.9	0.7162	26	18.8	31	19.6	0.7933
Total	153	100.0	164	100.0		138	100.0	158	100.0	
Week 3	44	28.8	52	31.7	0.5217	42	31.3	51	33.8	0.6551
Total	153	100.0	164	100.0		134	100.0	151	100.0	
Week 4	58	37.9	72	43.9	0.2715	55	43.3	69	46.6	0.6421
Total	153	100.0	164	100.0		127	100.0	148	100.0	
Week 5	71	46.4	84	51.2	0.3382	66	54.1	80	55.6	0.8207
Total	153	100.0	164	100.0		122	100.0	144	100.0	
Week 6	80	52.3	97	59.1	0.2091	71	65.1	92	65.7	0.9764
Total	153	100.0	164	100.0		109	100.0	140	100.0	
Week 7	85	55.6	99	60.4	0.4024	74	69.8	93	68.4	0.7960
Total	153	100.0	164	100.0		106	100.0	136	100.0	
Week 8	96	62.7	104	63.4	0.9392	88	82.2	98	73.7	0.1034
Total	153	100.0	164	100.0		107	100.0	133	100.0	

* 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 Cochran-Mantel-Haenszel test (after controlling for country)

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

Source: Section 13, Tables 9.4A, 9.4B

9.3.5 Secondary Measures of Quality of Life and Social and Sexual Function

9.3.5.1 Medical Outcomes Study Short-Form Self-evaluation Health Survey (SF-36)

The SF-36 scale measured quality of life in the following 8 domains: (1) Physical Functioning, (2) Role Physical, (3) Bodily Pain, (4) General Health Perceptions, (5) Vitality, (6) Social Functioning, (7) Role Emotional, and (8) Mental Health (Section 13, Tables 10.1A and 10.1B through 10.8A and 10.8B).

The mean change (improvement) from baseline in the Physical Functioning domain score was numerically greater in the reboxetine group at weeks 6, 7, and 8 in the LOCF analysis (without statistical significance between treatment groups) and at weeks 5 through 8 in the

OC analysis (statistically significant between treatment groups at week 8; p=0.0217) (Section 13, Tables 10.1A and 10.1B).

The mean change (improvement) from baseline in the Role Physical domain score was numerically greater in the reboxetine group in both the LOCF and OC analyses at weeks 1, 2, 5, 6, 7, and 8 (Section 13, Tables 10.2A and 10.2B). None of these values was statistically significant between treatment groups.

The mean change (improvement) from baseline in the Bodily Pain domain score was numerically greater in the paroxetine group at a majority of weeks in the LOCF analysis (5 out of 8 weeks), and was statistically significant between treatment groups at week 7 (p=0.0215) (Section 13, Tables 10.3A and 10.3B). In the OC analysis, the mean change in the baseline score was numerically greater in the paroxetine group at weeks 3, 6, and 7 and was statistically significant between treatment groups at week 7 (p=0.0057).

The mean change (improvement) from baseline in the LOCF analysis of the General Health Perceptions domain score was numerically greater in the reboxetine group at weeks 1, 4, 5, 6, and 8 and numerically equal to the mean change in the paroxetine group at week 7, with no statistical significance between treatment groups (Section 13, Tables 10.4A and 10.4B). In the OC analysis, the mean change from the baseline score was numerically greater in the reboxetine group at most of the visits (except for weeks 2 and 3), with no statistical significance between treatment groups.

The mean change (improvement) from baseline in the LOCF and OC analyses of the Vitality domain and Social Functioning domain scores (Section 13, Tables 10.5A, 10.5B, 10.6A, and 10.6B) was numerically greater in the reboxetine group at every visit, with no statistical significance between treatment groups.

The mean change (improvement) from baseline in the Role Emotional domain score was numerically greater in the reboxetine group at weeks 2, 3, 5, 6, 7, and 8 in the LOCF and OC analyses (Section 13, Tables 10.7A and 10.7B). In the LOCF analysis, none of the values were statistically significant between treatment groups; however, in the OC analysis, the difference was statistically significant between treatment groups at week 8 (p=0.0102).

The mean change (improvement) from baseline in the LOCF analysis of the Mental Health domain score was numerically greater in the paroxetine group at all visits except for week 2, at which the mean change was the same in both treatment groups (Section 13, Tables 10.8A and 10.8B). The values between treatment groups at weeks 4 and 8 were statistically significant (p=0.0361 and p=0.0429, respectively). In contrast to the findings of the LOCF analysis, the OC analysis showed the mean change from baseline score to be numerically greater in the reboxetine group at weeks 2 and 5 through 8; however, none of these differences was of statistical significance between the treatment groups.

9.3.5.2 Social Adaptation Self-evaluation Scale

9.3.5.3 Social Adaptation Self-evaluation Scale

The mean change (improvement) from baseline in the LOCF analysis of the SASS total score was numerically equal between treatment groups at week 3 and numerically greater in the reboxetine group at weeks 4 through 7 Table 24 None of these values was statistically significant. In the OC analysis, the mean change from the baseline SASS total score was numerically greater in the reboxetine group at weeks 4 through 7. Between treatment groups, the difference at week 5 was statistically significant (p=0.0330).

Table 24. Mean Change From Baseline in the SASS Total Score

Visit	LOCF					Observed Cases				
	Mean Change from Baseline				P Values*	Mean Change from Baseline				P Values*
	RBX		PAR		RBX vs PAR	RBX		PAR		RBX vs PAR
	n	X†	n	X†		n	X†	n	X†	
Baseline	136	28.8	146	27.7	-	136	28.8	146	27.7	-
Week 1	136	-0.3	146	0.2	0.4788	136	-0.3	146	0.2	0.4788
Week 2	137	-0.2	149	0.0	0.9297	119	-0.2	139	0.0	0.8471
Week 3	137	0.7	150	0.7	0.5227	118	0.7	136	0.8	0.4315
Week 4	137	1.5	150	1.1	0.4231	115	1.9	121	1.3	0.3017
Week 5	137	2.0	150	1.6	0.3410	102	2.6	128	1.6	0.0330‡
Week 6	137	2.2	150	2.0	0.5836	101	2.7	116	2.2	0.2924
Week 7	137	2.8	150	2.5	0.4880	96	4.0	119	3.0	0.1011
Week 8	137	2.8	150	3.0	0.9565	94	4.1	114	4.2	0.3811

* P values are based on ANCOVA with treatment and country as the main effect, and age and baseline SASS score as covariates.
† Mean at the baseline visit, mean change from baseline value for all other visits
‡ $p \leq 0.05$
Abbreviations: ANCOVA = analysis of covariance, LOCF = last observation carried forward, PAR = paroxetine, RBX = reboxetine, SASS = Social Adaptation Self-evaluation Scale
Source: Section 13, Tables 11.1A, 11.1B

9.3.5.4 Rush Sexual Inventory Visual Analogue Scales

Data for the RSI was windowed, see Section 9.3.1.

Visual Analogue Scales were used in the Rush Sexual Inventory evaluations. The scales ranged from zero, meaning infrequent, to 100, meaning very frequent. The mean change from baseline in the RSI score for the frequency of sexual thoughts, ability to become sexually excited, and frequency of desires to initiate sexual activity was numerically greater in the reboxetine group by a moderate margin at weeks 4 and 8 in the LOCF and OC analyses (Table 25) The mean change from baseline in the RSI score for frequency of initiating sexual activity was numerically greater in the paroxetine group by a small margin at weeks 4 and 8 in the LOCF and OC analyses. Finally, the mean change from baseline in the RSI score for the overall degree of sexual satisfaction attained was numerically greater in the reboxetine group by a small margin at weeks 4 and 8 in the LOCF and OC analyses. Section 13, Tables 12.2A, 12.2B, 12.3A, and 12.3B give LOCF and OC summaries of the yes/no responses that were given for each of the items of the RSI by males and females.

Table 25. Mean Change From Baseline in the RSI Total Score; ITT Patients

Variable (Visit)	LOCF				Observed Cases			
	Mean Change from Baseline				Mean Change from Baseline			
	RBX		PAR		RBX		PAR	
	n	X*	n	X*	n	X*	n	X*
Frequency of Pleasurable Thoughts								
Baseline	99	32.3	107	33.4	99	32.3	108	33.6
Week 4	99	2.1	107	-1.7	99	2.1	108	-1.7
Week 8	100	8.9	112	3.5	74	12.7	93	4.2
Ability to Become Sexually Excited								
Baseline	98	39.7	106	37.5	98	39.7	107	37.5
Week 4	98	1.3	106	-0.6	98	1.3	107	-0.5
Week 8	99	7.2	111	3.0	74	5.8	93	4.0
Frequency of Desires to Initiate Sexual Activity								
Baseline	97	27.8	107	30.0	97	27.8	108	30.0
Week 4	97	6.2	107	1.1	97	6.2	108	1.1
Week 8	99	10.5	112	5.3	74	10.1	92	7.9
Frequency of Initiating Sexual Activity								
Baseline	95	22.5	107	19.3	95	22.5	108	19.5
Week 4	95	3.8	107	5.5	95	3.8	108	5.5
Week 8	96	7.9	112	8.5	72	9.5	92	10.2
Overall Degree of Sexual Satisfaction Attained								
Baseline	95	33.1	106	29.6	95	33.1	107	29.7
Week 4	95	4.6	106	3.4	95	4.6	107	3.4
Week 8	96	7.8	111	6.6	72	8.6	92	7.9

* Mean at the baseline visit, mean change from baseline value for all other visits

Abbreviations: LOCF = last observation carried forward, PAR = paroxetine, RBX = reboxetine, RSI = Rush Sexual Inventory

Source: Section 13, Tables 12.1A, 12.1B

9.3.6 Efficacy Conclusions

In the LOCF analysis of the primary endpoint at week 8, although both reboxetine and paroxetine did show improvement in the 17-Item HAM-D total scores, paroxetine displayed better efficacy by demonstrating a statistically significant difference among treatment groups in the mean change from baseline in the 17-Item HAM-D total score (reboxetine mean change, -11.5; paroxetine mean change, -13.2; p=0.0345) (Table 26). The secondary endpoint LOCF analyses at week 8 continued to show a numerically greater mean change in the paroxetine group in all efficacy endpoints studied, however without statistical significance.

The results seen in the OC analysis (a secondary analysis) did not support the findings of the LOCF analysis. In the OC analysis of the primary endpoint at week 8, the mean change from baseline in the 17-Item HAM-D total score was –15.2 in both treatment groups (p=0.9881). The secondary endpoint analyses continued to show a numerically equal or greater mean change in the reboxetine group in all efficacy endpoints studied, except in HAM-D remission. None of these differences was statistically significant.

Table 26. Summary of Antidepressant Efficacy Measures at Week 8

Endpoints	Results by Treatment (LOCF)		P Values	Results by Treatment (OC)		P Values
	RBX N=154	PAR N=164		RBX N=154	PAR N=164	
Primary Endpoint						
17-Item HAM-D total score, mean change from baseline	-11.5	-13.2	0.0345†	-15.2	-15.2	0.9881
Secondary Endpoints						
Mean Change From Baseline						
21-Item HAM-D total score, mean change from baseline	-13.0	-14.7	0.0604	-17.0	-16.8	0.8261
28-Item HAM-D total score, mean change from baseline	-15.2	-16.4	0.1688	-19.1	-18.7	0.6980
HAM-D Item 1	-1.6	-1.7	0.2890	-2.0	-1.9	0.4971
HAM-D Retardation Cluster	-4.2	-4.4	0.3621	-5.3	-5.0	0.3240
MADRS Total Score	-15.1	-17.0	0.0907	-20.1	-19.8	0.9577
CGI Severity of Illness	-1.7	-2.0	0.1457	-2.3	-2.3	0.7412
% Responders or Remitters						
HAM-D Response	52.6	61.0	0.1644	71.4	71.4	0.9742
HAM-D Remission	45.4	54.3	0.1505	61.0	63.9	0.6186
CGI Global Improvement Response	62.7	63.4	0.9392	82.2	73.7	0.1034

* P values for comparisons between reboxetine and paroxetine are based on ANCOVA with treatment and country as the main effect, and age and baseline score as covariates; p values for response and remission comparisons between reboxetine and paroxetine are based on the Cochran-Mantel-Haenszel test (after controlling for country).

† $p \leq 0.05$

Abbreviations: CGI = Clinical Global Impression scale, HAM-D = Hamilton Depression Rating scale, LOCF = last observation carried forward, MADRS = Montgomery Asberg Depression Rating Scale, OC = Observed cases, PAR = paroxetine, RBX = reboxetine

Source: Section 13, Tables 3.1A, 3.1B, 3.4A, 3.4B, 3.6A, 3.6B, 4.1A, 4.1B, 5.1A, 5.1B, 6.1A, 6.1B, 6.4A, 6.4B, 8.1A, 8.1B, 9.1A, 9.1B, 9.4A, and 9.4B

The results from the secondary measures of quality of life and social and sexual function, (evaluated by the SF-36 survey and SASS and RSI scales [patient rated]) clearly indicate improvement in these areas among both treatment groups during the study. In the SF-36 scale, the reboxetine group showed greater improvement in the later weeks of treatment than the paroxetine group in a majority of the 8 domains of the scale, although most of these results were not statistically significant. In the LOCF analysis, the mean change (improvement) from baseline in the SASS total score at week 8 was 2.8 in the reboxetine group and 3.0 in the paroxetine group (p=0.9565). In the OC analysis, the mean change at week 8 was 4.1 in the reboxetine group and 4.2 in the paroxetine group (p=0.3811). In both the LOCF and OC analyses of the RSI scale, the mean change from baseline in the frequency of pleasurable thoughts and desires to initiate sexual activity, the ability to become sexually excited, and the overall degree of sexual satisfaction showed numerically superior improvements in the scores of the patients in the reboxetine group. Only in the category of

frequency of initiating sexual activity did paroxetine demonstrate numerically superior scores (LOCF and OC).

9.4 Safety Results

9.4.1 Adverse Events

9.4.1.1 Brief Summary

The percentage of patients reporting adverse events was approximately equivalent among the paroxetine (75.3%, 125/166) and reboxetine (73.2%, 115/157) treatment groups. The percentage of patients who discontinued due to adverse events was more than twice as high in the reboxetine group (19.7%) than in the paroxetine group (8.4%). Table 27 presents an overview of the percentage of patients in each treatment group who had at least one adverse event (overall, drug-related, or serious) or who discontinued due to an adverse event.

Table 27. Overall Summary of Adverse Events

	RBX N=157		PAR N=166	
	n	%	n	%
Patients with ≥1 adverse event	115	73.2	125	75.3
Drug-related*	99	63.1	104	62.7
Serious	8	5.1	3	1.8
Patients who discontinued due to adverse events	31	19.7	10	6.0

* Adverse events were considered 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, RBX = reboxetine

Source: Section 13, Tables 13.1A, 13.5A, 13.6A, and 13.8A

9.4.1.2 Adverse Events by COSTART Body System

The frequency of adverse events is summarized by body system in Table 28 28. In each of the treatment groups, the most frequently reported adverse events were related to the digestive and nervous systems and to the body as a whole.

Section 13, Table 13.1, summarizes the adverse events by body system, COSTART term, and treatment group. The patients who reported adverse events are listed in Appendix 16, Listing A1 (by patient) and Listing A2 (by body system and COSTART term).

Table 28. Frequency of Adverse Events by Body System

COSTART Body System*	RBX N=157		PAR N=166	
	n	%	n	%
Patients with ≥1 adverse event	**115**	**73.2**	**125**	**75.3**
Digestive	66	42.0	76	45.8
Nervous	54	34.4	62	37.3
Body	53	33.8	72	43.4
Urogenital	29	18.5	18	10.8
Cardiovascular	28	17.8	19	11.4
Skin	28	17.8	20	12.0
Special Senses	8	5.1	11	6.6
Respiratory	6	3.8	9	5.4
Musculoskeletal	1	0.6	3	1.8
Metabolic and nutritional	1	0.6	8	4.8
Hemic and lymphatic	1	0.6	4	2.4

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

Abbreviations: PAR = paroxetine, RBX = reboxetine

Source: Section 13, Table 13.1A

9.4.1.3 Adverse Events by COSTART Preferred Term

The adverse events that were reported in at least 1% of the patients in any treatment group are summarized in Table 29. In the reboxetine group, the most frequently reported adverse events (reported in at least 5% of reboxetine-treated patients) were dry mouth, constipation, insomnia, headache, diaphoretic, nausea, dizziness, impaired urination, palpitations, chills, and dysuria. The frequency of insomnia was the highest in week 1 (25/157, 15.9%), and the incidence decreased by week 2 (19 patients) and was the lowest in both weeks 7 and 8 (10 patients) (Section 13, Table 13.1B). In the paroxetine group, the most frequently reported adverse events (reported in at least 5% of paroxetine-treated patients) were headache, nausea, constipation, diarrhea, asthenia, dry mouth, insomnia, tremor, dizziness, somnolence, and diaphoretic. All adverse events by body system and COSTART preferred terms are summarized in Section 13, Table 13.1A. Weekly frequency of all adverse events by body system and COSTART terms is provided in Section 13, Table 13.1B.

Table 29. Adverse Events Reported in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=157		PAR N=166	
	n	%	n	%
DIGESTIVE				
Dry mouth	38	24.2	15	9.0
Constipation	29	18.5	19	11.4
Nausea	22	14.0	37	22.3
Decreased appetite	5	3.2	4	2.4
Vomiting	4	2.5	2	1.2
Anorexia	3	1.9	3	1.8
Diarrhea	3	1.9	18	10.8
Dyspepsia	2	1.3	8	4.8
Appetite Increased	0	0	2	1.2
Gastrointestinal disorder	0	0	2	1.2
Toothache	0	0	3	1.8
NERVOUS				
Insomnia	27	17.2	15	9.0
Dizziness	15	9.6	13	7.8
Anxiety	6	3.8	7	4.2
Agitation	3	1.9	3	1.8
Decreased libido	3	1.9	4	2.4
Tremor	3	1.9	14	8.4
Nervousness	2	1.3	4	2.4
Vertigo	2	1.3	1	0.6
Hostility	2	1.3	1	0.6
Hypertonia	1	0.6	2	1.2
Paresthesia	1	0.6	2	1.2
Somnolence	1	0.6	12	7.2
Amnesia	0	0	3	1.8
Concentration impaired	0	0	2	1.2
Restlessness	0	0	2	1.2
Sleep disorder	0	0	4	2.4
BODY				
Headache	25	15.9	40	24.1
Chills	8	5.1	4	2.4
Reaction unevaluable	6	3.8	1	0.6
Asthenia	4	2.5	15	9.0
Flu syndrome	4	2.5	5	3.0
Localized abdominal pain	4	2.5	3	1.8
Back pain	3	1.9	5	3.0
Upper respiratory infection	3	1.9	8	4.8
Abdominal cramp	2	1.3	0	0.0
Viral infection	2	1.3	1	0.6

continued

Table 29. Adverse Events Reported in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=157		PAR N=166	
	n	%	n	%
BODY (continued)				
Fatigue	1	0.6	5	3.0
Localized pain	1	0.6	5	3.0
Neck pain	1	0.6	2	1.2
Neck rigid	0	0	2	1.2
Trauma	0	0	3	1.8
UROGENITAL**				
Urination impaired	10	6.4	2	1.2
Dysuria	8	5.1	1	0.6
Abnormal ejaculation	6	3.8	4	2.4
Impotence	5	3.2	3	1.8
Urinary retention	3	1.9	0	0
Urinary tract infection	2	1.3	0	0
Anorgasmia	1	0.6	4	2.4
Menstrual disorder	0	0	2	1.2
CARDIOVASCULAR				
Palpitation	10	6.4	3	1.8
Vasodilatation	5	3.2	3	1.8
Tachycardia	4	2.5	2	1.2
Migraine	3	1.9	2	1.2
Peripheral vascular disorder	3	1.9	1	0.6
Hypertension	2	1.3	3	1.8
Hypotension	2	1.3	0	0
Postural hypotension	2	1.3	3	1.8
SKIN				
Diaphoretic	24	15.3	12	7.2
Pruritus, non-application site	2	1.3	3	1.8
Rash	1	0.6	2	1.2
SPECIAL SENSES				
Auditory disorder	2	1.3	0	0
Blurred vision	2	1.3	2	1.2
Abnormal accommodation	1	0.6	2	1.2
RESPIRATORY				
Bronchitis	2	1.3	1	0.6
Rhinitis	2	1.3	2	1.2
Sinusitis	2	1.3	0	0
Cough	0	0	2	1.2
Voice alteration	0	0	2	1.2

continued

Table 29. Adverse Events Reported in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=157		PAR N=166	
	n	%	n	%
METABOLIC AND NUTRITIONAL				
Weight loss	1	0.6	3	1.8
Weight gain	0	0	3	1.8
HEMIC AND LYMPHATIC				
Adenopathy	0	0	2	1.2

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

** For a breakdown of Urogenital adverse events by gender please see Table 31.

Abbreviations: PAR = paroxetine, RBX = reboxetine

Source: Section 13, Table 13.1A

9.4.1.4 Adverse Events by Intensity

The adverse events that were reported in at least 5% of the patients in any treatment group are summarized by maximum intensity in Table 30. The majority of adverse events reported by patients in both treatment groups were mild to moderate in intensity. Severe adverse events were reported in 26.1% (41/157) of the patients in the reboxetine group and in 18.7% (31/166) of the patients in the paroxetine group (Section 13, Table 13.2A). All adverse events are summarized by maximum intensity in Section 13, Table 13.2A. Weekly frequency of all adverse events by maximum intensity, body system, and COSTART term is provided in Section 13, Table 13.2B.

Table 30. Maximum Intensity of Adverse Events Reported in ≥5% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=157 n (%)		PAR N=166 n (%)	
	Mild/Mod	Severe	Mild/Mod	Severe
Patients with ≥1 adverse event	**74 (47.1)**	**41 (26.1)**	**94 (56.6)**	**31 (18.7)**
DIGESTIVE				
Dry mouth	32 (20.4)	6 (3.8)	13 (7.8)	2 (1.2)
Constipation	29 (18.5)	0	18 (10.8)	1 (0.6)
Nausea	19 (12.1)	3 (1.9)	36 (21.7)	1 (0.6)
Diarrhea	2 (1.3)	1 (0.6)	15 (9.0)	3 (1.8)
NERVOUS				
Insomnia	17 (10.8)	10 (6.4)	11 (6.6)	4 (2.4)
Dizziness	14 (8.9)	1 (0.6)	12 (7.2)	1 (0.6)
Tremor	3 (1.9)	0	12 (7.2)	2 (1.2)
Somnolence	1 (0.6)	0	11 (6.6)	1 (0.6)

continued

Table 30. Maximum Intensity of Adverse Events Reported in ≥5% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=157 n (%)		PAR N=166 n (%)	
	Mild/Mod	Severe	Mild/Mod	Severe
BODY				
Headache	22 (14.0)	3 (1.9)	37 (22.3)	3 (1.8)
Chills	4 (2.5)	4 (2.5)	4 (2.4)	0
Asthenia	3 (1.9)	1 (0.6)	12 (7.2)	3 (1.8)
UROGENITAL				
Impaired urination	8 (5.1)	2 (1.3)	2 (1.2)	0
Dysuria	7 (4.5)	1 (0.6)	1 (0.6)	0
CARDIOVASCULAR				
Palpitation	9 (5.7)	1 (0.6)	3 (1.8)	0
SKIN				
Diaphoretic	19 (12.1)	5 (3.2)	10 (6.0)	2 (1.2)

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

Abbreviations: PAR = paroxetine, RBX = reboxetine

Source: Section 13, Table 13.2A

9.4.1.5 Adverse Events by Age

The frequency of adverse events by age, body system, and COSTART term are summarized in Section 13, Table 13.3A and by week in Table 13.3B. One patient (No. 33233) was >65 years of age and reported insomnia in weeks 1 and 2 of reboxetine treatment, the remaining adverse events were reported by patients ≤65 years of age.

9.4.1.6 Adverse Events by Gender

The adverse events that were reported in ≥5% of the male or female patients in any treatment group are summarized by gender in Table 31 31. The overall frequency of patients who reported at least 1 adverse event were similar among males and females in both treatment groups (reboxetine females, 74.5%; paroxetine females, 74.8%; reboxetine males, 71.2%; paroxetine males, 76.2%).

Table 31. Adverse Events Reported in ≥5% of Male or Female Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=157		PAR N=166	
	Female N=98	Male N=59	Female N=103	Male N=63
	n (%)	n (%)	n (%)	n (%)
Patients with ≥1 adverse event	**73 (74.5)**	**42 (71.2)**	**77 (74.8)**	**48 (76.2)**
DIGESTIVE				
Dry mouth	26 (26.5)	12 (20.3)	10 (9.7)	5 (7.9)
Constipation	20 (20.4)	9 (15.3)	15 (14.6)	4 (6.3)
Nausea	18 (18.4)	4 (6.8)	28 (27.2)	9 (14.3)
Diarrhea	2 (2.0)	1 (1.7)	11 (10.7)	7 (11.1)
Dyspepsia	2 (2.0)	0	4 (3.9)	4 (6.3)
NERVOUS				
Insomnia	18 (18.4)	9 (15.3)	10 (9.7)	5 (7.9)
Dizziness	11 (11.2)	4 (6.8)	10 (9.7)	3 (4.8)
Tremor	3 (3.1)	0	11 (10.7)	3 (4.8)
Anxiety	4 (4.1)	2 (3.4)	7 (6.8)	0
Decreased libido	0	3 (5.1)	2 (1.9)	2 (3.2)
Somnolence	0	1 (1.7)	8 (7.8)	4 (6.3)
BODY				
Headache	18 (18.4)	7 (11.9)	27 (26.2)	13 (20.6)
Chills	6 (6.1)	2 (3.4)	1 (1.0)	3 (4.8)
Reaction unevaluable	3 (3.1)	3 (5.1)	0	1 (1.6)
Asthenia	2 (2.0)	2 (3.4)	7 (6.8)	8 (12.7)
Localized pain	0	1 (1.7)	1 (1.0)	4 (6.3)
UROGENITAL				
Impaired urination	1 (1.0)	9 (15.3)	1 (1.0)	1 (1.6)
Abnormal ejaculation	0	6 (10.2)	0	4 (6.3)
Dysuria	0	8 (13.6)	1 (1.0)	0
Impotence	0	5 (8.5)	0	3 (4.8)
Urinary retention	0	3 (5.1)	0	0
CARDIOVASCULAR				
Palpitation	3 (3.1)	7 (11.9)	2 (1.9)	1 (1.6)
Vasodilation	2 (2.0)	3 (5.1)	2 (1.9)	1 (1.6)
SKIN				
Diaphoretic	12 (12.2)	12 (20.3)	9 (8.7)	3 (4.8)

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

Abbreviations: PAR = paroxetine, RBX = reboxetine

Source: Section 13, Tables 1.6 and 13.4A

Among the adverse events that were reported in ≥5% of male or female reboxetine-treated patients, male patients experienced impaired urination, abnormal ejaculation, dysuria, impotence, urinary retention, decreased libido, palpitations, and vasodilation. Of these,

females experienced only 3 events (impaired urination, palpitations, and vasodilation), which were reported much less frequently than in the male population. Female reboxetine-treated patients did report more cases of nausea than did male reboxetine-treated patients (females: 18/98, 18.4%; males: 4/59, 6.8%).

Of the 12 male patients in the reboxetine group reporting urinary retention or impaired urination, only 3 were severe in intensity, and only 4 discontinued treatment due to one of these events. In addition, the concomitant medication records indicate that only 2 of the reboxetine-treated patients who reported either impaired urination or urinary retention received medication for their urinary symptoms: patient no. 12689 was treated with prazosin for urinary hesitancy and patient no. 88291 was treated with bethanechol chloride and echinacea for micturition difficulties (Appendix 19, Listing 20). None of the reboxetine-treated male patients was known to have required urinary catheterization for the treatment of symptoms of functional limitation of bladder outflow (Section 13, Table 13.9).

Among the adverse events that were reported in ≥5% of male or female paroxetine-treated patients, male patients experienced abnormal ejaculation and asthenia. Of these, females experienced only 1 event (asthenia), which was reported less frequently than in the male population. Female paroxetine-treated patients did report more cases of constipation, tremor, dizziness, anxiety, and nausea than did male paroxetine treated patients (see Table 31).

All adverse events are summarized by gender in Section 13, Table 13.4A. Weekly frequency of all adverse events by gender, body system, and COSTART terms is provided in Section 13, Table 13.4B.

9.4.1.7 Drug-Related Adverse Events

Adverse events that were judged by the investigators to have been caused by the study medication were reported in 63.1% (99/157) of reboxetine-treated patients and 62.7% (104/166) of paroxetine-treated patients. The drug-related adverse events that were reported in at least 5% of patients in any treatment group are summarized in Table 32 32..

Of the drug-related adverse events that were reported in ≥5% of patients in the reboxetine treatment group, the following events were reported: dry mouth, constipation, insomnia, diaphoretic, nausea, headache, dizziness, impaired urination, palpitations, and chills.

Of the drug-related adverse events that were reported in at least 5% of patients in the paroxetine treatment group, the following events were reported: nausea, headache, constipation, diarrhea, dry mouth, asthenia, tremor, insomnia, somnolence, diaphoretic, and dizziness.

All drug-related adverse events are summarized by COSTART body system and preferred term in Section 13, Table 13.5A. Weekly frequency of all drug-related adverse events by body system and COSTART terms is provided in Section 13, Table 13.1B.

Table 32. Drug-Related* Adverse Events Reported in ≥5% of Patients in Any Treatment Group

COSTART Body System/ Preferred Term†	RBX N=157		PAR N=166	
	n	%	n	%
Patients with ≥1 drug-related adverse event	**99**	**63.1**	**104**	**62.7**
DIGESTIVE				
Dry mouth	36	22.9	14	8.4
Constipation	26	16.6	18	10.8
Nausea	18	11.5	33	19.9
Diarrhea	1	0.6	14	8.4
NERVOUS				
Insomnia	26	16.6	12	7.2
Dizziness	13	8.3	11	6.6
Tremor	3	1.9	13	7.8
Somnolence	1	0.6	12	7.2
BODY				
Headache	16	10.2	25	15.1
Chills	8	5.1	3	1.8
Asthenia	4	2.5	13	7.8
CARDIOVASCULAR				
Palpitation	9	5.7	3	1.8
SKIN				
Diaphoretic	24	15.3	11	6.6
UROGENITAL				
Impaired urination	10	6.4	2	1.2

* Adverse events were considered 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, RBX = reboxetine

Source: Section 13, Table 13.5A

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 13.9).

9.4.2.2 Serious Adverse Events

Serious adverse events were reported in 5.1% (8/157) of reboxetine-treated patients and 1.8% (3/166) of paroxetine-treated patients. The frequency of patients who experienced serious adverse events is summarized in Table 33.. In the reboxetine group, the following seven non-drug-related serious adverse events were each reported for 1 patient: autolysis risk, acute pancreatitis, unilateral epididymec [sic], severe hemorrhage, high blood pressure and heart attack, overreaction to stress, and exacerbation of depression. One event, occurring in

patient no. 69302 in the reboxetine group, was judged by the investigator to have been related to the study medication (a peripheral vascular disorder [ie, cold extremities]). The patient recovered from this event 9 days after discontinuing the study (see narrative summary in Section 9.4.2.4). In the paroxetine group, the following non-drug-related serious adverse events were each reported for 1 patient: angina pectoris, suicide attempt, and cholecystectomy.

Narrative summaries for patients who experienced serious adverse events are provided in Section 9.4.2.4. All serious adverse events are summarized by COSTART body system and preferred term in Section 13, Table 13.8A and by week in Section 13, Table 13.8B. Patients who experienced serious adverse events are listed in Section 13, Table 13.9 (by patient).

Table 33. Frequency of Serious Adverse Events

COSTART Body System/Preferred Term*	RBX N=157		PAR N=166	
	n	%	n	%
Patients with ≥1 serious adverse event	**8**	**5.1**	**3**	**1.8**
BODY				
Reaction unevaluable†	2	1.3	1	0.6
Suicide attempt	0	0	1	0.6
CARDIOVASCULAR				
Hemorrhage	1	0.6	0	0
Hypertension	1	0.6	0	0
Myocardial infarction	1	0.6	0	0
Peripheral vascular disorder	1	0.6	0	0
Angina pectoris	0	0	1	0.6
DIGESTIVE				
Pancreatitis	1	0.6	0	0
NERVOUS				
Anxiety	1	0.6	0	0
Depressive symptoms	1	0.6	0	0

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

† Reboxetine group: reaction unevaluable events were autolysis risk and unilateral epididymec [sic]; Paroxetine group: reaction unevaluable event was cholecystectomy

Abbreviations: PAR = paroxetine, RBX = reboxetine

Source: Section 13, Tables 13.8A and 13.9

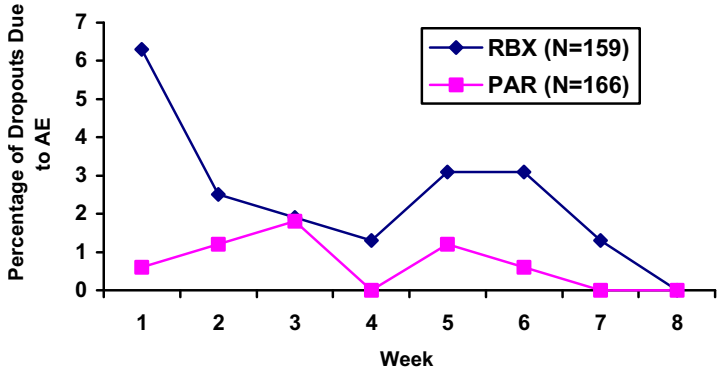
9.4.2.3 Discontinuations Due to Adverse Events

Of the patients evaluable for safety analysis, the percentage of patients who discontinued treatment due to adverse events at any time during the treatment period was higher in the reboxetine group (19.7%; 31/157) than in the paroxetine group (6.0%; 10/166) (Section 13, Table 13.6A).

Out of the randomized patient population, during the first week of treatment (reboxetine administered at a dose of 8 mg/day; paroxetine, 20 mg/day), the rate of discontinuations due to adverse event was higher in the reboxetine group (6.3% 10/159) than in the paroxetine group (0.6% 1/166). The number of discontinuations due to adverse events decreased steadily

in the reboxetine group until week 4 when 2 patients discontinued, while in the paroxetine group the number increased in week 2 (4 discontinuations) and then decreased to week 4 (0 discontinuations). After week 4, when reboxetine could have been increased to 10 mg/day and paroxetine to 40 mg/day, the number of discontinuations due to adverse events increased in both treatment groups and then decreased again. Patients who discontinued due to adverse events are listed in Tables 1.2 and 1.4.

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



Source: Section 13, Table 1.3B

Most adverse events that led to discontinuation of treatment were reported for only 1 or 2 patients in either treatment group. For patients evaluable for safety analysis, the treatment-emergent adverse events that led to discontinuation of treatment in ≥1% of patients in any treatment group are summarized in Table 34. Two patients in the reboxetine group discontinued to due adverse events which began before the first dose of study drug was administered (#55075 for insomnia on day 15 and #91550 for palpitations on day3).

Table 34. Adverse Events That Led to Discontinuation of Treatment in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=157		PAR N=166	
	n	%	n	%
Patients with ≥1 adverse event that led to discontinuation	**29†**	**18.5**	**10**	**6.0**
DIGESTIVE				
Nausea	5	3.2	3	1.8
Dry mouth	3	1.9	1	0.6
Constipation	2	1.3	1	0.6

Table 34. Adverse Events That Led to Discontinuation of Treatment in ≥1% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=157		PAR N=166	
	n	%	n	%
NERVOUS				
Insomnia	6	3.8	0	0
Anxiety	4	2.5	1	0.6
Dizziness	2	1.3	1	0.6
BODY				
Headache	3	1.9	3	1.8
Chills	2	1.3	0	0
UROGENITAL				
Impotence	3	1.9	0	0
Urinary retention	3	1.9	0	0
CARDIOVASCULAR				
Tachycardia	2	1.3	0	0
SKIN				
Diaphoretic	4	2.5	2	1.2

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

† Two patients discontinued due to adverse events which began pre-treatment.

Abbreviations: PAR = paroxetine, RBX = reboxetine

Source: Section 13, Table 13.6A

The most frequently reported adverse event that led to discontinuation of reboxetine treatment was insomnia, which led to discontinuation of treatment in 3.8% (6/157) of reboxetine-treated patients. The most frequently reported adverse events that led to discontinuation of paroxetine treatment were headache and nausea, each led to discontinuation of treatment in 1.8% (3/166) of paroxetine-treated patients. Patients who discontinued treatment due to adverse events are listed in Section 13, Table 13.7 (by patient, body system, and COSTART term). CRFs for patients who discontinued treatment due to adverse events are in Appendix 18.

Most of the adverse events that led to discontinuation of treatment were nonserious in nature. Serious adverse events led to the discontinuation of treatment in 3.2% (5/157) of reboxetine-treated patients and in 0.6% (1/166) of paroxetine-treated patients (Table 35 35). Patients who discontinued treatment due to serious adverse events are listed in Section 13, Table 13.9 (by patient, body system, and COSTART term).

Table 35. Serious Adverse Events Leading to the Discontinuation of Treatment

Patient #	Drug	Event/COSTART Term	Maximum Intensity	Related to Study Drug	Action Taken with Study Drug
3186	Reboxetine	Pancreatitis	Severe	No	Discontinued
61305	Paroxetine	Suicide attempt	Severe	No	Discontinued
63312	Reboxetine	Myocardial infarction	Severe	No	Discontinued
69302	Reboxetine	Peripheral vascular disorder (cold extremities)	Severe	Yes	Discontinued
85281	Reboxetine	Anxiety	Moderate	No	Discontinued
87269	Reboxetine	Depressive symptoms (exacerbation)	Severe	No	Discontinued

Source: Section 13, Table 13.9

9.4.2.4 Narratives

Patient No.: 3186
Investigator: Santos
Treatment: Reboxetine
Event: Acute pancreatitis

This 44-year-old male had a history of duodenal ulcers requiring surgery 20 years previously and an acute pancreatitis episode in June 1999. The current depressive episode was his first. He was on blinded study medication and took his first dose on 3/17/2000. The patient was on study treatment level 1, taking 4 mg Reboxetine twice daily. He was not taking any other concomitant medications. On 3/21/2000, the patient was admitted to the hospital with abdominal pain, nausea, and vomiting. He had consumed alcohol and reported he averaged about 60 gr/day. Upon admission to the hospital he was taken off study medication, rehydrated, and given pain and gastric treatments. The patient recovered and was discharged from the hospital 1 week later. The investigator considered the event not related to the study medication.

Patient No.: 61305
Investigator: Baldwin
Treatment: Paroxetine
Event: Suicide attempt

This 29-year-old female had no previous relevant medical history. She was experiencing her first depressive episode at the time of entry into this study. She began taking blinded study medication on 2/24/2000. The patient was on study treatment level 1, taking 40 mg/day paroxetine at the time of the event. Concomitant medications included Zopiclone, 7.5 mg in the evening for sleep disturbance and paracetamol from 3/1 until 3/16 for a cold accompanied by stuffiness. The patient superficially cut her forearm on 2/23/2000, but the investigator considered the event mild and did not change study medication dosage. On 4/29/2000, the

patient was admitted to the Accident and Emergency Department at Southampton General Hospital with a cut radial artery of the left arm, at the wrist, with severe blood loss. The event was considered a suicide attempt, and the patient hospitalized. Study medication was withdrawn, and the patient recovered with sequelae. The investigator considered the event not related to study medication.

Patient No.: 63312
Investigator: Isaac
Treatment: Reboxetine
Event: Myocardial infarction

This 33-year-old male had a history of ear infections, headaches, hypertension, musculoskeletal pain (lower back, neck, and hip), and non-symptomatic sickle cell trait. He had his first depressive episode at age 27, and had experienced 4 episodes at the time of study entry. There were external stress factors that the investigator felt contributed to the current depressive episode. The patient began blinded medication on 4/12/2000, and was on study treatment level 2 (Reboxetine, 4 mg in the morning and 6 mg in the evening). In addition to study medication, the patient was taking Diclofenac and Co-proxamol for pain; Amlodipine, Bendrofluazide, and Diltiazem SR for hypertension; and Lorazepam for insomnia. The patient had an exacerbation of his long-standing hypertension and was referred to a specialist on 5/10/2000. The patient was not hospitalized, but study medication was permanently withdrawn and he had not yet recovered at last contact with the investigator. The investigator considered the event not related to study medication.

Patient No.: 69302
Investigator: Khan
Treatment: Reboxetine
Event: Cold extremities

This 73-year-old male had a history of hypertension and dermatitis. His first episode of depression was at age 49 and lasted slightly over a year. The investigator felt that the current episode probably had external precipitating factors. The patient was on blinded medication, study treatment level 1 (4 mg Reboxetine twice daily). In addition to study medication, the patient was also taking Valspartin for hypertension and Zopiclone for insomnia. He experienced coldness of the extremities starting 3/28/2000 and the condition continued to worsen. On 4/11/2000, the investigator considered the event serious due to creating persistent or significant disability. Study medication was withdrawn and at follow-up on 4/20/2000, the event had resolved. The investigator felt that the study medication had contributed to the condition.

Patient No.: 85281
Investigator: Spiers
Treatment: Reboxetine
Event: Anxiety

This 42-year-old female had a history of hypothyroidism dating to 1976 (stable on medication) and a hysterectomy in June 1999. Her first episode of depression was at age 38 with 1 other occurrence prior to the present episode. The investigator considered the present depressive episode an exacerbation of a chronic condition without precipitating external stress. The patient was on study treatment level 1, blinded medication (4 mg Reboxetine twice daily), at the time of the event. In addition to study medication, the patient was taking Elthyrone for hypothyroidism, Aldactone for edema in the legs, and Lorazepam for sleep disturbance. On 11/23/1999 the patient ran away from work because of conflicts with her colleagues and asked to be admitted to the hospital. Study medication was withdrawn at the time of hospitalization. The investigator felt that the study medication had not contributed to the condition.

Patient No.: 87269
Investigator: Tack
Treatment: Reboxetine
Event: Depressive symptoms (exacerbation)

This 43-year-old male had no other relevant medical history. His first episode of depression was at age 29 with 1 other occurrence of depression prior to the present episode. The investigator considered this an exacerbation of a chronic condition with probable outside precipitating factors. The patient began taking study medication 7/23/1999 and was on study treatment level 1, blinded medication (4 mg Reboxetine twice daily). He was not taking any other medication. The patient was hospitalized due to exacerbation of his depression. Study medication was permanently withdrawn at the time of hospitalization, and the patient's condition was considered chronic by the investigator upon evaluation at a follow-up visit. The investigator considered the event not related to study medication.

9.4.3 Clinical Laboratory Evaluation

9.4.3.1 Hematology

Hematology results will be reported in an addendum to this report.

9.4.3.2 Chemistries

Chemistry results will be reported in an addendum to this report.

9.4.3.3 Urinalysis

Urinalysis results will be reported in an addendum to this report.

9.4.4 Vital Signs

9.4.4.1 Mean Change From Baseline

No statistically significant differences were observed between treatment groups in the mean change from baseline values for supine systolic blood pressure (Section 13, Table 14.1). Statistically significant differences were noted between treatment groups in the mean change from baseline values for supine diastolic blood pressures at weeks 1, 2, 4, 5, 6, and 8 (Section 13, Table 14.2). The reboxetine group experienced an increase from the baseline mean supine diastolic blood pressure at every visit, while the paroxetine group had a decrease from the baseline mean at every visit. The most substantial difference between treatment groups occurred at week 8 with the reboxetine group experiencing a mean change from baseline diastolic blood pressure of +3.3 and the paroxetine group reporting a mean change of –1.6 (p=0.0001).

Statistically significant differences were observed among the treatment groups in the mean change from baseline pulse rate, taken from the Vital Signs, at each visit (Section 13, Table 14.3). The mean change from the baseline pulse rate was significantly greater in the reboxetine group than in the paroxetine group at each visit. At the end of the study (week 8), the mean change from baseline pulse rate was +6.0 beats per minute in the reboxetine group and –1.6 beats per minute in the paroxetine group.

No statistically significant differences were observed between treatment groups in the mean change from baseline body weight at all visits (Section 13, Table 14.4).

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 11.7% (18/154) in the reboxetine group and 7.9% (13/164) in the paroxetine group (Section 13, Table 18.2). Appendix 17, Listings 1 provides a listing of patients with abnormal ECG findings.

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

PQ interval for reboxetine decreased by 6.0 msec and increased 1.1 msec for paroxetine (Table 36). QT interval decreased by 16.9 msec for reboxetine while increasing 1.3 msec for paroxetine. There was a mean increase in heart rate of 10.3 bpm fofr reboxetine, and a mean decrease in heartrate of 1.6 bpm for paroxetine. This change in heart rate may be clinically significant in some patients.

Section 13, Table 18.1, provides summary statistics for ECG intervals.

Table 36. Mean Change From Baseline ECG Intervals at Week 8; LOCF

Variable	RBX N=157			PAR N=166			P Value*
	n†	Baseline Mean	Mean Change	n†	Baseline Mean	Mean Change	
PQ interval (msec)	121	149.2	-6.0	132	153.0	1.1	0.0498‡
QRS interval (msec)	135	83.3	1.8	147	86.4	-0.6	0.2004
QT interval (msec)	135	359.5	-16.9	147	374.2	1.3	0.0064‡
QTc interval (msec)	133	388.6	7.3	144	398.7	-2.1	0.1718
Heart rate (bpm)	135	74.2	10.3	148	71.5	-1.6	<.0001‡

* P-values (on mean change) are based on one-way ANOVA with treatment as the main effect.

† Number of patients valid for safety analysis with the specified ECG measurement at screen and at end of study.

‡ $p \leq 0.05$

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

Source: Section 13, Table 18.1

9.4.6 Exposure in Utero

There were no known pregnancies during this study.

9.4.7 Safety Conclusions

The percentage of patients reporting adverse events was approximately equivalent among the paroxetine (75.3%, 125/166) and reboxetine (73.2%, 115/157) treatment groups.

The most frequently reported adverse event (reported in at least 5% of reboxetine-treated patients) were dry mouth, constipation, insomnia, headache, diaphoretic, nausea, dizziness, impaired urination, palpitations, chills, and dysuria. The frequency of insomnia was the highest in week 1 (25/157, 15.9%), and the incidence decreased by week 2 (19 patients) and was the lowest in both weeks 7 and 8 (10 patients). In the paroxetine group, the most frequently reported adverse events (reported in at least 5% of paroxetine-treated patients) were headache, nausea, constipation, diarrhea, asthenia, dry mouth, insomnia, tremor, dizziness, somnolence, and diaphoretic. The majority of adverse events reported by patients in both treatment groups were mild to moderate in intensity.

Adverse events that were judged by the investigators to have been caused by the study medication were reported in 63.1% (99/157) of reboxetine-treated patients and 62.7% (104/166) of paroxetine-treated patients. Of the drug-related adverse events that were reported in ≥5% of patients in the reboxetine treatment group, the following events were reported: dry mouth, constipation, insomnia, diaphoretic, nausea, headache, dizziness, palpitations, and chills. Of the drug-related adverse events that were reported in at least 5% of patients in the paroxetine treatment group, the following events were reported: nausea,

headache, constipation, diarrhea, dry mouth, asthenia, tremor, insomnia, somnolence, diaphoretic, and dizziness.

No deaths were reported during this study. Serious adverse events were reported in 5.1% (8/157) of reboxetine-treated patients and 1.8% (3/166) of paroxetine-treated patients. In the reboxetine group, the following non-drug-related serious adverse events were each reported in 1 patient: autolysis risk, acute pancreatitis, unilateral epididymec [sic], severe hemorrhage, high blood pressure and heart attack, overreaction to stress, and exacerbation of depression. One event, occurring in patient no. 69302 in the reboxetine group, was judged by the investigator to have been related to the study medication (a peripheral vascular disorder [ie, cold extremities]). The patient recovered from this event 9 days after discontinuing the study (see narrative summary in Section 9.4.2.4). In the paroxetine group, the following non-drug-related serious adverse events were each reported in 1 patient: angina pectoris, suicide attempt, and cholecystectomy.

Of the patients evaluable for safety analysis, the percentage of patients who discontinued treatment due to adverse events at any time during the treatment period was higher in the reboxetine group (19.7%; 31/157) than in the paroxetine group (8.4%; 14/166), perhaps due to a reboxetine non-titration-starting dose of 8mg/day. Most of the reboxetine patients that discontinued due to adverse events did so in the first week of treatment (6.3%; 10/159). Perhaps the relatively high rate of reboxetine discontinuations in the first week was due to a non-titration-starting dose of 8mg/day.

10 DISCUSSION AND OVERALL CONCLUSIONS

This phase III, multicenter, randomized, double-blind, and active-controlled, parallel-group study was conducted in 325 patients (randomized population) who suffered from MDD without psychotic features, as diagnosed using criteria defined by the DSM-IV. The primary objective was to assess the efficacy and tolerability of reboxetine in comparison with paroxetine, administered at a starting dose of 8mg/day and 20mg/day, respectively, as determined by ANCOVA of the mean change from baseline in the 17-Item HAM-D total score in the ITT patient population. Optional dosage increases were possible at day 28 to 10mg/day of reboxetine and 40mg/day of paroxetine.

A total of 325 patients were enrolled in the study and were randomized to receive treatment with reboxetine (159 patients) or paroxetine (166 patients). The ITT population (all patients who received at least 1 dose of study medication with at least 1 post-baseline efficacy follow-up evaluation) included 154 reboxetine-treated patients and 164 paroxetine-treated patients.

Overall, the patient population in this study was reflective of the general population of patients with depression [30]. The patients in the study ranged in age from 18 to 68 years, and the majority were female and white. No statistically significant differences were noted among the treatment groups in the severity of depression at baseline in randomized patients, as judged by the mean total scores for the HAM-D, MADRS, CGI Severity of Illness, or SASS.

Although both reboxetine and paroxetine did show improvement in the 17-Item HAM-D total scores, paroxetine displayed better efficacy by demonstrating a statistically significant difference among treatment groups in the mean change from baseline in the 17-Item HAM-D total score (reboxetine mean change, -11.5; paroxetine mean change, -13.2; p=0.0345). Possible reasons for these results are as follows:

- More than half of the investigators enrolled 5 or fewer patients; the small number of patients enrolled at a majority of investigative sites (up to 35 centers) could effect study outcomes. Note that for the purpose of statistical testing, data from investigators was pooled by country (instead of by investigator) in order to attempt to rectify any potential effect.
- The most common reason for discontinuation of study medication was due to adverse events, which occurred in a much higher percentage of reboxetine-treated patients (19.7%; 31/157) than paroxetine-treated patients (6.0%; 10/166). Most of the reboxetine patients that discontinued due to adverse events did so in the first week of treatment (6.3%; 10/159). Perhaps this relatively high rate of reboxetine discontinuations in the first week was due to a non-titration-starting dose of 8mg/day. Protocol 047 [31] administered reboxetine at 4mg during the first week of treatment and saw a decrease in the number of discontinuations due to adverse events (7.8%; 20/258). Thus, it appears the lack of reboxetine dose escalation may have contributed to the high number of discontinuations due to adverse events in this study (protocol 052).
- Finally, the HAM-D was primarily designed to measure the severity of depression [32, 20, 33, 34]. 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 [35, 36, 37, 38, 39, 40]. 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.. Cluster analyses of other HAM-D Items, as well as individual listings, can be found in Section 13 Tables 6.1A and 6.1B through 6.5A and 6.5B and in Appendix 15.

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 adverse event (reported in at least 5% of reboxetine-treated patients) were dry mouth, constipation, insomnia, headache, diaphoretic, nausea, dizziness, impaired urination, palpitations, chills, and dysuria. The frequency of insomnia was the highest in week 1 (25/157, 15.9%), and the incidence decreased by week 2 (19 patients) and was the lowest in both weeks 7 and 8 (10 patients). In the paroxetine group, the most frequently reported adverse events (reported in at least 5% of paroxetine-treated patients) were headache, nausea, constipation, diarrhea, asthenia, dry mouth, insomnia, tremor, dizziness, somnolence, and diaphoretic. The majority of adverse events that were reported by patients in each treatment group were mild to moderate in intensity. As discussed above, the percentage of patients who discontinued treatment due to adverse events was higher in the reboxetine group than in the paroxetine group, perhaps due to a reboxetine non-titration-starting dose of 8mg/day.

No statistically significant differences were observed between treatment groups in the mean change from baseline values for supine systolic blood pressure. The reboxetine group experienced an increase from the baseline mean supine diastolic blood pressure at every visit, while the paroxetine group had a decrease from the baseline mean at every visit. The most substantial difference between treatment groups occurred at week 8 with the reboxetine group experiencing a mean change from baseline diastolic blood pressure of +3.3 and the paroxetine group reporting a mean change of –1.6 ($p<0.0001$). This difference is not felt to be of clinical significance.

The majority of patients in each treatment group had ECG findings that were normal at baseline and at endpoint. The PQ interval for reboxetine decreased by 6.0 msec and increased 1.1 msec for paroxetine (Table 36). QT interval decreased by 16.9 msec for reboxetine while increasing 1.3 msec for paroxetine. There was a mean increase in heart rate of 10.3 bpm for reboxetine, and a mean decrease in heart rate of 1.6 bpm for paroxetine. This change in heart rate may be clinically significant in some patients.

In conclusion, although both reboxetine and paroxetine did show improvement in the 17-Item HAM-D total scores, paroxetine displayed better efficacy by demonstrating a statistically significant difference among treatment groups in the mean change from baseline in the 17-Item HAM-D total score (reboxetine mean change, -11.5; paroxetine mean change, -13.2; $p=0.0345$). 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.

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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. Paxil (paroxetine hydrochloride) [package insert]. Philadelphia, PA: SmithKline Beecham Pharmaceuticals; 1999.

20. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6(4):278-96.

21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.

22. Maier W, Philipp M. Comparative analysis of observer depression scales. Acta Psychiatr Scand 1985;72(3):239-45.

23. 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.

24. Davidson J, Turnbull C. The importance of dose in isocarboxazid therapy. J Clin Psychiatry 1984:45(7 Pt 2):49-52.

25. Kearns NP, Cruickshank CA, McGuigan KJ, Riley SA, Shaw SP, Snaith RP. A comparison of depression scales. Br J Psychiatry 1982;141:45-9.

26. Guy W. ECDEU Assessment Manual for Psychopharmacology, 1976, Revised (DHEW Publication No. ADM 76-338). Washington, DC: US Government Printing Office.

27. 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.

28. 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.

29. Zajecka J, Mitchell S, Fawcett J. Treatment emergent changes in sexual function with selective serotonin reuptake inhibitors; as measured with the Rush Sexual Inventory. (In press, Journal of Clinical Psychiatry).

30. 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.

31 Brown MT, Brinkman SA, Reisner JK, Rowland CR. 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 M/2020/0047). Pharmacia & Upjohn Study Report a0080877, 8 May 2000.

32. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.

33. Hamilton M. General problems of psychiatric rating scales. In: Pichot P, ed. Psychological measurements in psychopharmacology. Basel, Switzerland: Karger; 1974:125-38.

34. Hamilton M. Standardized assessment and recording of depressive symptoms. Psychiatr Neurol Neurochir 1969;72(2):201-5.

35. Bech P, Allerup P. The Hamilton Depression Scale: evaluation of objectivity using logistic models. Acta Psychiatr Scand 1981;63(3):290-99.

36. 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.

37. 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.

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

39. 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.

40. 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.