Studie 050

(97-CRBX-050)

Studienbericht

Reboxetine (PNU-155950E) Versus Placebo and Fluoxetine in a Controlled, Randomized, Double-Blind, Multicenter Study of Treatment in Major Depressive Disorders

Final Report of the Study
Protocol 97-CRBX-050

It is the policy of Pharmacia & Upjohn to conduct clinical studies in compliance with company SOPs and standards that incorporate the requirements of the ICH Guideline for Good Clinical Practice. These include study conduct and archiving of essential documents. section 10.1.2 describes protocol deviations.

Study Initiation Date	06 April 1998
Study Completion Date	21 May 1999
Sponsor's Responsible Medical Officer	Mark T. Brown, MD Clinical Development Therapeutic Area CNS Pharmacia & Upjohn, Inc. Kalamazoo, Michigan 49001
Development Phase of Study	Phase 3
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1 SIGNATURE PAGE

(Appendix 1 contains the scanned image of the approval signatures for this document. The original paper signature page has been retained in the paper document and is kept in the paper document archive.)

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2 SYNOPSIS

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

Title of study: Reboxetine (PNU-155950E) versus placebo and fluoxetine in a controlled, randomized, double-blind, multicenter study of treatment in major depressive disorders.

Protocol number: 97-CRBX-050

Investigators and study centers: This was a multicenter study conducted at 24 sites in the United States. The principal investigators were Robert M. Berman (New Haven CT), Harry Croft (San Antonio, TX), Jonathan Davidson (Durham, NC), Jose E. DeLaGandra (Miami, FL), Pedro Delgado (Tucson, AZ), Eugene A. Duboff (Denver, CO), Robert DuPont (Rockville, MD), Maurizio Fava (Boston, MA), John P. Feighner (San Diego, CA), James M. Ferguson (Salt Lake City, UT), William S. Gilmer (Chicago, IL), Wayne Goodman (Gainesville, FL), Jon Heiser (Newport Beach, CA), Marc Hertzman (Rockville, MD), Robert Hirshfeld (Houston, TX), Jeff Kelsey (Atlanta, GA), Barbara Kennedy (Louisville, KY), Ira Lesser (Torrance, CA), Mike Liebowitz (New York, NY), Fredrick W. Reimherr (Salt Lake City, UT), Ralph W. Richter (Tulsa, OK), Michael E. Thase (Pittsburgh, PA), Kenneth Weiss (King of Prussia, PA), John M. Zajecka (Chicago, IL)

Publication (reference): none

Studied period: 8 weeks
Date of first enrollment: 06 April 1998
Date of last completed patient: 21 May 1999

Phase of development: 3

Objectives: The primary objective of this study was to compare the safety and efficacy (risk/benefit ratio) of reboxetine, fluoxetine, and placebo in the treatment of outpatients suffering from a major depressive disorder (MDD).

Secondary objectives of this study (Amendment number 3 of the protocol, located in Appendix 2) were to demonstrate that treating outpatients suffering from MDD with reboxetine significantly improved vitality, general social function, and other mental health components, compared with treatment with either placebo or fluoxetine.

Methodology: This was a phase 3, multicenter, double-blind, randomized, parallel-group, fixed/flexible-dose, placebo- and fluoxetine-controlled study of reboxetine in outpatients aged 18 to 65 years who suffered from MDD. Following a pretreatment washout period, patients were randomized to receive treatment with reboxetine (8 mg/day), fluoxetine (20 mg/day), or placebo. The experimental treatment was administered orally, twice daily, for 8 weeks, with an optional dose increase after the first 4 weeks of treatment to 10 mg/day of reboxetine or 40 mg/day of fluoxetine, based on the judgment of the investigator. Efficacy and safety measures were obtained weekly.

Number of patients (planned and analyzed): The planned enrollment in the study was increased from 300 patients in the original protocol to 450 patients in Amendment number 2 of the protocol. A total of 450 patients were enrolled, randomized, and received treatment with reboxetine, fluoxetine, or placebo (150 patients per treatment group). All patients were included in the analyses.

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Diagnosis and main criteria for inclusion: Adult patients aged 18 to 65 years with a Diagnostic and Statistical Manual-IV (DSM-IV) diagnosis of MDD, without psychotic features and a total score of greater than or equal to 22 on the 21-item Hamilton Rating Scale for Depression (HAM-D) at both the screen and baseline visits, were eligible for this study. Patients were otherwise generally healthy.

Test product, dose and mode of administration, batch number: Reboxetine mesylate tablets (2 mg) were inserted into gelatin capsules for use in this randomized study. Capsules containing 4 mg of reboxetine (lot number 38,166) were administered orally, twice daily (morning and late afternoon), for a total daily dose of 8 mg reboxetine. After 4 weeks of treatment, the dose was allowed to be increased to 10 mg/day by including a 2-mg capsule of reboxetine (lot number 38,165) with the late afternoon dose.

Duration of treatment: 8 weeks

Reference therapy, dose and mode of administration, batch number: Prozac® Pulvules® (fluoxetine hydrochloride; DISTA Products) were inserted into gelatin capsules for use in this randomized study. Capsules containing 20 mg of fluoxetine (lot number 38,167) were administered orally, once daily, in the morning. A late afternoon placebo capsule (lot number 38,174) was administered to maintain the blinding of the study treatments. After 4 weeks of treatment, in patients whom the investigator believed would benefit in terms of response, the dose was increased to 40 mg/day by including a second 20-mg capsule of fluoxetine with the late afternoon placebo capsule.

In placebo-treated patients, placebo capsules (lot number 38,174) were administered orally, twice daily.

Criteria for evaluation:

Efficacy: The primary efficacy measure was the mean change from baseline in the 21-item HAM-D total score. A decrease of greater than or equal to 50% in the HAM-D total score compared with the baseline score was considered the index of response, whereas a HAM-D total score of less than or equal to 10 was considered the index of remission.

The secondary efficacy measures were the Clinical Global Impression (CGI) severity of illness total score and the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Other secondary endpoints included the HAM-D responder status; HAM-D remission status; CGI Global Improvement; CGI Global Improvement responder status; CGI Efficacy Index; Patient Global Impression (PGI) total score; Medical Outcomes Study SF-36 (SF-36); and the Modified Rush Sexual Inventory (RSI); Social Adaptation Self-evaluation Scale (SASS) total score; HAM-D Item 1- Depressed Mood; HAM-D Anxiety Cluster; HAM-D Cognitive Cluster; HAM-D Retardation Cluster; and the HAM-D Sleep Disturbance Cluster. A decrease of greater than or equal to 50% in the HAM-D total score compared with the baseline score was considered evidence of treatment response, whereas a HAM-D total score of 10 or less was considered evidence of remission.

Safety: The safety of the study medication was assessed by evaluation of newly emergent symptoms (treatment-emergent symptoms and discontinuation-emergent symptoms), vital signs, laboratory tests, and electrocardiograms (ECGs).

Statistical methods: The intent-to-treat (ITT) population, which included all patients who were randomized, received at least 1 dose of study medication, and had at least 1 postbaseline efficacy evaluation, was used for all of the efficacy analyses. Two types of analyses were performed for the efficacy variables: “last

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observation carried forward" (LOCF) and "observed cases" (OC). The LOCF analysis used the last valid assessment as an estimate for all subsequent missing values. The OC analysis did not replace missing data. The LOCF analysis was the primary analysis and the OC analysis was the secondary analysis. P-values, based on 2-sided tests, were considered statistically significant if they were less than or equal to 0.050.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: No statistically significant differences were noted between reboxetine and placebo or between fluoxetine and placebo on the primary efficacy endpoint (mean change from baseline in the HAM-D total score on day 56) for either the LOCF or OC analysis. Although the primary efficacy endpoint was not attained by patients in either the reboxetine or fluoxetine treatment group, the HAM-D total score decreased over time (corresponding to patient improvement) in each of the 3 treatment groups. Likewise, this study failed to demonstrate statistically significant differences between reboxetine and placebo or between fluoxetine and placebo on the secondary endpoints of antidepressant efficacy (eg, HAM-D response, remission, anxiety/somatization cluster, cognitive disturbance cluster, or retardation cluster; MADRS; CGI; PGI) on day 56 in either the LOCF or OC analysis. No statistically significant differences in favor of either reboxetine or fluoxetine over placebo were observed in the LOCF analysis at any evaluation time prior to the end of treatment on day 56. Although statistically significant differences in favor of either reboxetine or fluoxetine over placebo were noted occasionally in the OC analysis on days prior to day 56, these were not considered clinically significant. Patients showed improvement over time, regardless of which treatment was administered.

Statistically significant differences were noted among treatment groups in the change from baseline to day 56 in the SF-36 scale assessing mental health for both the LOCF and OC analyses. Fluoxetine was superior to both reboxetine and placebo on the mental health scale, whereas reboxetine was superior to placebo on the general health scale.

The RSI consisted of 5 visual analog scale questions, 3 questions regarding the frequency of sexual activities, 23 male-specific questions, and 16 female-specific questions. For most assessments, treatment with reboxetine and treatment with placebo had similar effects on sexual functioning. The combined results of males and females of the RSI visual analog scale questions demonstrated no significant differences between the reboxetine-treated and placebo-treated groups on the 5 visual analog questions. These questions relate to the frequency of pleasurable sexual thoughts, the ability to become sexually excited, the frequency of desire to initiate sexual acts, the frequency of initiating sexual acts, and overall sexual satisfaction. There were statistically significant differences in favor of the reboxetine-treated group over the fluoxetine-treated group in overall sexual satisfaction (LOCF analysis; $p< 0.02$) and in the ability to become sexually excited (OC analysis; $p < 0.04$). The frequency of various sexual activities remained fairly stable throughout the 56-day treatment period, with no significant differences among treatment groups. Statistically significant differences were noted among treatment groups (in favor of the reboxetine-treatment or placebo-treatment groups compared with the fluoxetine-treatment group) in the ability of female patients to achieve orgasm on day 28 (LOCF analysis; $p=0.0410$) and on day 56 ($p=0.0253$). On day 56, 89.7% of female patients in the reboxetine-treatment group were able to achieve orgasm, as were 89.3% in the placebo-treatment group, compared with 74.4% in the fluoxetine-treatment group. Statistically significant differences were noted among treatment groups for 6 male-specific questions. Of these, 4 were related to erectile function (eg, difficulty getting an erection when sexually stimulated [$p=0.0096$ among treatment groups in the LOCF analysis], requiring more stimuli than usual to achieve an erection [$p=0.0066$],

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decreased fullness of erection [p=0.0104], and painful orgasm/ejaculation [p=0.0013]); however, these problems did not produce the differences among treatment groups (concerning the ability to maintain an erection sufficient for completing the sexual act, morning erection, or delay in orgasm) that would have been expected from a widespread or common problem of purely physiological origin.

SAFETY RESULTS: TES were reported in 92.0% (138 of 150) of the patients in the reboxetine group, in 86.0% (129 of 150) in the fluoxetine group, and in 78.0% in the placebo group. Drug-related TES were reported in 84.7% (127 of 150) of the patients in the reboxetine group, in 68.7% (103 of 150) in the fluoxetine group, and in 50.7% (76 of 150) in the placebo group. No serious TES were reported in patients in the reboxetine group, whereas a serious TES was reported for 1 patient in the fluoxetine group and for 4 patients in the placebo group. The percentage of patients that discontinued study medication due to TES was highest in the reboxetine group (18.0%, 27 of 150), and similar between the fluoxetine (6.7%, 10 of 150) and placebo (8.0%, 12 of 150) groups. No clinically relevant differences among treatment groups were noted in the frequency of patients who had vital sign values outside of the predefined limits.

Of the reboxetine-treated patients, 18.3% (24 of 131) of those with a normal baseline ECG had an abnormal ECG at the end of the study, whereas 21.5% (29 of 137) of the fluoxetine-treated patients and 10.2% (13 of 137) of the placebo-treated patients had an abnormal end-of-study ECG after having had a normal baseline ECG. Although statistically significant differences were observed among treatment groups in the mean change from baseline at day 56 in QRS and QT intervals, the magnitude of the changes was small; additionally, when changes in the QT intervals were corrected for heart rate (ie, QTc), no statistically significant differences were observed among treatment groups. Few patients with normal baseline ECGs developed clinically significant postbaseline ECG abnormalities.

At least 1 DES was reported in similar percentages of patients in each of the 3 treatment groups: 58.3% (49 of 84) in the reboxetine group, 62.4% (53 of 85) in the fluoxetine group, and 58.8% (40 of 68) in the placebo group. Drug-related DES were reported in 15.5% (13 of 84) of the patients in the reboxetine group, in 10.6% (9 of 85) of the patients in the fluoxetine group, and in 14.7% (10 of 68) of the patients in the placebo group. Serious DES were reported in 2.4% (2 of 84) of the reboxetine group and in 1.2% (1 of 85) of the fluoxetine group, whereas none were reported in the placebo group. The percentages of patients discontinuing due to a serious DES were 3.6% (3 of 84) in the reboxetine group and 2.4% (2 of 85) in the fluoxetine group, whereas none of the patients in the placebo group discontinued due to a DES.

CONCLUSION: This study failed to demonstrate statistically significant differences between reboxetine and placebo or between fluoxetine and placebo on the primary efficacy endpoint (mean change from baseline in the HAM-D total score on day 56) for either the LOCF or OC analyses. Whereas the primary efficacy endpoint was not attained by patients in either the reboxetine or fluoxetine treatment group, the HAM-D total score decreased over time (corresponding to patient improvement) in each treatment group, including the placebo group. Likewise, this study failed to demonstrate statistically significant differences between reboxetine and placebo or between fluoxetine and placebo on the secondary endpoints of antidepressant efficacy on day 56 in either the LOCF or OC analyses. The scores of the secondary efficacy endpoints changed in the appropriate direction, indicating patient improvement.

Reboxetine was similar to placebo and superior to fluoxetine in its effect on overall sexual function. The frequency of sexual activities among patients in each of the treatment group changed little, if any, during the treatment period from baseline to day 56. Patients in the reboxetine and placebo groups expressed

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significantly greater degrees of overall sexual satisfaction and the ability to become sexually excited compared with those in the fluoxetine-treatment group, as assessed by the RSI visual analog questions. Significantly higher percentages of female patients in the reboxetine and placebo groups were able to achieve orgasm compared with the fluoxetine group. Statistically significant differences among treatment groups were noted for 4 male-specific questions related to erectile function for which treatment with reboxetine was worse than placebo or fluoxetine. However, the significance of these results with respect to overall male sexual function has not been determined since no differences were noted from other erectile function-related questions or from the answers to the visual analog scale questions.

TES were reported slightly more frequently in patients treated with reboxetine compared with patients treated with fluoxetine or placebo; however, no serious TES were reported in reboxetine-treated patients, whereas, 1 serious TES was reported in fluoxetine-treated patients and 4 in placebo-treated patients. No clinically relevant differences among treatment groups were noted in the frequency of patients who had vital sign values outside of the predefined limits. ECG abnormalities occurred approximately twice as frequently in the active treatment group patients as in the placebo-treated patients.

DES were reported in few patients in any of the 3 treatment groups. At least 1 DES was reported in similar percentages of patients in each of the 3 treatment groups; the same was true for drug-related DES. Although serious DES were reported in a higher percentage of patients in the reboxetine group than in the fluoxetine or placebo groups, nonetheless, there were very few patients in any group with a serious DES: 2 patients in the reboxetine group, 1 in the fluoxetine group, and none in the placebo group.

Over 30% of the patients in each treatment group dropped out prior to the end of the 8-week study, largely due to nonserious TES or lost to follow-up. Many of the dropouts due to TES were within the first 14 days of the study. Early dropouts such as these impair the ability to distinguish between the active treatments and the placebo, since these patients typically have not had sufficient time to respond to active medication and, consequently, their relatively high HAM-D total scores were carried forward in the LOCF analysis. A relatively high placebo effect was noted in this study, which may have further contributed to the inability to distinguish between active treatments and placebo.

Date of the report: March 26, 2001

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4 ABBREVIATIONS AND DEFINITION OF TERMS

ANOVA	Analysis of Variance
CGI	Clinical Global Impression Scale
CMH	Cochran-Mantel-Haenszel Test
CNS	Central Nervous System
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
DES	Discontinuation-Emergent Symptoms
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders— Fourth Edition
ECG	Electrocardiogram
FLX	Fluoxetine
GLM	General Linear Models
HAM-D	Hamilton Rating Scale for Depression
IRB	Institutional Review Board
ITT	Intent-to-treat Population
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
MDD	Major Depressive Disorder
OC	Observed Cases
PBO	Placebo
PGI	Patient Global Impression Scale
RBX	Reboxetine
RSI	Modified Rush Sexual Inventory
SAS	Statistical Analysis System
SASS	Social Adaptation Self-Evaluation Scale
SF-36	Medical Outcomes Study SF-36
SGPT	Serum glutamic-pyruvic transaminase
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Antidepressant
TES	Treatment-Emergent Symptoms
χ^2	Chi-squared Statistical Test

5 ETHICS

5.1 Institutional Review Board

The protocol and protocol amendments for this study were reviewed by, and conducted in compliance with, an Institutional Review Board (IRB) at each of the study sites. A list of all IRBs consulted is available in Appendix 4.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

5.3 Patient Information and Consent

Each patient was given adequate verbal and written information, prior to inclusion in the study, regarding the objectives and procedures of the study and the possible risks involved. A sample of the written patient information that was provided is contained in Appendix 5.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Twenty-four principal investigators participated in this study at 24 centers in the United States. Appendix 6 provides a complete list of investigators as well as those persons whose participation materially affected the conduct of the study, with their affiliations, their roles in the study, and their qualifications.

Appendix 7 contains the signature of the sponsor's responsible medical officer.

Statistical analyses of the data for this report were performed by Clinical Biostatistics, Pharmacia & Upjohn, Kalamazoo, MI. Laboratory tests were performed by Mayo Medical Laboratories, Rochester, MN. Electrocardiograms (ECGs) were interpreted by Premier Research Worldwide, Philadelphia, PA.

7 INTRODUCTION

Depressive illness is common in the general population and is associated with significant morbidity, mortality, and societal costs. Estimates of 1-year prevalence rates, based on diagnostic criteria applied to normal population samples, vary from 4% to 9% for major depression [1]. Depression is almost always a chronic or recurring disorder, with high levels of social and occupational impairment and an increased risk of mortality and comorbidity [1, 2, 3]. Although specific pharmacologic and psychotherapeutic interventions have been effective in treating major depression, fewer than half of individuals with depression currently receive such treatments [4]. This under-treatment is likely due to several factors, including the stigma of depression, the lack of recognition and diagnosis of depression in the

primary-care setting where patients are often first seen with somatic complaints, and the inadequate treatment of patients even when the depression is correctly diagnosed. Among those who do receive psychotherapeutic agents, fewer than 10% receive adequate doses of antidepressant agents and/or an adequate duration of therapy [4].

Tricyclic antidepressants (TCAs) are frequently used to treat depression and are effective in approximately 60% to 80% of patients. However, the TCAs have troublesome adverse effects, primarily anticholinergic (eg, dry mouth, constipation, urinary retention, blurred vision) and cardiovascular (eg, tachycardia) in nature, and some patients are unable to tolerate extended treatment with them. The selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine hydrochloride (hereafter referred to as fluoxetine), are comparable to the TCAs in efficacy but offer distinct advantages in terms of tolerability. These agents are associated with fewer anticholinergic, sedative, cardiovascular, or weight-gain effects than the TCAs and are safer in overdose. However, the SSRIs are associated with gastrointestinal adverse events (eg, diarrhea and nausea), as well as with some central nervous system (CNS) adverse events (eg, restlessness, agitation, insomnia, and somnolence). Thus, there is a need for new effective antidepressant agents that are devoid of the adverse effects associated with the currently used antidepressant agents.

Reboxetine mesylate (PNU-155950E; hereafter referred to as reboxetine) is a specific norepinephrine reuptake inhibitor, which has been shown to be highly potent in the rodent models that are considered predictive of antidepressant activity in humans (eg, reserpine antagonism, clonidine effects prevention, rapid eye movement, sleep latency increase) [5]. Reboxetine has no relevant affinity either for the serotonin or dopamine uptake sites or for the muscarinic or adrenergic receptors [6]. On the basis of reboxetine potency in the animal models combined with the relative absence of the properties that are reportedly responsible for the side-effects of the classical antidepressant agents, the clinical evaluation of reboxetine for the treatment of patients with depressive disorders was implemented.

Reboxetine has undergone extensive preclinical and clinical evaluation, primarily in Europe and Latin America, and has been proven an effective treatment for major depressive disorder (MDD). The drug received approval in the United Kingdom in April 1997 and has been approved in numerous countries since that time. The primary adverse events associated with the administration of reboxetine are dry mouth, constipation, nausea, insomnia, dizziness, headache, tachycardia, and sweating. Study 97-CRBX-050 was conducted as part of an international clinical development program for reboxetine and to allow physicians in the United States to gain experience with the drug prior to its approval in the United States.

8 OBJECTIVES

The primary objective of this study was to compare the safety and efficacy (risk/benefit ratio) of reboxetine, fluoxetine, and placebo in the treatment of outpatients suffering from MDD.

Secondary objectives were to demonstrate that the treatment of outpatients (suffering from MDD) with reboxetine significantly improved vitality, general social function, and other

mental health components including sexual function compared with treatment with either placebo or fluoxetine.

9 METHODS

9.1 Overall Study Design and Plan

This US, phase 3, multicenter study (24 sites) was conducted in 450 patients aged 18 to 65 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) [7]. After a washout period, the length of which depended on the class of drugs with which the patient was being treated at the time of enrollment, patients were randomized to receive 8 weeks of daily treatment with reboxetine* (8 mg/day), fluoxetine (20 mg/day), or placebo, with 150 patients per treatment group. An optional dose increase to 10 mg/day of reboxetine and to 40 mg/day of fluoxetine was allowed after 4 weeks of therapy, based on the judgment of the investigator. Efficacy and safety measures were obtained weekly.

Efficacy was evaluated weekly using the results of both clinician-rated and patient-rated psychological assessments. The primary efficacy endpoint was the mean change from baseline in the 21-item Hamilton Rating Scale for Depression (HAM-D) total score. Response was defined as a decrease of greater than or equal to 50% in the HAM-D total score compared with the baseline score. Remission was defined as a HAM-D total score of less than or equal to 10.

The secondary efficacy measures were the mean changes from baseline in the Clinical Global Impression (CGI) severity of illness total score and the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Other secondary efficacy measures included the HAM-D responder status; HAM-D remission status; CGI Global Improvement; CGI Global Improvement responder status; CGI Efficacy Index; Patient Global Impression (PGI) total score; Medical Outcomes Study SF-36 (SF-36); Modified Rush Sexual Inventory (RSI); Social Adaptation Self-evaluation Scale (SASS) total score; HAM-D Item 1- Depressed Mood; HAM-D Anxiety Cluster; HAM-D Cognitive Cluster; HAM-D Retardation Cluster; and the HAM-D Sleep Disturbance Cluster. The SF-36 and RSI scales each contained additional secondary efficacy measures that were evaluated.

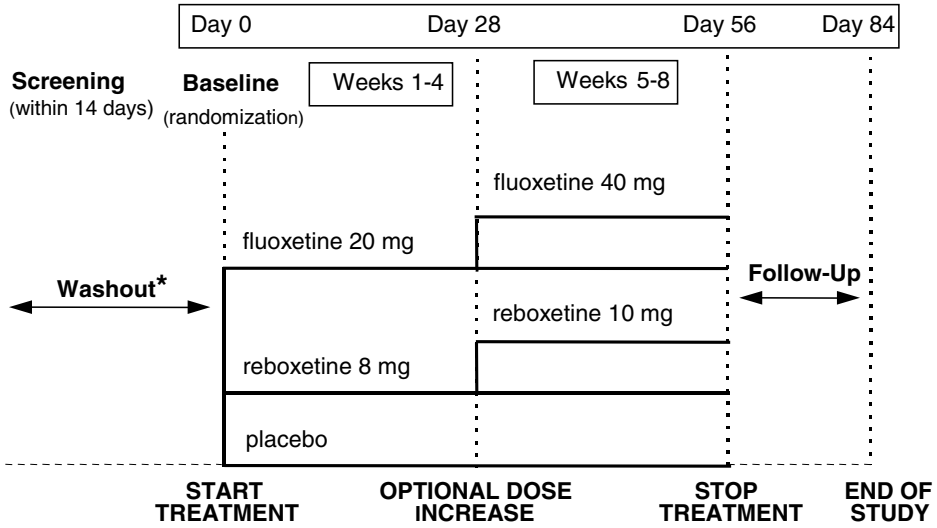
Safety was assessed through evaluation of newly emerged symptoms (treatment-emergent symptoms [TES] and discontinuation-emergent symptoms [DES]), vital signs, clinical laboratory tests, and ECGs.

After treatment completion, the patients did not receive further treatment during the 28-day follow-up period, during which time 2 follow-up visits (at 14-day intervals) were conducted to monitor possible withdrawal reactions (ie, DES).

* The strength of reboxetine mesylate administered is expressed as the strength of reboxetine free base (ie, 10.5 mg of reboxetine mesylate contains 8 mg of reboxetine free base).

The overall study design is presented in Figure 1.

Figure 1. Overall Study Design and Timeline



Source: Appendix 2

* The washout period varied according to the class of drugs with which the patient was being treated at the time of enrollment (eg, 4 days for TCAs, 14 days for MAO inhibitors and SSRIs other than fluoxetine, and 28 days for fluoxetine). Patients who were not being treated with a psychoactive drug at the time of study enrollment could be randomized as soon as their laboratory and ECG test results were available.

9.2 Discussion of Study Design

The double-blind, randomized, parallel-group design used in this study is generally recognized as one that provides an unbiased assessment of the efficacy and safety of an experimental drug. The washout period prior to administration of study medication varied according to the class of drugs with which the patient was being treated at the time of enrollment. The lengths of the washout periods were designed, based on the pharmacokinetics of each class of drugs, to allow sufficient time for elimination of the drug. This washout procedure had been used successfully in previous clinical studies with reboxetine. Fluoxetine was chosen as the comparator for reboxetine because it is currently the most commonly prescribed SSRI in the United States and investigators are familiar with it as a first-line drug for treatment of MDD. Additionally, Pharmacia & Upjohn had experience with fluoxetine as a comparator in previous clinical studies.

9.3 Study Population

Adult patients aged 18 to 65 years with a DSM-IV diagnosis of MDD, without psychotic features and a total score of 22 or greater on the HAM-D at both the screening and baseline visits, were eligible for this study. Patients were otherwise generally healthy.

9.3.1 Inclusion Criteria

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

- Diagnosis of MDD, as defined by DSM-IV, without psychotic features.
- Total score of 22 or greater on the HAM-D at the screening visit, and confirmed at the baseline visit.
- Male or female between the ages of 18 and 65 years. (Females must have been postmenopausal; or must have agreed to avoid pregnancy during the study, had a negative serum pregnancy test at screen, and used a reliable method of contraception during the study. They must not have been breast-feeding.)
- Consented to participate voluntarily and signed a written Patient Informed Consent Form prior to any study procedures at the screening visit.

9.3.2 Exclusion Criteria

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

- DSM-IV diagnosis of other major concomitant psychiatric disorders (eg, MDD with psychotic features, dysthymic or cyclothymic disorders, bipolar I or bipolar II disorders, substance-related disorders, schizophrenia, or other psychotic disorders), or having undergone electroconvulsive therapy within the previous 6 months.
- Patients who were considered by the investigator to have been at high risk for suicide or who had a score of 3 or greater on item 3 of the HAM-D (ie, suicide ideas, suicide gesture, or attempt at suicide).
- Axis IV history of psychosocial or environmental problems which, in the judgment of the investigator, might lead the patient to respond to placebo.
- Resistance to antidepressant treatment, defined as the lack of response to at least 2 previous courses of antidepressant medications given at the full doses for at least 1 month.
- History of MDD associated with endocrine disorders: hypo- and hyper-thyroidism tested by thyroid stimulating hormone and thyroxine, adrenal insufficiency, or Cushing's syndrome.
- Having participated in any clinical study with an investigational compound in the 4 weeks preceding the study.

- History or presence of gastrointestinal, liver, or kidney disease; or history or presence of other conditions known to interfere with the absorption, distribution, metabolism, and/or excretion of drugs.
- History of seizures or brain injury; current evidence of clinically important hematopoietic, respiratory, or cardiovascular diseases; or current evidence of urinary retention or glaucoma.
- Patients with an illness in the 4 weeks preceding the study that might interfere with the study conduct.
- Clinically relevant abnormal findings in the physical examination, laboratory tests, or ECG at admission.

9.3.3 Removal of Patients from Therapy or Assessment

Patients were withdrawn from the study treatment if, in the opinion of the investigator, it was medically necessary, or if it was the wish of the patient. Other reasons for withdrawal included adverse events, clinical deterioration (including mania), and patient refusal.

In case of treatment discontinuation, the reason(s) for the patient withdrawal was 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 considered necessary to define the event leading to patient withdrawal) and efficacy assessments (eg, HAM-D, MADRS, CGI, and Treatment Completion Report) were completed according to the final assessment schedule. The case report forms (CRFs) were completed and collected by the Pharmacia & Upjohn monitor.

9.4 Treatments

9.4.1 Treatments Administered

All patients received blister cards containing sufficient study medication for 1 week. The study medications (reboxetine, fluoxetine, or placebo) were provided as identically appearing capsules. Study medications were administered orally, twice daily. Optional placebo tablets were available for daily morning administration during the washout period at the investigator's discretion.

For weeks 1 through 4, reboxetine treatment consisted of twice daily doses of 4 mg of reboxetine, for a total daily dose of 8 mg. After 4 weeks of treatment, an optional dose increase to 10 mg/day of reboxetine (a 4-mg dose was administered in the morning and a 6-mg dose [consisting of one 4-mg capsule and one 2-mg capsule] was administered in the late afternoon) was allowed for the remainder of the study period, based on the judgment of the investigator.

For weeks 1 through 4, fluoxetine treatment consisted of a morning dose of 20 mg of fluoxetine and a late afternoon placebo capsule, for a total daily dose of 20 mg of fluoxetine.

After 4 weeks of treatment, an optional dose increase to 40 mg/day of fluoxetine (a 20-mg dose was administered in the morning and a second 20-mg dose [consisting of one 20-mg capsule and 1 placebo capsule] was administered in the late afternoon) was allowed for the remainder of the study period, based on the judgment of the investigator.

For weeks 1 through 8, placebo treatment consisted of twice daily doses of placebo capsules. After 4 weeks of treatment, an additional placebo capsule was allowed to be added to the late afternoon dose for the remainder of the study period. This optional dose increase similar to that available for the reboxetine and fluoxetine treatment groups allowed the blind to remain unbroken.

9.4.2 Identity of Investigational Products

Study medications for the randomized treatments consisted of identically appearing capsules containing reboxetine, fluoxetine, or placebo. The reboxetine and placebo supplies were manufactured and supplied by Pharmacia & Upjohn. Placebo capsules consisted of lactose-filled gelatin capsules. The fluoxetine (Prozac® Pulvules®; DISTA Products) comparator was commercially available and was inserted into gelatin capsules by Pharmacia & Upjohn. Information about the study medications is summarized in Table 1.

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

Study Medication	Capsule Strength	Suppliers	Lot Number
Reboxetine	2 mg (one 2-mg tablet)	P&U	38,165
Reboxetine	4 mg (two 2-mg tablets)	P&U	38,166
Fluoxetine	20 mg	DISTA Products, (repackaged by P&U)*	Supplier lot no. 1AF24B (P&U lot no. 38,167)
Placebo capsules		P&U	38,174
Placebo tablets (washout period)		P&U	37,461

Source: Appendix 2

* Prozac® Pulvules® supplied by DISTA Products were inserted into gelatin capsules by P&U.

Abbreviation: P&U=Pharmacia & Upjohn

The placebo tablets used during the pretreatment washout period were packaged and labeled in plastic bottles (20 tablets/bottle); no patient numbers were assigned.

The study medications were packaged in blister cards labeled with the patient number and the study week (weeks 1 through 8). Each blister card provided the study medication for 1 week. Medications were dispensed to patients at each weekly visit. At the same visit, the patients returned the cards that had been dispensed at the previous visit. All unused medications and empty cards were returned to Pharmacia & Upjohn.

Cards for weeks 1 through 4 contained 2 rows of capsules (1 row for the morning dose and 1 row for the late afternoon dose) divided into 7 columns (1 column for each day of the week). A detachable third row was available for weeks 5 through 8. An example of a blister card for reboxetine treatment is shown in Table 2, and an example of a blister card for fluoxetine treatment is shown in Table 3. Placebo cards (depicted in Table 4) consisted of a placebo capsule for each dose (morning and late afternoon). A detachable third row, also containing placebo, was available for weeks 5 through 8 for the placebo blister cards.

Table 2. Example of Blister Cards for Reboxetine Treatment

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM	RBX 4 mg	RBX 4 mg	RBX 4 mg	RBX 4 mg	RBX 4 mg	RBX 4 mg	RBX 4 mg
PM	RBX 4 mg	RBX 4 mg	RBX 4 mg	RBX 4 mg	RBX 4 mg	RBX 4 mg	RBX 4 mg
PM∗ option	RBX 2 mg	RBX 2 mg	RBX 2 mg	RBX 2 mg	RBX 2 mg	RBX 2 mg	RBX 2 mg

Source: Appendix 2
∗Added detachable row for weeks 5-8.
Abbreviation: RBX = Reboxetine

Table 3. Example of Blister Cards for Fluoxetine Treatment

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM	FLX 20 mg	FLX 20 mg	FLX 20 mg	FLX 20 mg	FLX 20 mg	FLX 20 mg	FLX 20 mg
PM	PBO	PBO	PBO	PBO	PBO	PBO	PBO
PM∗ option	FLX 20 mg	FLX 20 mg	FLX 20 mg	FLX 20 mg	FLX 20 mg	FLX 20 mg	FLX 20 mg

Source: Appendix 2
∗Added detachable row for weeks 5-8.
Abbreviations: FLX = Fluoxetine: PBO= Placebo

Table 4. Example of Blister Cards for Placebo Treatment

Time	Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM	PBO	PBO	PBO	PBO	PBO	PBO	PBO
PM	PBO	PBO	PBO	PBO	PBO	PBO	PBO
PM∗ option	PBO	PBO	PBO	PBO	PBO	PBO	PBO

Source: Appendix 2
∗Added detachable row for weeks 5-8.
Abbreviations: PBO= Placebo

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

9.4.3 Method of Assigning Patients to Treatment Groups

Pharmacia & Upjohn prepared a randomization list for assignment of the patients to 1 of the 3 treatment groups. Study medication for each treatment group was prepared on this basis by Pharmacia & Upjohn and 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 8).

9.4.4 Selection of Doses in the Study

The selection of daily doses of reboxetine from 8 to 10 mg was based on the results of previous phase 2/3 studies, in which these doses were shown to provide maximal response rates with minimal adverse events. The fluoxetine doses administered (20 mg/day, with an optional increase to 40 mg/day) were the recommended doses for treatment of MDD.

9.4.5 Selection and Timing of Dose for Each Patient

Patients were randomized prior to treatment with reboxetine, fluoxetine, or placebo. During the first 4 weeks of the study, each patient took 1 capsule at an approximately fixed time between 8 and 9 AM, and the second capsule at an approximately fixed time between 5 and 6 PM, for a total daily dose of 8 mg of reboxetine, 20 mg of fluoxetine, or placebo. Patients were assessed at the 4-week evaluation. Those who were doing well at the 4-week evaluation, as judged by the investigator, continued to take the same doses of medication for the remainder of the study period (weeks 5 through 8) as they had taken during the first 4 weeks.

An optional dose increase was permitted for weeks 5 through 8 if the investigator believed the patient would benefit in terms of response and would adequately tolerate the increased dose. The dose was increased by administration of the capsule from row 3 of the blister card at the afternoon dose along with the capsule from row 2, as shown in Table 2 for patients in the reboxetine group, in Table 3 for patients in the fluoxetine group, and in Table 4 for patients in the placebo group. Patients taking an increased dose of study medication beginning at week 5 continued at the higher dose throughout the remainder of the study. However, if the patient was unable to tolerate the higher dose, that patient returned to taking the lower tolerated dose for the remainder of the study.

9.4.6 Blinding

Placebo tablets were administered during the washout period in a single-blind fashion. Randomized medications were used during the treatment period 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, fluoxetine, or placebo. The capsules were packaged in blister cards labeled by patient number.

Investigators were given sealed drug disclosure sheets containing the information about each patient's treatment. These were opened only in case of emergency, when knowledge of the treatment was necessary for proper management of the patient. If the treatment blind was broken, the reason and the date were recorded and 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. After breaking the code, the patient was withdrawn from the study.

The sealed disclosure sheets were returned to Pharmacia & Upjohn at the end of the study.

9.4.7 Prior and Concomitant Therapy

No concomitant psychotropic medications other than temazepam or chloral hydrate, which could be administered on an as-needed basis, were allowed during the study. The use of any other concomitant psychotropic drug was considered a protocol violation, and the patient was withdrawn from the study.

Other therapy considered necessary for the patient's welfare was permitted at the discretion of the investigator. All such therapy was recorded on the Noninvestigational Medication CRF. No other investigational drug was allowed 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; they were recorded along with other medications on the Noninvestigational Medication CRF.

9.4.8 Treatment Compliance

Study medication was administered for 8 weeks. Patient compliance was monitored through the use of the subject-dosing diary (see Appendix 3) and the return of the study medication blister cards each week. Diaries remained source documents and were retained by the investigator. Discrepancies between dispensed and returned study medications were recorded.

9.5 Efficacy and Safety Variables

9.5.1 Study Schedule

The schedule of study activities is summarized in Table 5.

Table 5. Schedule of Activities

Study Activity	Study Day*											
	Screen†	0	7	14	21	28	35	42	49	56‡	70	84‡
Informed consent	X											
Admission checklist	X											
Medical history	X											
Physical examination	X											
History of mental disorder	X											
Randomization		X										
ECG	X					X				X		
Serum chemistry, hematology	X					X				X		
Serum pregnancy test, Urine drug screen	X									X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
21-item HAM-D	X	X	X	X	X	X	X	X	X	X	X	X
MADRS, CGI, SF-36, SASS		X	X	X	X	X	X	X	X	X	X	X
PGI			X	X	X	X	X	X	X	X	X	X
RSI		X				X				X		X
Compliance			X	X	X	X	X	X	X	X		X
Medication record form		X	X	X	X	X	X	X	X			
Noninvestigational medication form	X	X	X	X	X	X	X	X	X	X	X	X
Treatment/Study completion report										X		X
Adverse event form		X	X	X	X	X	X	X	X	X	X	X

Source: Appendix 2

* Visits were targeted to occur within 1 day of the scheduled study day.

† The screening visit must have occurred within 2 weeks prior to baseline.

‡ For a patient who withdrew between study days 0 and 56, all tests and forms listed for the day 56 visit and the Treatment/Study Completion Forms were completed. For any patient who withdrew between study days 57 and 84, all tests and forms listed for the day 84 visit were completed.

Abbreviations: CGI = Clinical Global Impressions, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery Asberg Depression Rating Scale, PGI = Patient Global Impressions, RSI = Modified Rush Sexual Inventory Scale, SASS = Social Adaptation Self-evaluation Scale, SF-36 = Medical Outcomes Study SF-36.

9.5.1.1 Pretreatment Washout Period

All patients signed an informed consent form prior to enrollment in the study. Patients who were eligible based on the inclusion/exclusion criteria underwent a screening laboratory and ECG assessment prior to beginning an appropriate washout period. Optional placebo tablets (once in the morning) were administered in a single-blind fashion during the washout period at the investigator's discretion. The length of the washout period depended on the class of drugs with which the patient was being treated at the time of enrollment (4 days for TCAs, 14 days for MAOIs or SSRIs other than fluoxetine, and 4 weeks for fluoxetine). Patients who were not being treated with a psychoactive drug at the time of study enrollment could be randomized as soon as their laboratory test and ECG results were available. In addition, patients whose conditions were deteriorating, in the opinion of the investigator, and who required treatment could be randomized as soon as their laboratory test and ECG results were available, even if they had not completed an optimal washout period. Patients who were taking fluoxetine at study entry required an initial screen to determine eligibility and a second screen after week 2 of the 4-week washout period to comply with the requirement that screening labs and ECGs take place within 2 weeks prior to baseline (day 0).

9.5.1.1.1 Screen Visit

The following activities and evaluations were completed at the screen visit:

- Informed consent
- Admission checklist
- Medical history, psychiatric history, history of mental disorder, history of the use of antidepressant medications and other psychoactive drugs
- Demographic/social/occupational status form
- 21-Item HAM-D
- Physical examination and vital signs
- Laboratory evaluations (serum chemistry, hematology, and pregnancy test; and urine drug screen)
- ECG
- Noninvestigational medication form

9.5.1.1.2 Baseline/Randomization Visit (Day 0)

Following the washout period, patients were assessed at baseline using standardized clinical psychopathological evaluations. Information about patients who were screened for the study and were determined ineligible for participation in the study was collected on the appropriate form (screening form). Eligible patients were randomized to receive reboxetine, fluoxetine, or placebo.

The following activities and evaluations were completed at the baseline visit:

- Randomization
- 21-Item HAM-D
- MADRS
- CGI (Severity of Illness index)
- SF-36
- SASS
- RSI
- Vital signs
- Investigational medication record form
- Noninvestigational medication form
- Adverse event form

9.5.1.2 Treatment Period

The following activities or measurements were performed at each visit during the treatment period (days 7, 14, 21, 28, 35, 42, 49, and 56):

- 21-Item HAM-D
- MADRS
- CGI (all indices)
- PGI
- SF-36
- SASS
- Vital signs
- Investigational medication record form
- Noninvestigational medication form
- Adverse event form

The following activities or measurements were performed at both the midpoint and the end of the treatment period (days 28 and 56) or at the end of the treatment period (day 56), as noted:

- Laboratory evaluations (serum chemistry and hematology) (days 28 and 56)
- ECG (days 28 and 56)
- RSI (days 28 and 56)

- Serum pregnancy test and urine drug test (day 56)
- Treatment completion report (day 56)

9.5.1.3 Posttreatment Follow-up Period

The following activities or measurements were performed during the posttreatment follow-up period (days 70 and 84):

- 21-Item HAM-D
- MADRS
- CGI
- PGI
- SF-36
- SASS
- Vital signs
- Noninvestigational medication form
- Adverse event form

The following additional activities or measurements were performed at the end of the posttreatment follow-up period (day 84):

- RSI
- Study completion report

9.5.2 Efficacy Variables

Efficacy was evaluated weekly using the results of both clinician-rated and patient-rated psychological assessments. The primary efficacy endpoint was the mean change from baseline in the 21-item Hamilton Rating Scale for Depression (HAM-D) total score. Response was defined as a decrease of greater than or equal to 50% in the HAM-D total score compared with the baseline score. Remission was defined as a HAM-D total score of less than or equal to 10.

The secondary efficacy measures were the mean changes from baseline in the Clinical Global Impression (CGI) severity of illness total score and the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Other secondary endpoints included the HAM-D responder status; HAM-D remission status; CGI Global Improvement; CGI Global Improvement responder status; CGI Efficacy Index; Patient Global Impression (PGI) total score; Medical Outcomes Study SF-36 (SF-36); Modified Rush Sexual Inventory (RSI); Social Adaptation Self-evaluation Scale (SASS) total score; HAM-D Item 1- Depressed Mood; HAM-D Anxiety Cluster; HAM-D Cognitive Cluster; HAM-D Retardation Cluster; and the HAM-D Sleep Disturbance Cluster.

The efficacy assessments are described below.

9.5.2.1 Hamilton Depression Rating Scale

The HAM-D [8] is an observer-rated scale that is based on both a clinical interview and behavioral observations made by a suitably trained 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 items on the HAM-D are graded according to severity either on a 0- to 2-point scale or on a 0- to 4-point scale, with the total score ranging from 0 to 62. Scores greater than or equal to 25 are associated with severe depression, scores between 18 and 24 are associated with moderate depression, and scores between 8 and 17 are associated with mild depression. Scores less than or equal to 10 are often used as the definition of disease remission. Response to study medication is defined as a decrease of at least 50% from baseline in the HAM-D total score at the postbaseline assessment. Patient improvement is indicated by a mean decrease in the postbaseline score compared with the baseline score.

The 21 items of the HAM-D and the scoring range for each item are summarized in Table 6. Items 10, 11, 12, 13, 15 and 17 on the HAM-D scale were clustered to measure anxiety; items 2, 3, 9, 19, 20 and 21 were clustered to measure cognitive disturbance; and items 1, 7, 8, and 14 were clustered to measure retardation.

Table 6. Hamilton Depression Rating Scale: Items and Scoring Ranges

Item	Scoring Range
1. Depressed Mood	0-4
2. Feelings of Guilt	0-4
3. Suicide	0-4
4. Insomnia Early	0-2
5. Insomnia Middle	0-2
6. Insomnia Late	0-2
7. Work and Activities	0-4
8. Retardation	0-4
9. Agitation	0-4
10. Anxiety Psychic	0-4
11. Anxiety Somatic	0-4
12. Somatic Symptoms Gastrointestinal	0-2
13. Somatic Symptoms General	0-2
14. Genital Symptoms	0-2
15. Hypochondriasis	0-4
16. Loss of Weight	0-2
17. Insight	0-2
18. Diurnal Variation	0-2
19. Depersonalization	0-4
20. Paranoid Symptoms	0-3
21. Obsessional and Compulsive Symptoms	0-2

Source: Reference 8.

9.5.2.2 Montgomery Asberg Depression Rating Scale

The MADRS [9], also based on a clinical interview, satisfactorily distinguishes between 5 grades of depression. The overall performance from this evaluation is equal to that from the HAM-D. The MADRS consists of 10 items, each of which is scored on a 7-point scale, in which 0 corresponds to the absence of the symptom and 6 corresponds to the most extreme form of the symptom.

9.5.2.3 Clinical Global Impression

The CGI [10] 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. Questions from the Global Improvement and Efficacy indices refer to changes since the beginning of the study, as evaluated at each postbaseline visit, and were not asked at baseline. Lower scores on the CGI Global Improvement indicate

patient improvement; a responder is defined as having a score less than or equal to 2 (very much improved or much improved). Lower scores on the CGI Efficacy Index indicate a more favorable ratio of therapeutic effects to adverse events.

9.5.2.4 Patient Global Impression

The PGI is a single-item patient-rated scale, with a total score ranging from 0 to 10 points. A score greater than 5 indicates patient improvement since the beginning of the study, a score less than 5 indicates patient worsening since the beginning of the study, and a score equal to 5 indicates no change in patient condition since the beginning of the study.

9.5.2.5 Medical Outcomes Study SF-36

The SF-36 [11, 12] is a general self-administered quality of life instrument composed of 8 scales that each address a different quality of life aspect. Each scale is scored separately; no composite total is calculated. The 8 scales are physical functioning, role physical, bodily pain, general health, vitality, mental health, social functioning, and role emotional. The SF-36 contains a total of 36 items and is expected to take less than 20 minutes to complete. The reliability and validity of this scale 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.

9.5.2.6 The Social Adaptation Self-evaluation Scale

The SASS [13] is a 21-question self-evaluation questionnaire that explores the patient's social functioning using the domains of work and leisure, relationships, and perceptions of management of environment. The scale was validated using data from 4000 individuals in a general population survey along with data from 549 depressed patients enrolled in clinical studies comparing the efficacy of reboxetine with placebo and/or fluoxetine [13]. 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 normal (ie, this range was observed in 80% of the general population) [13]. The SASS represents a useful tool for the evaluation of social functioning in depression both because it is relatively simple to use and because it may help differentiate the effects of different classes of antidepressants (eg, serotonergic agents regulating mood, noradrenergic agents sustaining drive) in a manner that syndromic clinical rating scales cannot.

9.5.2.7 The Modified Rush Sexual Inventory

The RSI [14] is a comprehensive, succinct, self-rated patient inventory created to assess changes in sexual function over time. Each inventory consists of 5 visual analog questions, 3 frequency of sexual activity items, and individual "yes/no" gender-specific items (ie, 23 male-specific items and 16 female-specific items).

9.5.3 Safety Variables

The safety variables analyzed were the nature and incidence of all adverse events, vital signs, clinical laboratory and ECG test results. At the screening visit, the patient's medical history was taken, and the patient underwent a standard clinical and physical examination. At each weekly visit, patient vital signs were recorded and any abnormalities or adverse events were recorded. At the 28-day and 56-day visits, additional laboratory and ECG tests were performed.

9.5.3.1 Adverse Events

All adverse events that occurred in patients during their participation in this study were reported to Pharmacia & Upjohn, whether or not the events were considered medication related.

9.5.3.1.1 Definition of Adverse Events

An adverse event was defined as any untoward medical occurrence in a patient administered study medication that happened during the protocol-specified adverse event reporting period (defined in this study beginning at baseline and ending 4 weeks after the last dose of study medication), regardless of whether it was considered medication related. In addition, adverse events were also any known untoward medical occurrence subsequent to the adverse event reporting period that the investigator assessed as possibly related to the study medication.

Adverse events included all suspected adverse medication reactions; all reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity; apparently unrelated illnesses, including the worsening or increase in frequency of a preexisting illness; any injury or accident; or any abnormality in physical examination or laboratory test results determined clinically relevant (ie, requiring clinical intervention or further investigation beyond a repeat or 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 under the Comments section on the CRF. Laboratory abnormalities associated with an adverse event (eg, elevated liver enzymes in a patient with jaundice) were recorded under the comments section on the CRF, rather than listed as a separate adverse event.

9.5.3.1.2 Eliciting Adverse Event Information

Investigators reported all directly observed adverse events as well as all adverse events spontaneously reported in the patient. In addition, at each weekly visit, patients were asked whether any adverse events had been experienced since the beginning of treatment, in the following manner: "Since your last clinic visit have you had any health problems?"

9.5.3.1.3 Adverse Events Reporting Period

Previous studies of reboxetine did not prospectively collect detailed data regarding possible adverse events that followed discontinuation of treatment. In this study, the adverse events

reporting period began at baseline (day 0) and continued for 4 weeks following the last dose of study medication (day 84). Adverse events were classified as either treatment-emergent adverse events, if they occurred within the study medication treatment period (days 0 to 56), or discontinuation-emergent adverse events, if they occurred during the follow-up period (days 57 to 84).

A disorder or symptom that was present before the adverse events reporting period began, and which was noted on either the pretreatment medical history/physical form or the baseline adverse event form, was not reported as an adverse event, unless the condition either worsened in intensity or increased in frequency during the adverse events reporting period (days 0 to 84). If the onset of a newly observed adverse event followed the last dose of study medication (ie, this event was not reported during the treatment period), or if the event had already been reported during the treatment period but became more severe following the last dose of study medication, then the event was considered a discontinuation-emergent symptom. Evaluation of discontinuation-emergent symptoms permitted an assessment of adverse events that may have been associated with drug withdrawal.

9.5.3.1.4 Assessment of Gravity and Intensity

All reported adverse events were classified as either serious or nonserious. The classification of the gravity of the event determined the reporting procedures that were followed. A serious adverse event was one that was either fatal or life-threatening (ie, resulted in immediate risk of death); required or prolonged hospitalization; resulted in persistent or significant disability/incapacity; resulted in permanent impairment of function or permanent damage to a body structure (or required intervention to prevent permanent impairment or damage); or was a congenital anomaly, cancer, or medication overdose. This category also included any other adverse event that was judged serious by the investigator. Serious adverse events were reported immediately (within 24 hours of occurrence) by telephone to Pharmacia & Upjohn. The telephone report was followed by submission of a completed Adverse Event Form—Supplemental Information within 5 working days of the event. If unexpected, serious adverse advents were also reported immediately to the IRB.

Nonserious and serious adverse events were reported on an Adverse Events Report Form, which was submitted to Pharmacia & Upjohn as specified in the case report submission procedure for this protocol. On the form, the investigator used the adjectives mild, moderate, or severe to describe the maximum intensity of the adverse event. For the purposes of consistency, the intensity grade of mild was defined as an adverse event that did not interfere with the patient's usual function, an intensity grade of moderate was defined as an adverse event that did interfere to some extent with the patient’s usual function, and an intensity grade of severe was defined as an adverse event that interfered significantly with the patient’s usual function. Noted was a distinction between gravity and intensity of an adverse event. Since severe was a measure of intensity, a severe reaction was not necessarily a serious reaction.

9.5.3.1.5 Assessment of Drug-relatedness

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

9.5.3.1.6 Follow-up of Unresolved Events

All adverse events were followed until they were resolved or until the patient's participation in the study ended (ie, until a treatment completion report was finalized for that patient). In addition, all serious adverse events and those nonserious adverse events assessed by the investigator as possibly related to the study medication were followed even after the patient's participation in the study was over. Such events were followed until resolution, or until the investigator assessed them as either "chronic" or "stable." A poststudy follow-up report form was provided for such events.

9.5.3.1.7 *Exposure In Utero*

If pregnancy was discovered during the treatment period, study medication was immediately discontinued. If any patient became, or was found to be, pregnant either while receiving study medication or within 30 days of discontinuing the study medication, the investigator submitted an adverse events report form that included the anticipated date of birth or pregnancy termination. The patient was followed by the investigator until the completion of the pregnancy. Near the anticipated date listed on the form, Pharmacia & Upjohn provided an Exposure-In-Utero CRF, on which the investigator listed the outcome of the pregnancy. The following pregnancy outcomes were reported as serious adverse events: spontaneous abortion (including miscarriage and missed abortion), stillbirth, neonatal death within 1 month of birth, infant death after 1 month of birth that the investigator assessed as possibly related to in utero exposure to study medication, or congenital anomaly (including that in an aborted fetus assessed by gross visual inspection).

9.5.3.2 Laboratory Tests

Hematology and serum chemistries were evaluated at the screening visit and on days 28 and 56. A urine drug screen was performed at screen and day 56. Screening labs were performed within the 2 weeks immediately preceding enrollment. Laboratory assessments performed are listed in Appendix 3 of the protocol, which is located in Appendix 2 of this report.

9.5.3.3 Vital Signs

Systolic and diastolic blood pressure, and pulse rate were measured (patients in a sitting position) at screen, at baseline (day 0), at weekly intervals during the treatment period, and at biweekly intervals during the posttreatment follow-up period.

9.5.3.4 Electrocardiograms

ECGs were performed at screen and on days 28 and 56. Analysis included assessment of abnormal ECG patterns and measurement of appropriate intervals (eg, heart rate, and PR, QRS, QT, and QTc intervals).

9.5.3.5 Physical Exams

Standard medical history and standard clinical and physical examinations were performed at screen.

9.5.4 Pharmacogenomic Analysis

As described in Amendment 1 of the protocol (located in Appendix 2 of this report), an additional blood sample was collected from a subset of randomized patients for future pharmacogenomic analysis. Although all randomized patients were encouraged to participate in the pharmacogenomic analysis, participation was not mandatory (ie, patients could refuse to submit a blood sample for the pharmacogenomic analysis and still participate in the rest of the clinical study). A separate pharmacogenomic protocol and patient informed consent form were presented to patients who elected to participate in the pharmacogenomic protocol.

For patients who agreed to participate in the pharmacogenomic analysis and who signed the informed consent form, a blood sample was taken after randomization (at any time). The blood sample was analyzed for the presence of specific candidate genes thought to be important in depression, response to antidepressant therapy, or adverse events. The genotypic data from this study will be combined with genotypic data from other studies in an effort to correlate the genetic analysis data with clinical data such as response or nonresponse to reboxetine, fluoxetine, or placebo. The results of the pharmacogenomic study will be reported separately.

9.6 Data Quality Assurance

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

- An investigator's training meeting was held to familiarize the investigators with the protocol and with the assessment instruments (eg, HAM-D, CGI).
- A reference manual was given to each investigator.
- Data were collected on standard CRFs provided to each investigator by the sponsor.
- Investigators and institutions guaranteed access to source documents for quality assurance audits by Pharmacia & Upjohn personnel as well as by 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 for verification of agreement with data on the patient CRFs.
- All safety laboratory measurements were conducted by Mayo Medical Laboratories, Rochester, MN, a central laboratory certified by the Clinical Laboratory Improvement Act and the College of American Pathologists.
- Laboratory data entered at Mayo Medical Laboratories were transmitted electronically to Pharmacia & Upjohn for analysis.
- ECGs were evaluated by Premier Research Worldwide, Philadelphia, PA.
- Pharmacia & Upjohn's Standard Operating Procedures (SOPs) were followed in the conduct and analysis of the study.

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

9.7.1 Determination of Sample Size

The calculated power to detect an efficacy difference between the placebo and reboxetine treatment groups was used to determine the number of patients required in each treatment arm (ie, sample size). Using data from a previous study [15, 16], in which the difference in the mean change from baseline of the 21-item HAM-D total score between the placebo and reboxetine groups was 4.7 with a standard deviation of ± 9.5, it was determined that 100 patients would be required per treatment arm to provide the test with a power of 93% and a 2-sided alpha equal to 0.05. The sample size of 100 patients per arm would still provide an 88% power in the observed case analyses if 20% of the patients dropped out.

The protocol was later amended (Amendment 2, 18 November 1998; Appendix 2) to increase the planned total enrollment in the study from 300 patients (100 per treatment arm) to 450 patients (150 per treatment arm), based on additional sample size calculations to determine the number of patients required to show statistically significant differences between reboxetine and fluoxetine on improvement in the patients social function, as measured by SASS total scores.

9.7.2 Data Sets Analyzed

The intent-to-treat (ITT) population, which included all patients who were randomized, received at least 1 dose of study medication, was used for all of the analyses. The study days used for the efficacy analyses were identical to those listed on the preprinted CRF, regardless of whether the actual assessment day matched the date reported on the CRF. Two types of analyses were performed for the efficacy variables: "last observation carried forward" (LOCF) and "observed cases" (OC). The LOCF analyses used the last valid assessment as an estimate for all subsequent missing values. The OC analysis did not replace missing data. The LOCF analyses were the primary analyses and the OC analyses were the secondary.

P-values, based on 2-sided tests, were considered statistically significant if they were ≤ 0.0500.

All data processing, summarization, and analyses were performed using the Statistical Analysis System, Cary, NC, Version 6.12 software package on the UNIX platform. The ANOVA results were based on Type III sums of squares computed by the General Linear Models (GLM) procedure.

9.7.3 Demographic and Baseline Characteristics

Baseline/demographic characteristics (eg, age, sex, race) for patients assigned to each study medication group were compiled. Categorical variables were summarized using frequency counts. The association between treatment groups and categorical variables was assessed using the chi-squared test (χ^2). Continuous variables were summarized using treatment group means, standard deviations, and ranges. The association between treatment groups and continuous variables was assessed using a 1-way ANOVA.

9.7.4 Efficacy Evaluations

For continuous variables (eg, HAM-D total mean change from baseline and MADRS total mean change from baseline), overall differences among the treatment groups were tested using a 2-way ANOVA model that included treatment, investigator, and treatment-by-investigator terms. The treatment-by-investigator interaction was tested to decide whether the data could be successfully pooled. If the interaction effect was significant at the 0.10 level ($p < 0.10$), the individual investigator results were presented to identify the source of the interactions. Tests of main effects (ie, the treatment effect on various endpoints) were independent of the significance of the interaction term. Additionally, subset analyses were performed using severity of illness and patient sex. Patient illness was labeled as severe if patients scored between 5 and 7 (markedly to severely ill) on the CGI Severity of Illness scale at baseline, whereas the illness of a patient with a baseline score less than 5 was labeled as nonsevere. Categorical data (eg, response and remission) were analyzed by the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.

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

9.7.5 Safety Evaluations

9.7.5.1 Adverse Events

The original terms used by investigators to identify adverse events on the CRFs were translated into Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) terms, which were then grouped according to COSTART body systems and preferred terms. Each adverse event was counted once according to the date of onset. If the adverse event

began prior to the first dose of study medication and did not increase in either severity or frequency after the first dose of study medication, then the adverse event was considered a pretreatment adverse event and was not included in the adverse event frequency tables. If the onset was prior to the first dose of study medication, but increased in severity or frequency after the first dose of study medication, then the event was considered an adverse event and was included in the adverse event frequency tables. This rule was consistent with the TES convention for counting adverse events.

The incidence of TES was summarized as follows: 1) by body system and preferred term; 2) by maximum severity; 3) by patient age; 4) by patient sex; 5) by relationship to study medication; and 6) by seriousness. Drug-related events were those determined by the investigator to be related to the study medication. The frequency of adverse events that resulted in termination of patients from the study medication was also prepared. Corresponding patient data listings were also prepared to support each of the above summaries.

9.7.5.2 Laboratory Tests

Summary statistics (mean, mean change from baseline, median change from baseline, and standard deviation) were calculated for each laboratory test. Differences among treatment groups in the mean change from baseline at each postbaseline evaluation were analyzed using a 1-way ANOVA. Differences between each treatment group and placebo were analyzed using a pairwise t-test.

The number of patients with a clinically significant abnormal laboratory assay value was tabulated, and data from each patient were listed. The criteria used to identify patients with clinically significant abnormal laboratory values were determined using the central laboratory's normal ranges (see Appendix 11).

9.7.5.3 Vital Signs

Summary statistics (mean, mean change from baseline, median change from baseline, and standard deviation) were calculated for systolic and diastolic blood pressure, and pulse rate. Differences among treatment groups in the mean change from baseline at each postbaseline evaluation were analyzed using a 1-way ANOVA. Differences between each active treatment group and placebo were analyzed using a pairwise t-test.

The numbers of patients with a clinically significant abnormal vital sign were tabulated, and data from each patient were listed. Clinically significant values for vital signs were defined as a heart rate less than or equal to 50 beats/minute or greater than or equal to 120 beats/minute, systolic blood pressure less than or equal to 90 mm Hg or greater than or equal to 180 mm Hg, or diastolic blood pressure less than or equal to 50 mm Hg or greater than or equal to 105 mm Hg.

9.7.5.4 Electrocardiograms

ECG intervals were assessed by Premier Research Worldwide, Philadelphia, PA.

Summary statistics (mean, mean change from baseline, median change from baseline, and standard deviation) were calculated for each of the following ECG intervals: PR, QRS, QT, QTc, and heart rate. Differences among treatment groups in the mean change from baseline at each postbaseline evaluation were analyzed using a 1-way ANOVA. Differences between each active treatment group and placebo were analyzed using a pairwise t-test.

A "shift" table was prepared to show the numbers and percentages of patients who had normal and abnormal ECG findings at the end of treatment evaluation compared with the pretreatment assessment. Patients who had abnormal ECG findings were listed.

The frequency of patients that had clinically significant abnormal ECGs was tabulated, and data for individual patients were listed. Table 7 lists the criteria used to identify patients with clinically significant values for ECG findings.

Table 7. Clinically Significant Abnormal ECG Values

Variable	Criteria
Bradycardia	≤ 50 bpm
Tachycardia	≥ 120 bpm
PR Interval	≤ 110 msec
	≥ 210 msec
QRS Interval	≤ 30 msec
	≥ 110 msec
QT Interval	≥ 470 msec
QTc Interval	≥ 450 msec (males)
	≥ 470 msec (females)

Source: Appendix 2

9.7.6 Rules for Estimation of Missing Data

9.7.6.1 Efficacy Data

If an individual component score from either the HAM-D or MADRS assessment was missing at baseline, the total baseline score for the assessment was treated as if it were missing, for both the LOCF and OC analyses.

For missing postbaseline individual component scores in the LOCF analysis, the last observed total score was carried forward to estimate subsequent missing scores. If the final valid assessment was the baseline assessment, no observations were carried forward.

For missing postbaseline individual component scores in the OC analysis, previous scores were not imputed, and so the total score for the patient on a particular visit was set to missing.

9.7.6.2 Safety Data

If the date of onset of an adverse event was missing, the study period on the adverse event CRF and the stop date were used to determine whether the event was treatment emergent.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Amendments to the Protocol

Changes to Protocol 97-CRBX-050 were detailed in 7 amendments. The protocol and protocol amendments are located in Appendix 2. All of the amendments were implemented prior to breaking of the blind on 22 September 1999. This includes amendment number 7, which was implemented prior to breaking the blind, which occurred later the same day (22 September 1999). The protocol amendments, along with the reason(s) for each, are briefly summarized as follows:

Amendment 1 (3 November 1998)

The protocol was amended to add an optional pharmacogenomic component to this study, as discussed in section 9.5.4.

Amendment 2 (18 November 1998)

The protocol was amended to increase the planned total enrollment in the study from 300 patients to 450 patients, based on additional sample size calculations to determine the number of patients required to show statistically significant differences between reboxetine and fluoxetine on improvement in the patients social function, as measured by SASS total scores. The sample size calculations were based on results from the previously conducted reboxetine study 20124/014 [15, 16], which compared the change in total SASS scores in patients treated with reboxetine, fluoxetine, or placebo.

Amendment 3 (3 May 1999)

Secondary objectives were added to the primary study objective. The secondary objectives were assessed using the secondary efficacy measures, which were unaltered from the original protocol. Secondary efficacy measures were expanded to include the HAM-D cluster analysis (HAM-D anxiety/somatization factor, HAM-D cognitive disturbance factor, and HAM-D retardation factor); to specify the individual items of the HAM-D that would be analyzed (items 1, 3, 7, and 8); and to specify the SF-36 scales that will be analyzed (scales for vitality, social function, role-emotional, mental health, physical function, role-physical, pain, and general health). Because the secondary efficacy measures were more clearly described, the analysis plan was amended. An analysis of variance was added to examine the

relationship between individual scales and component summaries. This included addition of a longitudinal analysis of individual scales and component summaries.

Amendment 4 (18 May 1999)

The protocol was amended to define nonevaluable efficacy measurements (final efficacy measurements for the 8-week treatment period that are taken more than 7 days after the date of the last dose of study medication), and to specify that nonevaluable measurements will be excluded from the efficacy analysis. The amendment specified that a patient data listing will be provided for all patients with a nonevaluable efficacy measurement.

Amendment 5 (29 June 1999)

The protocol was amended to specify an integrated analysis plan and minimum important treatment differences for the secondary objectives described in Amendment 3, as requested by the FDA.

Integrated Analysis Plan:

If the primary efficacy objective demonstrated a significant difference between reboxetine and placebo in the change from baseline in the HAM-D total score, then the following secondary objectives would be explored, using an alpha adjustment for multiple endpoint comparisons: 1) to demonstrate that treating outpatients suffering from MDD with reboxetine significantly improved vitality, as measured by the SF-36 vitality scale, compared with treatment with placebo, and 2) to demonstrate that treating outpatients suffering from MDD with reboxetine significantly improved general social function, as measured by SASS, compared with treatment with fluoxetine.

Minimum Important Treatment Differences:

The minimum important treatment difference between reboxetine and placebo in the mean change from baseline in the SF-36 vitality scale is 5 percentage points, after converting the raw scores to percentile scores. The minimum important treatment difference between reboxetine and fluoxetine or between reboxetine and placebo on the SASS is a mean change from baseline of 4 points.

Amendment 6 (19 July 1999)

This amendment prospectively specified an analysis plan for the RSI that was broken down into components containing specific questions for the visual analog scale, frequency of sexual activity, and the dichotomous questions for each sex. This plan included completion of CRFs prior to the beginning of the study that contained the baseline form of the RSI.

Amendment 7 (22 September 1999)

This amendment nullified the analysis plan that was described in amendment 5, and reinstated the plan described in the original protocol in addition to amendments 3 and 6.

9.8.2 Changes in Planned Analyses

For the baseline and demographic characteristics, comparability between treatment groups at baseline was assessed using a 1-way analysis of variance (ANOVA) for continuous variables and a chi-squared test for categorical variables.

ECGs from all patients were read at Premier Research Worldwide by a single cardiologist who measured PR, QRS, and QT intervals, as well as calculated QTc intervals using the Bassett's formula correction. Additionally, the QTc intervals were calculated using the Fridericia's formula correction by Pharmacia & Upjohn using data obtained from the Premier analyses.

Efficacy assessments that were completed more than 7 days following the last dose of study medication were considered unscheduled visits and were not included in the analyses. These efficacy assessments were summarized separately as unscheduled visits following the treatment visits. A list of all patients with unscheduled visits was prepared.

Treatment groups from sites that treated a small number of patients were combined with similar sites (and analyzed as 1 larger-size site) whenever assessing site interactions in the statistical model.

10 RESULTS

Key data displays are included in the text. More detailed, supportive tables are included in section 14; references to these tables are included in the text.

10.1 Study Patients

10.1.1 Disposition of Patients

Four hundred fifty patients were enrolled, randomized, and treated with at least 1 dose of study medication: 150 each with reboxetine, fluoxetine, or placebo. Greater than 30% of the patients in each treatment group discontinued prior to the end of the study. The percentages of patients who completed the 8-week treatment period were comparable between the reboxetine (58.0%) and placebo (60.0%) groups, but lower than in the fluoxetine (68.7%) group. The 2 most commonly reported reasons for patient discontinuation were nonserious adverse events and lost to follow-up. The reasons for patient discontinuation by treatment group are summarized in Table 8.

Table 8. Patient Disposition

	RBX		FLX		PBO	
	n	%	n	%	n	%
Number of Patients:						
Randomized	150	100	150	100	150	100
Intent-to-Treat*	150	100	150	100	150	100
Completed study	87	58.0	103	68.7	90	60.0
Discontinued study	63	42.0	47	31.3	60	40.0
Reason for Discontinuation:						
Lack of efficacy	6	4.0	5	3.3	7	4.7
Improvement	0	0	0	0	0	0
Death of subject	0	0	0	0	0	0
Adverse events						
Serious	0	0	1	0.7	2	1.3
Nonserious	28	18.7	10	6.7	12	8.0
Protocol noncompliance	8	5.3	4	2.7	4	2.7
Ineligible after medication started	0	0	1	0.7	0	0
Subject's personal request	7	4.7	12	8.0	11	7.3
Subject lost to follow-up	11	7.3	14	9.3	22	14.7
Other	3	2.0	0	0	2	1.3

Source: section 14, Table 1.3

* The ITT safety population includes all patients who were randomized and received at least 1 dose of study medication.

Abbreviations:FLX=fluoxetine, PBO=placebo, RBX=reboxetine

None of the patients in the reboxetine group discontinued treatment due to a serious adverse event, but 28 patients (18.7%) in this group discontinued due to 1 or more nonserious adverse events. One patient (0.7%) in the fluoxetine group discontinued due to 1 or more serious adverse events, and 10 patients (6.7%) in this group discontinued due to 1 or more nonserious adverse events. Two patients (1.3%) in the placebo group discontinued due to 1 or more serious adverse events, and 12 patients (8.0%) discontinued due to 1 or more nonserious adverse events. Eleven patients in the reboxetine group (7.3%) were lost to follow-up, as were 14 patients in the fluoxetine group (9.3%), and 22 in the placebo group (14.7%).

A large number of discontinuations due to nonserious adverse events occurred within the first 14 days of the study. This was especially true in the reboxetine- and placebo-treatment groups. Twelve of the 28 reboxetine-treated patients who dropped out at any time during the study due to 1 or more nonserious adverse events did so within the first 14 days. Two of the

10 fluoxetine-treated patients who dropped out at any time during the study due to 1 or more nonserious adverse events did so within the first 14 days, as did 5 of the 12 placebo-treated patients who dropped out at any time during the study due to 1 or more nonserious adverse events. Additional information is available in Appendix 13, Table 1.4.

10.1.2 Protocol Deviations

The concurrent use of psychotropic medications other than temazepam or chloral hydrate was not allowed during the study. As shown in Appendix 14, Table 26.2, a small number of patients used concurrent psychotropic medications during treatment. However, the concurrent use of psychotropic medications (eg, antianxiety medications, antidepressants, St. John's Wort, narcotic agonist analgesics, narcotic analgesic combinations, narcotic antitussives, and nonbarbiturate sedatives and hypnotics) was infrequent and was comparable among the 3 treatment groups.

Patient numbers 1226, 1264, and 1410 had baseline HAM-D scores of 21; however, data from all patients were included in all analyses. These data are listed in Appendix 14, Table 26.1.

At any evaluation, patient urine drug screens that exceeded the normal range for a particular test were considered protocol deviations (listed in Appendix 15, Table 20.3). Forty-nine reports of abnormal urine drug screens were made in 45 patients. The number of reports made in each drug category were as follows: 2 for alcohol, 6 for amphetamines, 2 for barbiturates, 21 for benzodiazepines, 4 for cocaine, 6 for opiates, and 8 for tetrahydrocannabinols.

10.1.3 Data Sets Analyzed

The analyses of demographic and other baseline characteristics were based on the ITT population, which included patients who received at least 1 dose of study medication. Of the 450 patients randomized into the study, all satisfied this criterion (150 per treatment group) and so were included in the ITT analyses (section 14, Table 1.3).

10.1.4 Demographic and Other Baseline Characteristics

10.1.4.1 Demographic Characteristics

Overall, no statistically significant differences were noted among treatment groups in the demographic characteristics (eg, age, sex, and race) collected at baseline. The majority of the patients were female and white. The mean patient age was 40 years (range between 18 and 64 years). Selected demographic characteristics are compared by treatment group in Table 9.

Table 9. Patient Demographics at Screen

Variable	Statistic	RBX N=150	FLX N=150	PBO N=150	P-Value
Age, years	Mean ± SD	39.8±11.4	40.7±10.6	39.8±11.1	0.7030*
	Range	18-64	19-64	18-63	
Sex: n (%)	Male	56 (37.3)	51 (34.0)	60 (40.0)	0.5594†
	Female	94 (62.7)	99 (66.0)	90 (60.0)	
Race: n (%)	White	125 (83.3)	132 (88.0)	115 (76.7)	0.0621†‡
	Black	10 (6.7)	5 (3.3)	18 (12.0)	
	Asian	0	2 (1.3)	1 (0.7)	
	Other	15 (10.0)	11 (7.3)	16 (10.7)	

Source: section 14, Tables 2.1 and 2.2
* 1-way ANOVA
† χ^2 test
‡ χ^2 test may not be valid due to low expected cell counts.
Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, SD=standard deviation

No statistically significant differences were noted among treatment groups in the other continuous (eg, systolic and diastolic blood pressure and pulse) or categorical demographic characteristics (eg, education, occupation group, living situation, or current employment status) collected at the screening visit. The majority of patients lived with family and were employed full-time. Data are available in section 14, Tables 2.1 and 2.2. Likewise, no statistically significant differences were noted among the groups in the proportion of patients with normal or abnormal physical examinations (section 14, Table 2.6) or medical histories (section 14, Table 2.7).

10.1.4.2 Psychiatric History

10.1.4.2.1 Previous History of Depression

No statistically significant differences were noted among treatment groups at screen in the mean age of onset of MDD, in the mean number of previous episodes, or in the mean duration of the previous episode. The mean age at onset of MDD was in the mid- to late twenties. These data are summarized in Table 10.

Table 10. Previous History of Depression

	RBX N = 150	FLX N = 150	PBO N = 150	P-Value*
Age (years) at Onset of Major Depression				0.9079
Number of patients†	149	149	150	
Mean ± SD	26.8 ± 13.1	26.9 ± 12.2	27.4 ± 12.4	
Range	3 – 63	6 – 56	0 – 63	
Number of Previous Episodes				0.3016
Number of patients†	144	143	146	
Mean ± SD	3.0 ± 5.3	4.7 ± 13.1	3.7 ± 8.3	
Range	0 – 50	0 – 99	0 – 75	
Approximate Duration of Last Episode (weeks)				0.4635
Number of patients†	119	113	115	
Mean ± SD	64.9 ± 79.9	82.9 ± 153.9	81.9 ± 130.9	
Range	0 – 468	0 – 1196	0 – 728	

Source: section 14, Table 2.4
* P-values were based on a 1-way ANOVA with treatment as the main effect.
† Number of patients for whom data were available.
Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, SD=standard deviation

10.1.4.2.2 Characteristics of the Present Depressive Episode

No statistically significant differences were noted among treatment groups at screen in the approximate duration of the present episode or in the characterization of the present episode; however, statistically significant differences were observed for the absence or presence of a precipitating stress (highlighted in Table 11). Similar percentages of patients in the reboxetine (44.0%) and fluoxetine (44.7%) groups had a probable precipitating stress associated with their present episode, whereas fewer patients (27.3%) in the placebo group had a probable precipitating stress. Table 11 summarizes the characteristics of the present depressive episode.

Table 11. Characteristics of the Present Depressive Episode

	RBX N=150	FLX N=150	PBO N=150	P-Value*
Approximate Duration of Present Episode (weeks)				0.9272
Mean ± SD	112.2 ± 166.8	114.3 ± 196.3	120.4 ± 200.8	
Range	3 – 1040	1 – 1820	1 – 1508	
Present Episode is Best Characterized as:				0.1342†
Exacerbation of Chronic Condition	22 (14.7%)	13 (8.7%)	22 (14.7%)	
Recurrence of Similar Previous Conditions	96 (64.0%)	102 (68.0%)	82 (54.7%)	
Significantly Different From Any Previous Conditions	2 (1.3%)	5 (3.3%)	3 (2.0%)	
First Occurrence, No Previous Psychiatric Diagnosis	30 (20.0%)	30 (20.0%)	43 (28.7%)	
Precipitating Stress Was:				**0.0051**
Absent	48 (32.0%)	40 (26.7%)	65 (43.3%)	
Probably Present	66 (44.0%)	67 (44.7%)	41 (27.3%)	
Definitely Present	36 (24.0%)	43 (28.7%)	44 (29.3%)	

Source: section 14, Tables 2.4 and 2.5
***** P-values were based on a 1-way ANOVA with treatment as the main effect.
† χ^2 test may not be valid due to low expected cell counts.
Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, SD=standard deviation

10.1.4.2.3 Severity of Depression at Baseline

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

Table 12. Severity of Depression at Baseline

	RBX N = 150	FLX N = 150	PBO N = 150	P-Value*
HAM-D Total Score				0.5331
Number of patients†	150	150	150	
Mean ± SD	25.6 ±3.4	26.0±3.3	25.5±3.3	
Range	21 – 35	22 – 36	22 – 37	
CGI: Severity of Illness				0.9183
Number of patients†	150	150	150	
Mean ± SD	4.4±0.5	4.4±0.5	4.4±0.6	
Range	4 – 6	4 – 6	3 – 7	
MADRS Total Score				0.8445
Number of patients†	150	148	150	
Mean ± SD	29.6±5.2	29.9±4.9	29.8±5.1	
Range	12 – 42	16 – 41	15 - 45	
SASS Total Score				0.5716
Number of patients†	149	150	149	
Mean ± SD	29.6±8.2	30.4±7.1	30.4±7.8	
Range	9 -47	11 - 53	11 - 50	

Source: section 14, Table 2.3

* P-values were based on a 1-way ANOVA with treatment as the main effect.

† Number of patients for whom data were available.

Abbreviations: CGI=Clinical Global Impression, FLX=fluoxetine , HAM-D=Hamilton Rating Scale for Depression, MADRS=Montgomery-Asberg Depression Rating Scale, RBX=reboxetine, SD=standard deviation

10.1.4.3 Sexual History

No statistically significant differences were noted among treatment groups in the sexual history recorded at baseline. These data are shown in Table 13.

Table 13. Sexual History at Baseline

Variable	Attribute	Treatment Group						P-value*
		RBX N=150		FLX N=150		PBO N=150		
		n	%	n	%	n	%	
Have you ever experienced sexual dysfunction while taking any medication?	No	125	83.3	121	81.2	123	82.6	0.8880
	Yes	25	16.7	28	18.8	26	17.4	
	NR			1		1		
Do you and/or your sexual partner(s) presently use birth control?	No	37	24.8	33	22.4	33	22.3	0.8058
	Yes	61	40.9	70	47.6	64	43.2	
	NA	51	34.2	44	29.9	51	34.5	
	NR	1		3		2		
Have you ever had any surgical or medical procedure performed on your reproductive organs?	No	105	70.0	107	72.3	112	74.7	0.6650
	Yes	45	30.0	41	27.7	38	25.3	
	NR			2				
Have you ever had a nonroutine investigation of your reproductive organs?	No	139	92.7	139	93.9	136	91.3	0.6839
	Yes	11	7.3	9	6.1	13	8.7	
	NR			2		1		
Have you ever been evaluated for a sexual dysfunction?	No	145	96.7	145	97.3	149	99.3	0.2640†
	Yes	5	3.3	4	2.7	1	0.7	
	NR			1				
Have you ever received treatment for a sexual dysfunction?	No	147	98.0	145	98.6	148	98.7	0.8710†
	Yes	3	2.0	2	1.4	2	1.3	
	NR					3		

Source: section 14, Table 2.11

* P-values were based on χ^2 test (excluding not reported).

† χ^2 test may not be valid due to low expected cell counts.

Abbreviations: FLX=fluoxetine, NA=not applicable, NR=not reported, PBO=placebo, RBX=reboxetine

10.1.5 Concomitant Medications

10.1.5.1 Prior to the Study

At the screening evaluation, similar percentages of patients in each treatment group were taking at least 1 medication: 63.3% (95/150) in the reboxetine group, 68.0% (102/150) in the fluoxetine group, and 60.7% (91/150) in the placebo group. Concomitant medications taken most frequently (at least 5% in any treatment group) at pretreatment included acetaminophen, systemic antihistamines, estrogens, multivitamins and vitamin combinations, nonsteroidal anti-inflammatory agents, ibuprofen, oral contraceptives, vitamin C, and aspirin. A detailed summary of concomitant medications is in section 14, Table 2.9.

10.1.5.2 During the Treatment Period

Noninvestigational medications were taken concomitantly with the study medications by similar percentages of patients in each treatment group: 90.0% (135/150) in the reboxetine group, 86.7% (130/150) in the fluoxetine group, and 83.3% (125/150) in the placebo group. Concomitant medications taken most frequently (at least 5% in any treatment group) during the study period included acetaminophen, systemic antihistamines, antacids, antidepressants, antitussive combinations, calcium, decongestant combinations, estrogens, histamine H2 antagonists, multivitamins, nasal decongestants, nonbarbiturate sedatives and hypnotics, nonnarcotic analgesic combinations, nonsteroidal anti-inflammatory agents, oral contraceptives, penicillins, aspirin, vitamin C, and vitamin E. A detailed summary of concomitant medications is in section 14, Table 2.10.

The concurrent use of psychotropic medications other than temazepam or chloral hydrate was not allowed during the study. A small number of patients used concurrent psychotropic medications during treatment. However, the concurrent use of psychotropic medications (eg, antianxiety medications, antidepressants, St. John's Wort, narcotic agonist analgesics, narcotic analgesic combinations, narcotic antitussives, and nonbarbiturate sedatives and hypnotics) was infrequent and was comparable across the 3 treatment groups. A list of restricted concomitant medications that were used during the study is available in Appendix 13, Table 26.2.

10.2 Dosage Information

10.2.1 Extent of Exposure

The mean daily dose by visit (ie, the average dose that was taken over the week preceding the specified visit) is summarized in Table 14 for the reboxetine and fluoxetine groups.

Table 14. Mean Daily Dose by Visit

Study Day	Reboxetine		Fluoxetine	
	Number of Patients†	Mean Dose* (mg/day)	Number of Patients†	Mean Dose* (mg/day)
7	142	8.0	137	19.7
14	126	7.9	130	19.8
21	114	8.1	123	20.0
28	106	7.9	125	19.3
35	104	9.3	114	33.2
42	90	9.2	105	35.0
49	93	9.2	103	34.2
56	89	9.5	101	36.1

Source: section 14, Table 2.8

* Mean daily dose was based on the average daily dose during the previous week for all patients who took the study medication during that week.

† Number of patients who completed the specified visit.

During weeks 1, 2, 3, and 4, reboxetine-treated patients took mean doses of 8.0, 7.9, 8.1, and 7.9 mg/day, respectively, while during the same period, the fluoxetine-treated patients took mean doses of 19.7, 19.8, 20.0, and 19.3 mg/day, respectively. The mean daily dose taken by reboxetine-treated patients was similar to the expected daily dose of 8 mg, and the mean daily dose for fluoxetine-treated patients was similar to the expected daily dose of 20 mg.

During weeks 5, 6, 7, and 8, reboxetine-treated patients took mean doses of 9.3, 9.2, 9.2, and 9.5 mg/day, respectively, while during the same period, the fluoxetine-treated patients took mean doses of 33.2, 35.0, 34.2, and 36.1 mg/day, respectively. These doses were within the 8 to 10 mg/day range specified for reboxetine and the 20 to 40 mg/day range specified for fluoxetine. These data also implied that the doses of approximately two-thirds of the patients remaining in the study were escalated in the final 4 weeks of the study.

10.2.2 Measurements of Treatment Compliance

Patient compliance was monitored through the use of the subject-dosing diary (see Appendix 3) and the return of the study medication blister cards each week. During the first 4 weeks, the mean daily doses of reboxetine and fluoxetine were similar to the expected doses. Data from the second 4 weeks implied that approximately two-thirds of the patients remaining in the study were administered the higher dose of study medication that was available.

10.3 Efficacy Results

10.3.1 Primary Efficacy Endpoint: Mean Change from Baseline in the HAM-D Total Score

No statistically significant differences were noted among treatment groups in the mean change from baseline in the HAM-D total score in either the LOCF or OC analysis at any visit. The mean total score decreased, indicating patient improvement, at each weekly evaluation in both the LOCF and OC analyses for all of the treatment groups. Table 15 summarizes the mean change from baseline in the HAM-D total score at each visit during the treatment period for both the LOCF and OC analyses.

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

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	142	-4.2	144	-6.6	144	-8.0	144	-9.3	144	-10.2	144	-10.4	144	-10.8	144	-10.8
		FLX	138	-4.5	144	-6.7	144	-9.7	144	-9.9	144	-11.4	144	-11.6	144	-12.6	144	-13.1
		PBO	139	-4.0	142	-7.0	143	-8.8	143	-9.3	143	-10.3	143	-10.5	143	-10.7	143	-11.1
	P-Value‡		0.9578		0.5896		0.1218		0.6352		0.4271		0.3815		0.1292		0.0707	
Observed Cases	Mean Change From Baseline	RBX	142	-4.2	128	-7.1	114	-8.9	107	-10.9	105	-12.5	89	-12.9	94	-13.2	90	-13.3
		FLX	138	-4.5	131	-6.9	124	-9.8	124	-10.6	115	-12.5	104	-13.1	102	-15.1	101	-15.4
		PBO	139	-4.0	125	-7.1	123	-8.8	116	-9.8	107	-11.4	99	-11.8	89	-12.5	89	-14.1
	P-Value‡		0.9578		0.6576		0.7490		0.5795		0.3574		0.3615		0.2261		0.4986	

Source: section 14, Tables 3.1A, 3.1B, and 3.2

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1).

† Mean change from baseline value.

‡ P-value calculated using a 2-way ANOVA.

Abbreviations: FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX=reboxetine

10.3.2 Secondary Efficacy Variables

10.3.2.1 HAM-D Secondary Variables

10.3.2.1.1 HAM-D Response Status

No statistically significant differences were noted among treatment groups in the frequency of patient response (defined as the proportion of patients who experienced at least 50% decrease from baseline in the HAM-D total score) in either the LOCF or OC analysis at any visit. The number of patients in each treatment group considered responders increased with each weekly evaluation for patients in all of the treatment groups. Table 16 summarizes the HAM-D response status at each visit during the treatment period for both the LOCF and OC analyses.

10.3.2.1.2 HAM-D Remission Status

No statistically significant differences were noted among treatment groups in the frequency of patients in remission (defined as the proportion of patients with a postbaseline HAM-D total score less than or equal to 10) in either the LOCF or OC analysis at any visit. The number of patients in each treatment group who were considered in remission increased with each weekly evaluation for patients in all of the treatment groups. Table 17 summarizes the HAM-D remission status at each visit during the treatment period for both the LOCF and OC analyses.

10.3.2.2 HAM-D Clusters and Individual Items

10.3.2.2.1 HAM-D Anxiety/Somatization Factor

On days 49 and 56, a statistically significant difference was observed among treatment groups in the decrease from baseline in the HAM-D anxiety/somatization factor scores (items 10 through 13, 15, and 17) for the LOCF analysis. The mean changes from baseline for the LOCF analysis on day 49 were – 2.5 for the reboxetine group, – 3.3 for the fluoxetine group, and – 2.7 for the placebo group, whereas on day 56, the mean changes from baseline were – 2.6 for the reboxetine group, – 3.4 for the fluoxetine group, and – 2.8 for the placebo group. No statistically significant differences were noted among treatment groups in the mean decrease from baseline in the HAM-D anxiety/somatization factor score in the OC analysis at any visit. No statistically significant difference between reboxetine and placebo (or between fluoxetine and placebo) was noted at any evaluation in either the LOCF or OC analysis; the significance apparently was because of the difference between reboxetine and fluoxetine.

Table 18, with statistically significant differences highlighted, summarizes the mean change from baseline in the HAM-D anxiety/somatization factor score at each visit during the treatment period for both the LOCF and OC analyses.

10.3.2.2.2 HAM-D Cognitive Disturbance Factor

No statistically significant differences were noted among treatment groups in the mean decrease from baseline in the HAM-D cognitive disturbance factor score (items 2, 3, 9, and 19 through 21) in either the LOCF or OC analysis at any visit. Table 19 summarizes the mean change from baseline in the HAM-D cognitive disturbance factor score at each visit during the treatment period for both the LOCF and OC analyses.

Table 16. HAM-D Response Status

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
LOCF	Responder†	RBX	11	7.7	26	18.1	38	26.4	51	35.4	56	38.9	59	41.0	62	43.1	60	41.7
		FLX	8	5.8	26	18.1	50	34.7	53	36.8	63	43.8	67	46.5	75	52.1	79	54.9
		PBO	8	5.8	23	16.2	41	28.7	46	32.2	59	41.3	58	40.6	61	42.7	63	44.1
	P-Value‡		0.7595		0.9272		0.3418		0.7729		0.7378		0.6492		0.2582		0.0718	
Observed Cases	Responder†	RBX	11	7.7	25	19.5	34	29.8	47	43.9	52	49.5	47	52.8	52	55.3	47	52.2
		FLX	8	5.8	26	19.8	43	34.7	51	41.1	57	49.6	55	52.9	67	65.7	68	67.3
		PBO	8	5.8	21	16.8	36	29.3	39	33.6	50	46.7	45	45.5	44	49.4	50	56.2
	P-Value‡		0.7595		0.8923		0.7336		0.1450		0.8510		0.4932		0.0973		0.2580	

Source: section 14, Tables 3.7A, 3.7B, and 3.8

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1).

† Responders are patients who experienced at least a 50% decrease from baseline in the HAM-D total score.

‡ P-value calculated using the CMH test.

Abbreviations: CMH= Cochran-Mantel-Haenszel test ,FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 17. HAM-D Remission Status

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
LOCF	Remission†	RBX	5	3.5	18	12.5	23	16.0	38	26.4	43	29.9	48	33.3	51	35.4	48	33.3
		FLX	5	3.6	17	11.8	39	27.1	36	25.0	51	35.4	48	33.3	60	41.7	66	45.8
		PBO	5	3.6	16	11.3	30	21.0	33	23.1	42	29.4	50	35.0	49	34.3	54	37.8
	P-Value‡		0.9915		0.9642		0.0796		0.8006		0.5126		0.9032		0.4498		0.0940	
Observed Cases	Remission†	RBX	5	3.5	17	13.3	21	18.4	36	33.6	40	38.1	38	42.7	45	47.9	38	42.2
		FLX	5	3.6	17	13.0	34	27.4	34	27.4	47	40.9	39	37.5	55	53.9	57	56.4
		PBO	5	3.6	15	12.0	27	22.0	30	25.9	35	32.7	40	40.4	36	40.4	44	49.4
	P-Value‡		0.9915		0.9869		0.3411		0.2446		0.4478		0.6766		0.1647		0.3177	

Source: section 14, Tables 3.12A, 3.12B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1).

† Remission is defined as a HAM-D total score of ≤10.

‡ P-value calculated using the CMH test.

Abbreviations: CMH= Cochran-Mantel-Haenszel test, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 18. Mean Change From Baseline in the HAM-D Anxiety/Somatization Factor Score*

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	142	-1.1	144	-1.6	144	-1.8	144	-2.3	144	-2.4	144	-2.4	144	-2.5	144	-2.6
	Change	FLX	139	-1.1	144	-1.8	144	-2.5	144	-2.6	144	-3.0	144	-3.0	143	-3.3	144	-3.4
	From Baseline	PBO	139	-1.1	142	-1.7	143	-2.2	143	-2.4	143	-2.6	143	-2.7	144	-2.7	143	-2.8
	P-Value‡		0.9213		0.5337		0.0730		0.5159		0.2047		0.0892		**0.0357**		**0.0448**	
Observed Cases	Mean	RBX	142	-1.1	128	-1.7	114	-2.1	107	-3.0	105	-3.2	89	-3.1	94	-3.2	90	-3.4
	Change	FLX	139	-1.1	131	-1.9	124	-2.5	125	-2.9	116	-3.4	105	-3.5	104	-4.0	101	-4.1
	From Baseline	PBO	139	-1.1	125	-1.8	124	-2.2	116	-2.6	107	-2.9	99	-3.0	90	-3.1	89	-3.6
	P-Value‡		0.9213		0.7115		0.6329		0.5857		0.5518		0.3494		0.1770		0.4091	

Source: section 14, Tables 3.16A and 3.16B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1).
† Mean change from baseline value.
‡ P-value based on 2-way ANOVA
Abbreviations: ANOVA=analysis of variance, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 19. Mean Change From Baseline in the HAM-D Cognitive Disturbance Factor Score

Type of Analysis	Statistic	Treat-met Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	142	-1.4	144	-1.9	144	-2.1	144	-2.3	144	-2.4	144	-2.6	144	-2.7	144	-2.6
	Change	FLX	139	-1.2	144	-1.8	144	-2.4	144	-2.4	144	-2.7	144	-2.9	144	-3.0	144	-3.1
	From Baseline	PBO	139	-1.0	142	-1.8	143	-2.2	143	-2.1	143	-2.3	143	-2.4	143	-2.4	143	-2.5
	P-Value‡		0.6068		0.8245		0.6407		0.9016		0.6011		0.2406		0.2646		0.1901	
Observed Cases	Mean	RBX	142	-1.4	128	-2.0	114	-2.3	107	-2.5	105	-2.8	89	-3.1	94	-3.1	90	-3.1
	Change	FLX	139	-1.2	131	-1.8	124	-2.5	124	-2.5	116	-2.9	105	-3.2	104	-3.4	101	-3.4
	From Baseline	PBO	139	-1.0	125	-1.8	124	-2.2	116	-2.2	109	-2.6	99	-2.7	90	-2.8	89	-3.2
	P-Value‡		0.6068		0.5056		0.9236		0.7282		0.4000		0.1974		0.4599		0.9860	

Source: section 14, Tables 3.17A, 3.17B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1) .

† Mean change from baseline value

‡ P-value based on 2-way ANOVA.

Abbreviations: ANOVA=analysis of variance, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

10.3.2.2.3 HAM-D Retardation Factor

On day 42, statistically significant differences were noted among treatment groups (p=0.042) in the OC analysis of the mean decrease from baseline in the HAM-D retardation factor score (items 1, 7, 8, and 14). Between reboxetine and placebo (p=0.024) and between fluoxetine and placebo (p=0.039), statistically significant differences were also noted. No other statistically significant differences among treatment groups were noted at any visit in either the LOCF or OC analysis. Table 20 summarizes the mean change from baseline in the HAM-D retardation factor score at each visit during the treatment period for both the LOCF and OC analyses; statistically significant differences are highlighted.

10.3.2.2.4 HAM-D Item 1 (Depressed Mood)

On days 7, 42, 49, and 56, statistically significant differences were noted among treatment groups in the mean decreases from baseline in the HAM-D depressed mood item (item 1) in both the LOCF and OC analyses (section 14, Tables 3.15A and 3.15B, respectively). On each day, the statistical significance resulted from fluoxetine treatment being superior to placebo, and not from reboxetine treatment being superior to placebo. At the end of the treatment period (day 56), the mean decrease from baseline in the HAM-D depressed mood item was – 1.3 in the reboxetine group, – 1.6 in the fluoxetine group, and – 1.2 in the placebo group based on the LOCF analysis. The mean decrease from baseline in the HAM-D depressed mood item was – 1.5 in the reboxetine group, – 1.9 in the fluoxetine group, and – 1.6 in the placebo group based on the OC analysis. Table 21 summarizes the mean change from baseline in the HAM-D depressed mood item (item 1) at each visit during the treatment period for both the LOCF and OC analyses; statistically significant differences are highlighted.

10.3.2.2.5 HAM-D Item 3 (Suicide)

On days 21 and 49, statistically significant differences were noted among treatment groups in the mean decreases from baseline in the HAM-D suicide item (item 3) in the LOCF analysis (section 14, Table 3.22A). On day 21, treatment with both reboxetine and fluoxetine was inferior to placebo. On day 49, the statistical significance resulted from fluoxetine treatment being superior to placebo, and not from reboxetine treatment being superior to placebo. At the end of the treatment period (day 56), the mean decrease from baseline in the HAM-D suicide item was – 0.4 in the reboxetine group, – 0.7 in the fluoxetine group, and – 0.4 in the placebo group based on the LOCF analysis. No statistically significant differences were noted among treatment groups on any treatment day for the OC analysis. At the end of the treatment period (day 56), the mean decrease from baseline in the HAM-D suicide item was – 0.5 in the reboxetine group, – 0.6 in the fluoxetine group, and – 0.6 in the placebo group based on the OC analysis. Table 22 summarizes the mean change from baseline in the HAM-D suicide item (item 3) at each visit during the treatment period for both the LOCF and OC analyses; statistically significant differences are highlighted.

10.3.2.2.6 HAM-D Item 7 (Work and Activities)

No statistically significant differences were noted among treatment groups in the mean decrease from baseline in the HAM-D work and activities item (item 7) in the LOCF analysis (section 14, Table 3.23A) at any visit. Statistically significant differences were noted among treatment groups in the OC analysis on days 28, 35, and 42. On these days, statistically significant differences were noted between the reboxetine group and the placebo group, but not between the fluoxetine group and the placebo group. Table 23 summarizes the change from baseline in the HAM-D work and activities item at each visit during the treatment period for both the LOCF and OC analyses; statistically significant differences are highlighted.

10.3.2.2.7 HAM-D Item 8 (Retardation)

No statistically significant differences were noted among treatment groups in the mean decreases from baseline in the HAM-D retardation item (item 8) in the LOCF analysis (section 14, Table 3.23A) at any visit. Statistically significant differences were noted among treatment groups in the OC analysis on days 35 and 49. On day 35, a statistically significant difference was noted between both the reboxetine and placebo treatment groups (p=0.021) and the fluoxetine and placebo treatment groups (p=0.047). On day 49, a statistically significant difference was noted among treatment groups; however, the major contribution to this difference was from the difference between fluoxetine and placebo (p=0.015) rather than between reboxetine and placebo (p=0.283). Table 24 summarizes the change from baseline in the HAM-D retardation item at each visit during the treatment period for both the LOCF and OC analyses; statistically significant differences are highlighted.

10.3.2.3 HAM-D Analysis of Covariance

10.3.2.3.1 HAM-D Analysis of Covariance Adjusting for Gender

No statistically significant differences were noted among treatment groups in the mean change from baseline in the HAM-D total score in either the LOCF or OC analysis at any visit after correcting for differential effects based on gender. Detailed summaries of the analysis of covariance adjusting for gender are in section 14, Tables 3.20A and 3.20B.

10.3.2.3.2 HAM-D Analysis of Covariance Adjusting for Baseline Severity

No statistically significant differences were noted among treatment groups in the mean change from baseline in the HAM-D total score in either the LOCF or OC analysis at any visit after correcting for differential effects based on severity. Detailed summaries of the analysis of covariance adjusting for severity are in section 14, Tables 3.21A and 3.21B.

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

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	142	-1.4	144	-2.1	144	-2.7	144	-2.9	144	-3.3	144	-3.4	144	-3.6	144	-3.5
	Change	FLX	139	-1.4	144	-1.9	144	-2.7	144	-3.0	144	-3.4	144	-3.4	144	-3.8	144	-4.0
	From Baseline	PBO	139	-1.0	142	-1.8	143	-2.4	143	-2.7	143	-3.0	143	-3.0	143	-3.1	143	-3.3
	P-Value‡		0.0836		0.5235		0.3581		0.6068		0.5127		0.3680		0.2346		0.1080	
Observed Cases	Mean	RBX	142	-1.4	128	-2.3	114	-3.0	107	-3.4	105	-4.0	89	-4.3	94	-4.4	90	-4.4
	Change	FLX	139	-1.4	131	-1.9	124	-2.7	125	-3.2	116	-3.7	105	-4.0	104	-4.7	101	-4.9
	From Baseline	PBO	139	-1.0	125	-1.8	124	-2.3	116	-2.7	108	-3.3	99	-3.2	89	-3.7	89	-4.1
	P-Value‡		0.0836		0.4766		0.2873		0.1243		0.0961		**0.0418**		0.1508		0.3310	

Source: section 14, Tables 3.18A, 3.18B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1).

† Mean change from baseline value.

‡ P-value based on 2-way ANOVA.

Abbreviations: ANOVA=analysis of variance, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 21. Mean Change From Baseline in HAM-D Depressed Mood (Item 1) Score

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	142	-0.5	144	-0.8	144	-1.0	144	-1.0	144	-1.2	144	-1.2	144	-1.2	144	-1.3
	Change	FLX	139	-0.6	144	-0.9	144	-1.1	144	-1.2	144	-1.4	144	-1.4	144	-1.6	144	-1.6
	From Baseline	PBO	139	-0.4	142	-0.7	143	-0.9	143	-1.0	143	-1.1	143	-1.1	143	-1.1	143	-1.2
	P-Value‡		**0.0280**		0.2324		0.0888		0.2939		0.0852		**0.0283**		**0.0143**		**0.0120**	
Observed Cases	Mean	RBX	142	-0.5	128	-0.9	114	-1.1	107	-1.2	105	-1.4	89	-1.4	94	-1.5	90	-1.5
	Change	FLX	139	-0.6	131	-0.9	124	-1.2	125	-1.3	116	-1.5	105	-1.6	104	-1.9	101	-1.9
	From Baseline	PBO	139	-0.4	125	-0.7	124	-0.9	116	-1.1	109	-1.2	99	-1.2	90	-1.4	89	-1.6
	P-Value‡		**0.0280**		0.4537		0.2234		0.3474		0.0855		**0.0073**		**0.0311**		0.2001	

Source: section 14, Tables 3.15A, 3.15B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Tables 3.15 A and 3.1.1).

† P-value based on 2-way ANOVA.

Abbreviations: ANOVA=analysis of variance, FLX= fluoxetine, LOCF= last observation carried forward, PBO=placebo, RBX= reboxetine

Table 22. Mean Change From Baseline in HAM-D Suicide (Item 3) Score

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	142	-0.2	144	-0.3	144	-0.4	144	-0.4	144	-0.4	144	-0.4	144	-0.4	144	-0.4
	Change	FLX	139	-0.3	144	-0.4	144	-0.4	144	-0.4	144	-0.6	144	-0.6	144	-0.7	144	-0.7
	From Baseline	PBO	139	-0.3	142	-0.4	143	-0.6	143	-0.6	143	-0.4	143	-0.4	143	-0.3	143	-0.4
	P-Value‡		0.8219		0.7404		**0.0344**		0.1513		0.1708		0.0877		**0.0241**		0.0803	
Observed Cases	Mean	RBX	142	-0.2	128	-0.3	114	-0.3	107	-0.3	105	-0.5	89	-0.6	94	-0.5	90	-0.5
	Change	FLX	139	-0.3	131	-0.4	124	-0.6	125	-0.5	116	-0.6	105	-0.6	104	-0.7	101	-0.6
	From Baseline	PBO	139	-0.3	125	-0/4	124	-0.4	116	-0.4	109	-0.5	99	-0.5	90	-0.4	89	-0.6
	P-Value‡		0.8219		0.7109		0.0532		0.1904		0.3958		0.5510		0.0729		0.9008	

Source: section 14, Tables 3.22A, 3.22B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Tables 3.1.1).

† P-value based on 2-way ANOVA.

Abbreviations: ANOVA=analysis of variance, FLX= fluoxetine, LOCF= last observation carried forward, PBO=placebo, RBX= reboxetine

Table 23. Mean Change From Baseline in HAM-D Work and Activities (Item 7) Score

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	142	-0.5	144	-0.8	144	-1.0	144	-1.1	144	-1.2	144	-1.3	144	-1.3	144	-1.3
	Change	FLX	139	-0.4	144	-0.6	144	-0.9	144	-1.0	144	-1.2	144	-1.2	144	-1.3	144	-1.5
	From Baseline	PBO	139	-0.3	142	-0.5	143	-0.7	143	-0.8	143	-1.0	143	-1.0	143	-1.3	143	-1.1
	P-Value‡		0.0677		0.1484		0.3548		0.2289		0.2198		0.0741		0.3678		0.0584	
Observed Cases	Mean	RBX	142	-0.5	128	-0.8	114	-1.1	107	-1.3	105	-1.5	89	-1.6	94	-1.7	90	-1.6
	Change	FLX	139	-0.4	131	-0.6	124	-0.9	125	-1.1	116	-1.3	105	-1.4	104	-1.6	101	-1.7
	From Baseline	PBO	139	-0.3	125	-0.5	124	-0.8	116	-0.8	109	-1.1	99	-1.0	90	-1.3	89	-1.5
	P-Value‡		0.0677		0.0938		0.2607		**0.0053**		**0.0379**		**0.0121**		0.2642		0.2517	

Source: section 14, Tables 3.23A, 3.23B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Tables 3.1.1).

† P-value based on 2-way ANOVA.

Abbreviations: ANOVA=analysis of variance, FLX= fluoxetine, LOCF= last observation carried forward, PBO=placebo, RBX= reboxetine

Table 24. Mean Change From Baseline in HAM-D Retardation (Item 8) Score

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	142	-0.3	144	-0.4	144	-0.5	144	-0.5	144	-0.6	144	-0.6	144	-0.5	144	-0.6
	Change	FLX	139	-0.1	144	-0.3	144	-0.5	144	-0.5	144	-0.6	144	-0.6	144	-0.6	144	-0.6
	From Baseline	PBO	139	-0.1	142	-0.3	143	-0.4	143	-0.4	143	-0.5	143	-0.5	143	-0.5	143	-0.5
	P-Value‡		0.1605		0.7537		0.1861		0.3593		0.1836		0.4623		0.1956		0.1686	
Observed Cases	Mean	RBX	142	-0.3	128	-0.4	114	-0.6	107	-0.6	105	-0.7	89	-0.7	94	-0.6	90	-0.8
	Change	FLX	139	-0.1	131	-0.3	124	-0.5	125	-0.5	116	-0.6	105	-0.7	104	-0.8	101	-0.9
	From Baseline	PBO	139	-0.1	125	-0.3	124	-0.4	116	-0.4	109	-0.4	99	-0.4	90	-0.5	89	-0.6
	P-Value‡		0.1605		0.5120		0.0544		0.1443		**0.0437**		0.1017		**0.0498**		0.0683	

Source: section 14, Tables 3.24A, 3.24B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1).

† P-value based on 2-way ANOVA.

Abbreviations: ANOVA=analysis of variance, FLX= fluoxetine, LOCF= last observation carried forward, PBO=placebo, RBX= reboxetine

10.3.2.4 Montgomery-Asberg Depression Rating Total Scale

No statistically significant differences were noted among treatment groups in the mean decrease from baseline in the MADRS total score in either the LOCF or OC analysis at any visit. The MADRS total score continued to decrease with elapsed time, indicating improvement in all of the treatment groups. Table 25 summarizes the mean change from baseline in the MADRS score at each visit during the treatment period for both the LOCF and OC analyses.

10.3.2.5 Clinical Global Impression

10.3.2.5.1 Global Improvement

No statistically significant differences were noted among treatment groups for the number of patients who were responders, which was defined as having CGI Global Improvement score of 2 or less (very much improved or much improved) on any visit for the LOCF analysis. Table 26 summarizes the CGI Global Improvement response status at each visit during the treatment period for both the LOCF and OC analyses; statistically significant differences are highlighted.

10.3.2.5.2 Severity of Illness

Regardless of treatment group, the severity of illness score decreased in the postbaseline visits, indicating patient improvement; however, no statistically significant differences were noted among treatment groups in the mean CGI Severity of Illness score at any visit in either the LOCF or OC analysis. Table 27 summarizes the mean change from baseline for the CGI Severity of Illness score at each visit during the treatment period for both the LOCF and OC analyses.

10.3.2.5.3 Efficacy Index

No statistically significant differences were noted among treatment groups in the mean CGI Efficacy Index scores (in which the investigator evaluated the therapeutic effect of the study medication in relation to the severity of the adverse events at each postbaseline study visit) in either the LOCF or OC analysis at any visit. Table 28 summarizes the mean CGI Efficacy Index score at each visit during the treatment period for both the LOCF and OC analyses.

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

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	141	-3.0	144	-6.2	144	-8.0	144	-9.1	144	-10.7	144	-10.7	144	-11.3	144	-11.6
	Change	FLX	137	-4.3	141	-6.4	141	-10.0	141	-9.9	141	-12.3	141	-13.1	141	-13.6	141	-14.4
	From Baseline	PBO	137	-4.5	142	-6.7	143	-9.2	143	-9.7	143	-11.1	143	-10.9	143	-11.3	143	-11.5
	P-Value‡		0.1443		0.9251		0.1350		0.7574		0.4037		0.0826		0.1781		0.0793	
Observed Cases	Mean	RBX	141	-3.0	128	-6.8	114	-9.2	107	-10.8	105	-13.5	89	-14.2	94	-14.4	90	-14.9
	Change	FLX	137	-4.3	129	-6.4	120	-10.0	122	-10.6	115	-13.4	104	-14.9	103	-16.3	99	-17.1
	From Baseline	PBO	137	-4.5	125	-6.8	124	-9.4	116	-9.9	109	-12.4	99	-12.2	90	-13.6	89	-15.2
	P-Value‡		0.1443		0.8741		0.6398		0.6404		0.4367		0.0932		0.3501		0.6648	

Source: section 14, Tables 3.5A, 3.5B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.5B).

† Mean change from baseline value

‡ P-value based on 2-way ANOVA.

Abbreviations: ANOVA=analysis of variance, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 26. CGI Global Improvement Response Status

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
LOCF	Responder†	RBX	11	7.7	26	18.1	52	36.1	58	40.3	63	43.8	63	43.8	65	45.1	73	50.7
		FLX	10	7.2	19	13.2	46	31.9	53	36.8	65	45.1	71	49.3	76	52.8	75	52.1
		PBO	8	5.7	30	21.0	41	28.7	50	35.0	54	37.8	62	43.4	65	45.5	70	49.0
	P-Value‡		0.7404		0.1972		0.4119		0.6062		0.4291		0.6292		0.3867		0.8604	
Observed Cases	Responder†	RBX	11	7.7	25	19.5	47	41.6	51	47.7	59	56.2	50	56.2	54	57.4	59	65.6
		FLX	10	7.2	19	14.5	42	33.6	51	40.8	60	51.7	63	59.4	71	68.3	66	65.3
		PBO	8	5.7	27	21.6	34	27.4	43	37.1	44	40.7	46	47.4	46	51.7	54	60.7
	P-Value‡		0.7404		0.2940		0.0691		0.1404		**0.0490**		0.1643		0.0703		0.6293	

Source: section 14, Tables 3.6A, 3.6B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1).

† Responders are patients who were rated as much improved or very much improved on the CGI Global Improvement scale.

‡ P-value calculated using the CMH test.

Abbreviations: CMH=Cochran-Mantel-Haenszel test, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 27. Mean Change From Baseline in the CGI Severity of Illness Score

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	142	-0.3	144	-0.6	144	-0.8	144	-1.0	144	-1.1	144	-1.2	144	-1.3	144	-1.3
	Change	FLX	138	-0.3	144	-0.5	144	-0.8	144	-0.9	144	-1.1	144	-1.2	144	-1.4	144	-1.4
	From Baseline	PBO	140	-0.3	143	-0.6	143	-0.8	143	-0.9	143	-1.0	143	-1.1	143	-1.2	143	-1.3
	P-Value‡		0.6080		0.3187		0.7965		0.7941		0.2294		0.4733		0.7799		0.8199	
Observed Cases	Mean	RBX	142	-0.3	128	-0.6	114	-0.9	107	-1.1	105	-1.4	89	-1.5	94	-1.6	90	-1.6
	Change	FLX	138	-0.3	131	-0.5	125	-0.8	125	-1.0	116	-1.2	106	-1.5	104	-1.7	101	-1.7
	From Baseline	PBO	140	-0.3	125	-0.7	124	-0.9	116	-1.0	108	-1.1	97	-1.2	89	-1.5	89	-1.8
	P-Value‡		0.6080		0.3365		0.8559		0.2017		0.0842		0.2117		0.7970		0.9018	

Source: section 14, Tables 3.10A, 3.10B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 3.1.1).

† Mean change from baseline value

‡ P-value based on 2-way ANOVA.

Abbreviations: FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 28. Clinical Global Impression (CGI) Efficacy Index

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
LOCF	Mean	RBX	142	11.5	144	10.1	144	9.2	144	8.5	144	8.2	144	8.2	144	7.9	144	7.8
		FLX	138	11.1	144	9.8	144	9.0	144	8.6	144	7.8	144	7.6	144	7.2	144	6.7
		PBO	140	11.4	143	10.2	143	9.3	143	8.7	143	8.4	143	8.0	143	7.8	143	7.7
	P-Value†		0.6342		0.7414		0.9391		0.9047		0.7463		0.8132		0.8684		0.2540	
Observed Cases	Mean	RBX	142	11.5	128	9.9	114	8.5	105	7.7	105	6.8	89	6.7	94	6.5	90	6.3
		FLX	138	11.1	131	9.7	125	9.0	125	8.2	116	7.3	106	6.6	104	5.8	101	5.3
		PBO	140	11.4	125	10.2	124	9.3	116	8.4	108	7.8	97	7.2	89	6.6	89	6.1
	P-Value†		0.6342		0.7476		0.7003		0.2807		0.1247		0.5274		0.7871		0.3588	

Source: section 14, Tables 3.9A, 3.9B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Table 1.1.1).

† P-value based on 2-way ANOVA.

Abbreviations: ANOVA=analysis of variance, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

10.3.2.6 Patient Global Impression

No statistically significant differences were noted among treatment groups in the mean PGI scores in the LOCF analysis at any visit. Statistically significant differences in the mean PGI scores were observed among treatment groups in the OC analysis on days 28, 35, and 42. Statistically significant differences were noted between reboxetine and placebo on days 28 (p=0.0149), 35 (p=0.0006), and 42 (p=0.0054); statistically significant differences were not noted between fluoxetine and placebo on days 28 (p=0.6614), 35 (p=0.3314), and 42 (p=0.1440). The mean PGI score based on both the LOCF and OC analyses increased with elapsed time corresponding to patient improvement. Table 29 summarizes the mean PGI score at each visit during the treatment period for both the LOCF and OC analyses; statistically significant differences are highlighted.

10.3.2.7 Social Adaptation Self-evaluation Scale

No statistically significant differences were noted among treatment groups in the mean change from baseline in either the LOCF or OC analysis at any visit. The mean SASS total score based on both the LOCF and OC analyses increased with elapsed time corresponding to patient improvement. Table 30 summarizes the mean SASS total score at each visit during the treatment period for both the LOCF and OC analyses; statistically significant differences are highlighted.

Table 29. Patient Global Impression (PGI)

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
LOCF	Mean	RBX	142	5.4	144	5.8	144	6.0	144	6.0	144	6.2	144	6.3	144	6.4	144	6.4
		FLX	137	5.5	144	5.8	144	5.9	144	5.9	144	6.0	144	6.2	144	6.4	144	6.5
		PBO	137	5.4	143	5.6	143	5.8	143	5.9	143	5.8	143	6.0	143	6.0	143	6.2
	P-Value†		0.6409		0.2556		0.5291		0.6024		0.2106		0.5217		0.4717		0.6508	
Observed Cases	Mean	RBX	142	5.4	126	5.9	112	6.2	106	6.5	103	6.8	89	7.0	94	7.1	88	7.1
		FLX	137	5.5	131	5.9	125	6.0	124	6.1	113	6.3	104	6.6	102	7.0	101	7.1
		PBO	137	5.4	123	5.7	123	5.9	116	6.0	106	6.0	99	6.2	89	6.3	89	6.8
	P-Value†		0.6409		0.4272		0.4408		**0.0349**		**0.0021**		**0.0204**		0.1220		0.6616	

Source: section 14, Tables 3.13A, 3.13B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Tables 3.1.1 and 3.13B).

† P-value based on 2-way ANOVA.

Abbreviations: FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 30. Mean Change From Baseline in the SASS Total Score

Type of Analysis	Statistic	Treatment Group	Study Visit During the Treatment Period*															
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42		Day 49		Day 56	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	140	1.2	143	1.6	143	2.5	143	3.0	143	3.6	143	4.1	143	4.4	143	4.5
		FLX	137	1.8	144	2.3	144	2.8	144	3.0	144	3.5	144	4.2	144	4.6	144	4.8
		PBO	137	0.8	142	1.5	142	2.0	142	2.6	142	3.2	142	3.0	142	3.2	142	3.5
	P-Value‡		0.1631		0.0927		0.4441		0.7107		0.8086		0.4025		0.3056		0.3178	
Observed Cases	Mean Change From Baseline	RBX	140	1.2	125	1.6	113	2.8	105	3.9	104	5.0	88	5.7	93	6.2	88	6.1
		FLX	137	1.8	131	2.4	125	2.8	124	3.5	113	4.1	105	5.2	103	6.1	101	5.9
		PBO	137	0.8	123	1.5	122	2.2	115	2.5	105	3.8	99	3.3	90	3.9	89	5.0
	P-Value‡		0.1631		0.0512		0.6911		0.1789		0.5686		0.0500		0.0677		0.3459	

Source: section 14, Tables 3.14A, 3.14B

* The efficacy assessments from patients who completed their last visit 7 days or more after the date of last dose of study medication were treated as unscheduled visits (section 14, Tables 3.1.1 and 3.14B).

† Mean change from baseline value.

‡ P-value based on 2-way ANOVA.

Abbreviations: FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

10.3.2.8 Medical Outcomes Study SF-36

Results of the SF-36 quality of life data are shown in Table 31 through Table 35, in which statistically significant differences are highlighted. The tables show the mean change from baseline; higher differences correspond to increasing patient improvement. Table 31 and Table 32 provide an analysis of the mean change from baseline for reboxetine, fluoxetine, and placebo for the LOCF and OC analyses, respectively. Fluoxetine was significantly better than either reboxetine or placebo on the mental health scale (for the LOCF analysis). Reboxetine was statistically significantly better than placebo on the general health scale (for the OC analysis), whereas fluoxetine was significantly better than placebo on the mental health scale (for the OC analysis). Table 33 and Table 34 provide p-values for instances in which differences among treatment groups were close to statistically significant for the LOCF and OC analyses, respectively; statistically significant differences are highlighted. For the LOCF analysis, statistically significant differences between treatment groups were noted on the mental health scale (between fluoxetine and placebo, p=0.0004; between fluoxetine and reboxetine, p=0.0106). For the OC analysis, statistically significant differences were noted between reboxetine and placebo on the general health scale (p=0.0408) and between fluoxetine and placebo on the mental health scale (p=0.0002). Table 35 compares the SF-36 scores from this study at baseline and on day 56 with SF-36 norms for the general population [17] as well as from a population of patients with depression/dysthymia.

Table 31. SF-36— LOCF Analysis

SF-36 Scale	Mean Change From Baseline (Day 56 Score – Baseline Score)		
	RBX	FLX	PBO
Physical Functioning (N = 444)	3.25	4.77	4.59
Role Physical (N=428)	6.47	5.38	6.38
Bodily Pain (N=427)	7.16	7.35	1.92
General Health (N=427)	5.18	3.90	3.47
Vitality (N=446)	19.46	20.53	15.78
Mental Health (N=441)	16.87	**23.79***	14.12
Social Functioning (N=427)	20.51	23.87	19.77
Role Emotional (N=420)	31.65	32.62	26.90

Source: section 14, Table 27.1

Abbreviations: FLX = fluoxetine, PBO= placebo, RBX = reboxetine

* Fluoxetine is statistically significantly better than placebo and reboxetine (p≤0.05).

Table 32. SF-36— OC Analysis

SF-36 Scale	Mean Change From Baseline (Day 56 Score – Baseline Score)		
	RBX	FLX	PBO
Physical Functioning (N = 210)	4.92	7.73	3.60
Role Physical (N=212)	18.66	14.29	9.93
Bodily Pain (N=212)	11.10	12.86	5.68
General Health (N=211)	**10.38∗**	6.30	4.51
Vitality (N=210	26.89	29.61	22.16
Mental Health (N=209)	25.67	**32.26†**	18.06
Social Functioning (N=212)	25.37	31.98	24.08
Role Emotional (N=209)	49.75	40.09	36.76

Source: section 14, Table 27.2
Abbreviations: FLX = fluoxetine, PBO= placebo, RBX = reboxetine
∗ Reboxetine is statistically significantly better than placebo (p≤0.05).
† Fluoxetine is statistically significantly better than placebo (p≤0.05).

Table 33. Treatment Comparison for SF-36—LOCF Analysis

SF-36 Scale	Treatment Comparison (P-Value)∗		
	RBX versus PBO	FLX versus PBO	FLX versus RBX
Physical Functioning	0.5269	0.9337	0.4722
Role Physical	0.9876	0.8555	0.8428
Bodily Pain	0.0781	0.6665	0.9486
General Health	0.3510	0.8164	0.4812
Vitality	0.2065	0.1018	0.7114
Mental Health	0.3116	**0.0004**	**0.0106**
Social Functioning	0.8262	0.2229	0.3169
Role Emotional	0.3745	0.2834	0.8559

Source: section 14, Table 27.3
∗P-values were based on a 2-way ANOVA.
Abbreviations: ANOVA=analysis of variance, FLX = fluoxetine, PBO= placebo, RBX = reboxetine

Table 34. Treatment Comparison for SF-36—OC Analysis

SF-36 Scale	Treatment Comparison (P-Value)*		
	RBX versus PBO	FLX versus PBO	FLX versus RBX
Physical Functioning	0.6827	0.1840	0.3716
Role Physical	0.2689	0.5675	0.5680
Bodily Pain	0.2043	0.0829	0.6723
General Health	**0.0408**	0.5162	0.1416
Vitality	0.2976	0.0894	0.5359
Mental Health	0.0520	**0.0002**	0.0813
Social Functioning	0.7824	0.0818	0.1466
Role Emotional	0.0818	0.6468	0.1856

Source: section 14, Table 27.4
*P-values were based on a 2-way ANOVA.
Abbreviations: ANOVA=analysis of variance, FLX = fluoxetine, PBO= placebo, RBX = reboxetine

Table 35. Comparison of SF-36 Scales at Baseline (Day 0) and Day 56 With Population Norm and Depression/Dysthymia Norm

SF-36 Scale	Study Day 0 (± SD)	Study Day 56 (± SD)	Population Norm* (± SD)	Depression Norm*† (± SD)
	N = 450	N = 427	N = 2474	
Physical Functioning	77.18 (± 24.42)	81.39 (± 23.37)	84.15 (± 23.28)	71.58 (± 27.17)
Role Physical	57.24 (± 41.35)	63.32 (± 41.85)	80.96 (± 34.00)	44.39 (± 40.26)
Bodily Pain	65.49 (± 24.29)	70.97 (± 24.94)	75.15 (± 23.69)	58.84 (± 26.74)
General Health	59.58 (± 22.23)	63.76 (± 22.65)	71.95 (± 20.34)	52.94 (± 22.98)
Vitality	24.64 (± 18.06)	43.24 (± 25.44)	60.86 (± 20.96)	40.12 (± 21.08)
Mental Health	36.96 (± 16.51)	55.27 (± 23.68)	74.74 (± 18.05)	46.26 (± 20.83)
Social Functioning	43.82 (± 24.56)	65.22 (± 26.61)	83.28 (± 22.69)	57.16 (± 27.67)
Role Emotional	22.54 (± 30.90)	52.94 (± 43.08)	81.26 (± 33.04)	38.90 (± 39.80)

Source: section 14, Table 27.5
* Reference [17]
† Defined as patients with depression or dysthymia using NIMH (DIS) criteria.
Abbreviations: DIS=diagnostic interview schedule**,** FLX = fluoxetine, NIMH=National Institutes of Mental Health, PBO= placebo, RBX = reboxetine, SD = standard deviation

10.3.2.9 RSI

Although the frequency of various sexual activities remained fairly constant throughout the study period for patients in each treatment group, the satisfaction derived from the activities themselves (or thinking about them) increased for patients in the reboxetine- and placebo-treatment groups, whereas the level of satisfaction for patients in the fluoxetine treatment group decreased. Results of the gender-specific questions showed greater percentages of female patients in the reboxetine- and placebo- treatment groups were able to achieve orgasm compared with those in the fluoxetine-treatment group. Results for the male patients were ambiguous. More difficulties in erectile function were noted for patients in the reboxetine-treatment group compared with the placebo- and fluoxetine-treatment groups; however, these did not impair the patient's ability to awaken with morning erection, to complete the sexual act, or result in delayed orgasm.

10.3.2.9.1 Visual Analog Scale Questions

Reboxetine treatment was not statistically significantly different from placebo treatment in the mean change from baseline in the RSI Visual Analog Scale Scores for either the LOCF or OC analysis on days 28 or 56. Statistically significant differences favoring placebo over fluoxetine were noted on questions for both the LOCF and OC analyses. For female and male patients combined, treatment with reboxetine was similar to placebo in the effects on human sexual function for each question; both were superior to fluoxetine. These data are summarized in Table 36 for the LOCF analysis and in Table 37 for the OC analysis; statistically significant differences are highlighted. For each of the questions in the visual analog scale, a mean change from baseline in the positive direction indicates improvement of sexual function, whereas a mean change from baseline in the negative direction indicates worsening of sexual function.

For the LOCF analysis, the mean change from baseline on day 56 showed an improvement in sexual function, as judged by scores from each of the 5 questions, for patients treated with reboxetine as well as for those treated with placebo. The mean changes from baseline to days 28 and 56 for the "frequency of pleasurable sexual thoughts" are presented for each of the treatment groups in Figure 2. Treatment with fluoxetine was statistically significantly worse on days 28 and 56 than treatment with placebo. The mean changes from baseline to days 28 and 56 for the "ability to become sexually excited" are presented for each of the treatment groups in Figure 3. Treatment with fluoxetine was statistically significantly worse on days 28 and 56 than treatment with placebo. The mean changes from baseline to days 28 and 56 for the "frequency of desire to initiate sexual activity" are presented for each of the treatment groups in Figure 4. Treatment with fluoxetine was statistically significantly worse on day 56 than treatment with placebo. The mean changes from baseline to days 28 and 56 for the "frequency of initiating sexual activity" are presented for each of the treatment groups in Figure 5. No statistically significant differences among treatment groups were noted on days 28 and 56. The mean changes from baseline to days 28 and 56 for the "overall degree of sexual satisfaction" are presented for each of the treatment groups in Figure 6. Treatment with fluoxetine was statistically significantly worse on days 28 and 56 than treatment with

either placebo or reboxetine. With the exception of "frequency of initiating sexual activity" for which the mean change from baseline to day 56 improved slightly with fluoxetine, all of the other 4 questions indicated a deterioration of sexual function with fluoxetine treatment. In Figure 2 through Figure 6, positive changes represent patient improvement and negative changes represent patient worsening.

For the OC analysis, the mean change from baseline on day 56 showed an improvement in sexual function, as judged by scores from each of the 5 questions, for patients treated with reboxetine as well as for those treated with placebo. With the exceptions of "frequency of initiating sexual activity" and "frequency of pleasurable sexual thoughts" for which the mean change from baseline to day 56 improved slightly with fluoxetine, all of the other questions indicated a deterioration of sexual function with fluoxetine treatment.

Table 36. Mean Change From Baseline in the RSI Visual Analog Scale Scores (LOCF Analysis)

Question	Statistic	Treatment Group	Study Visit			
			Day 28		Day 56	
			n	X†	n	X†
Frequency of Pleasurable Sexual Thoughts	Mean Change From Baseline	RBX	124	-0.9	127	2.3
		FLX	128	-4.4	130	-0.6
		PBO	121	1.5	122	3.7
	P-Value‡	RBX vs PBO	0.2574		0.2972	
		FLX vs PBO	**0.0096**		**0.0328**	
		RBX vs FLX	0.1525		0.2597	
Ability to Become Sexually Excited	Mean Change From Baseline	RBX	124	-1.5	128	1.9
		FLX	127	-6.0	129	-3.5
		PBO	117	3.8	121	4.7
	P-Value‡	RBX vs PBO	0.0774		0.4824	
		FLX vs PBO	**0.0033**		**0.0155**	
		RBX vs FLX	0.2518		0.0853	
Frequency of Desire to Initiate Sexual Activity	Mean Change From Baseline	RBX	123	-0.8	127	4.2
		FLX	128	-3.6	122	-1.8
		PBO	120	1.6	130	4.2
	P-Value‡	RBX vs PBO	0.1383		0.5988	
		FLX vs PBO	0.0566		**0.0284**	
		RBX vs FLX	0.7175		0.1014	
Frequency of Initiating Sexual Activity	Mean Change From Baseline	RBX	123	0.4	127	5.2
		FLX	128	-1.0	130	1.3
		PBO	118	0.4	120	3.7
	P-Value‡	RBX vs PBO	0.3860		0.9559	
		FLX vs PBO	0.3058		0.2112	
		RBX vs FLX	0.8941		0.2282	
Overall Degree of Sexual Satisfaction	Mean Change From Baseline	RBX	124	1.3	128	3.7
		FLX	118	-6.6	130	-3.6
		PBO	128	7.2	120	7.1
	P-Value‡	RBX vs PBO	0.2201		0.4106	
		FLX vs PBO	**0.0004**		**0.0016**	
		RBX vs FLX	**0.0192**		**0.0185**	

Source: section 14, Tables 3.28A-3.32A

† Mean change from baseline value. Positive changes represent patient improvement; negative changes represent patient worsening.

‡ P-value based on 2-way ANOVA

Abbreviations: ANOVA=analysis of variance, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX= reboxetine

Table 37. Mean Change From Baseline in the RSI Visual Analog Scale Scores (OC Analysis)

Question	Statistic	Treatment Group	Day 28		Day 56	
			n	X†	n	X†
Frequency of Pleasurable Sexual Thoughts	Mean Change From Baseline	RBX	124	- 0.9	92	4.2
		FLX	128	-4.4	103	1.8
		PBO	121	1.5	96	3.1
	P-Value‡	RBX vs PBO	0.2754		0.9258	
		FLX vs PBO	**0.0096**		0.2778	
		RBX vs FLX	0.1525		0.2597	
Ability to Become Sexually Excited	Mean Change From Baseline	RBX	124	-1.5	94	4.2
		FLX	127	-6.0	103	-3.0
		PBO	117	3.8	95	5.5
	P-Value‡	RBX vs PBO	0.0774		0.9383	
		FLX vs PBO	**0.0033**		**0.0250**	
		RBX vs FLX	0.2518		**0.0377**	
Frequency of Desire to Initiate Sexual Activity	Mean Change From Baseline	RBX	123	-0.8	93	6.6
		FLX	128	-3.6	104	-0.7
		PBO	120	1.6	96	4.5
	P-Value‡	RBX vs PBO	0.1383		0.8637	
		FLX vs PBO	0.0566		0.0761	
		RBX vs FLX	0.7175		0.0668	
Frequency of Initiating Sexual Activity	Mean Change From Baseline	RBX	123	0.4	93	7.0
		FLX	128	-1.0	104	2.4
		PBO	118	1.4	93	3.2
	P-Value‡	RBX vs PBO	0.3860		0.3818	
		FLX vs PBO	0.3058		0.4584	
		RBX vs FLX	0.8941		0.1056	
Overall Degree of Sexual Satisfaction	Mean Change From Baseline	RBX	124	1.3	93	4.3
		FLX	128	-6.6	102	-2.3
		PBO	118	7.2	94	6.2
	P-Value‡	RBX vs PBO	0.2201		0.6625	
		FLX vs PBO	**0.0004**		**0.0245**	
		RBX vs FLX	**0.0192**		0.0827	

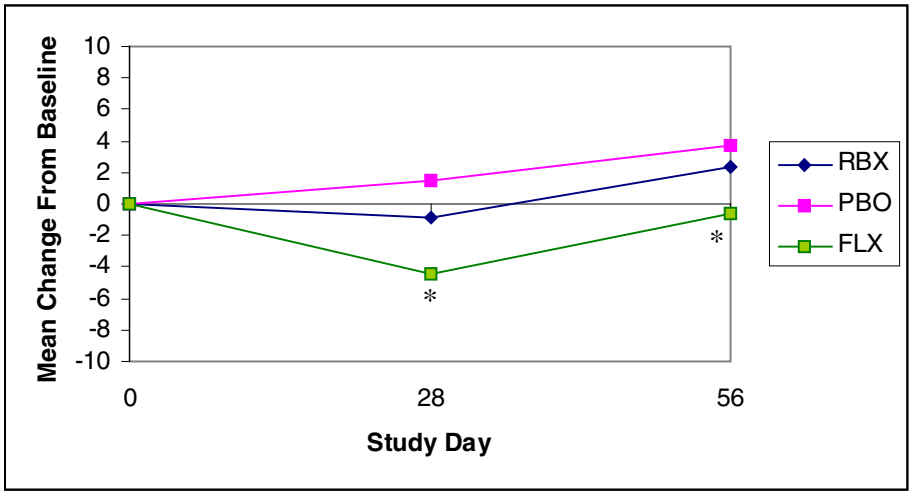
Source: section 14, Tables 3.28B - 3.32B

† Mean change from baseline value. Positive changes represent patient improvement; negative changes represent patient worsening.

‡ P-value based on 2-way ANOVA.

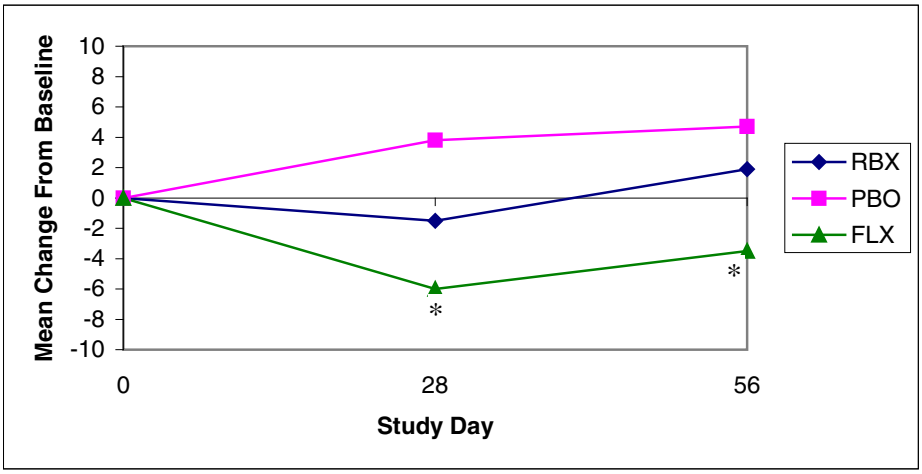
Abbreviations: ANOVA=analysis of variance, FLX=fluoxetine, LOCF=last observation carried forward, PBO=placebo, RBX=reboxetine

Figure 2. Frequency of Pleasurable Sexual Thoughts (LOCF Analysis)



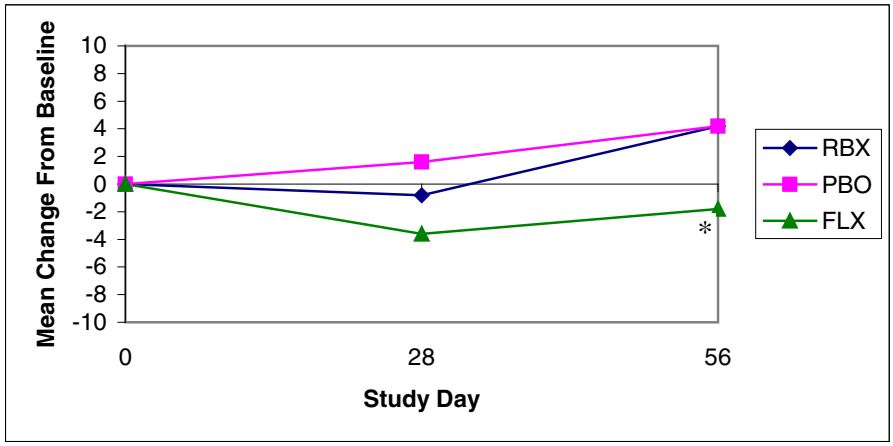
* Statistically significant difference compared with placebo. On day 28, p = 0.0096; on day 56, p = 0.0328.
Abbreviations: FLX = fluoxetine; LOCF = last observation carried forward; PBO = placebo; RBX = reboxetine
Source: Section 14, Tables 3.28A – 3.32A

Figure 3. Ability to Become Sexually Excited (LOCF Analysis)



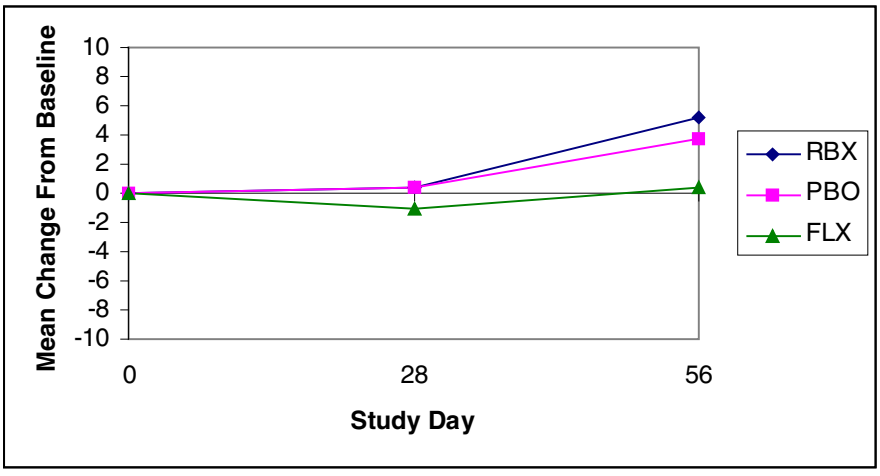
* Statistically significant difference compared with placebo. On day 28, p = 0.0033; on day 56, p = 0.0155.
Abbreviations: FLX = fluoxetine' LOCF = last observation carried forward; PBO = placebo; RBX = reboxetine
Source: Section 14, Tables 3.28A – 3.32A.

Figure 4. Frequency of Desire to Initiate Sexual Activity (LOCF Analysis)



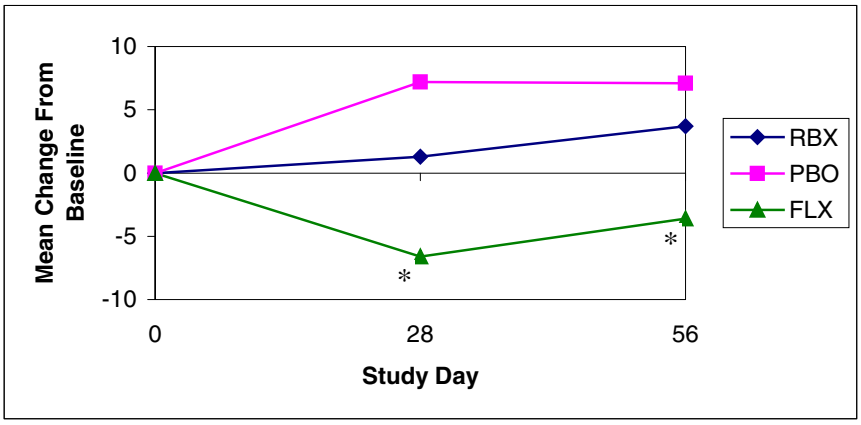
* Statistically significant difference compared with placebo. On day 56, p = 0.0284.
Abbreviations: FLX = fluoxetine; LOCF = last observation carried forward; PBO = placebo; RBX = reboxetine
Source: Section 14, tables 3.28A – 3.32A

Figure 5. Frequency of Initiating Sexual Activity (LOCF Analysis)



Abbreviations: FLX = fluoxetine; LOCF = last observation carried forward; PBO = placebo; RBX = reboxetine
Source: Section 14, Tables 3.28A – 3.32A

Figure 6. Overall Degree of Sexual Satisfaction (LOCF Analysis)



* Statistically significant difference compared with placebo (p = 0.0004 on day 28 and p = 0.0016 on day 56) and compared with reboxetine (p = 0.0192 on day 28 and p = 0.0185 on day 56).
Abbreviations: FLX = fluoxetine; LOCF = last observation carried forward; PBO = placebo; RBX = reboxetine
Source: Section 14, Tables 3.28A – 3.32A

10.3.2.9.2 Frequency of Sexual Activities

The frequency of 3 sexual activities (eg, masturbation, intercourse, and oral sex) was assessed at baseline and on day 28 and 56. The frequency of most sexual activities (as determined by the percentage of patients engaging in that activity at each evaluation) was similar from baseline through day 56. No statistically significant differences were noted among treatment groups for the LOCF or OC analysis. The LOCF data are summarized in Table 38 and the OC data are summarized in Table 39. The tables summarize the patients who never engaged in the specific sexual activity at baseline and again on day 56. Improvement in patient sexual health is indicated by decreases in the numbers of patients who never engaged in a particular sexual activity (ie, increases in the numbers of patients who engaged in a particular activity).

For patients in all treatment groups, the frequency of masturbation decreased from baseline to day 56; however, the change from baseline for patients reporting no masturbation in the reboxetine- and placebo-treatment groups was similar to each other and was of a lower magnitude than the change from baseline for patients reporting no masturbation in the fluoxetine-treatment group. The changes for masturbation as a function of time, expressed as the percent change from baseline through day 56, are shown graphically in Figure 7.

The frequency of intercourse increased slightly for patients in the reboxetine group, whereas the frequency of intercourse for patients in both the placebo and fluoxetine groups did not show much change. The change from baseline for patients reporting no intercourse in the reboxetine-treatment group decreased, whereas the change from baseline for patients reporting no intercourse in the fluoxetine- and placebo-treatment groups was minimal. The changes for intercourse as a function of time, expressed as the percent change from baseline, are shown graphically in Figure 8.

The frequency of oral sex decreased for patients in all of the treatment groups, although the decrease in the placebo-treatment group was minimal. Fewer patients were engaging in oral sex on day 56 than at baseline. The change from baseline for patients reporting no oral sex in the reboxetine- and fluoxetine-treatment groups increased, whereas the change from baseline for patients reporting no oral sex in the placebo-treatment group was minimal. The changes for oral sex as a function of time, expressed as the percent change from baseline, are shown graphically in Figure 9.

In each of the graphs discussed above, negative changes represent patient improvement and positive changes represent patient worsening.

Table 38. Percent of Patients Having No Sexual Activities∗ at Baseline and Day 56 (LOCF Analysis)

Sexual Activity	RBX				FLX				PBO			
	Baseline		Day 56		Baseline		Day 56		Baseline		Day 56	
Never	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Masturbation	68/149	45.6	63/128	49.2	71/48.3	48.3	76/129	58.9	75/149	50.3	66/124	53.2
Intercourse	80/149	53.7	61/127	48.0	77/149	51.7	65/130	50.0	81/148	54.7	70/124	56.5
Oral Sex	108/148	73.0	99/127	78.0	95/148	64.2	92/130	70.8	111/148	75.0	93/123	75.6

Source: section 14, Tables 3.25A-3.27A

∗ Patients checked “never” on the form.

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

Table 39. Percent of Patients Having No Sexual Activities∗ at Baseline and Day 56 (OC Analysis)

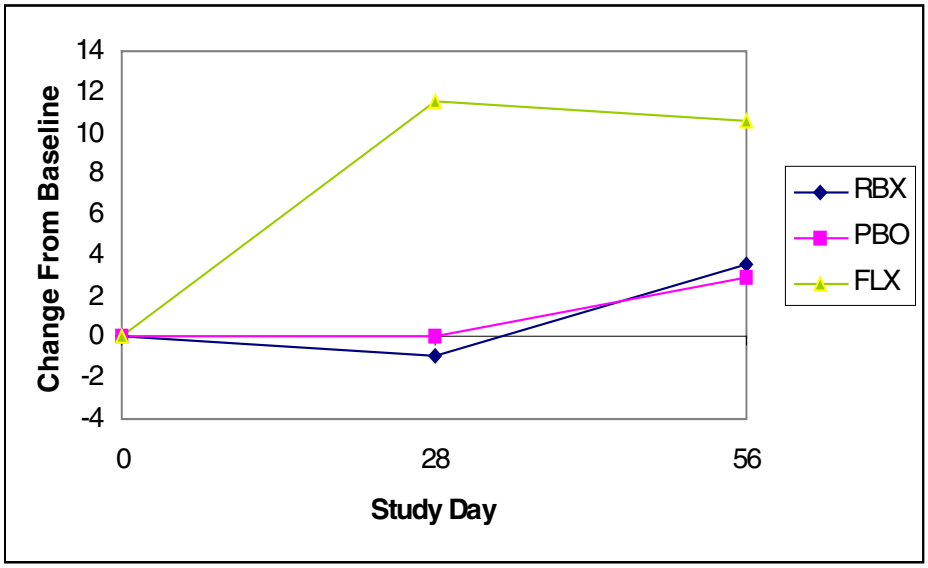
Sexual Activity	RBX				FLX				PBO			
	Baseline		Day 56		Baseline		Day 56		Baseline		Day 56	
Never	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Masturbation	68/149	45.6	46/93	49.5	71/48.3	48.3	62/104	59.6	75/149	50.3	45/95	47.4
Intercourse	80/149	53.7	44/94	46.8	77/149	51.7	51/104	49.0	81/148	54.7	52/97	53.6
Oral Sex	108/148	73.0	74/93	79.6	95/148	64.2	75/104	72.1	111/148	75.0	69/94	73.4

Source: section 14, Tables 3.25B-3.27B

∗ Patients checked “never” on the form.

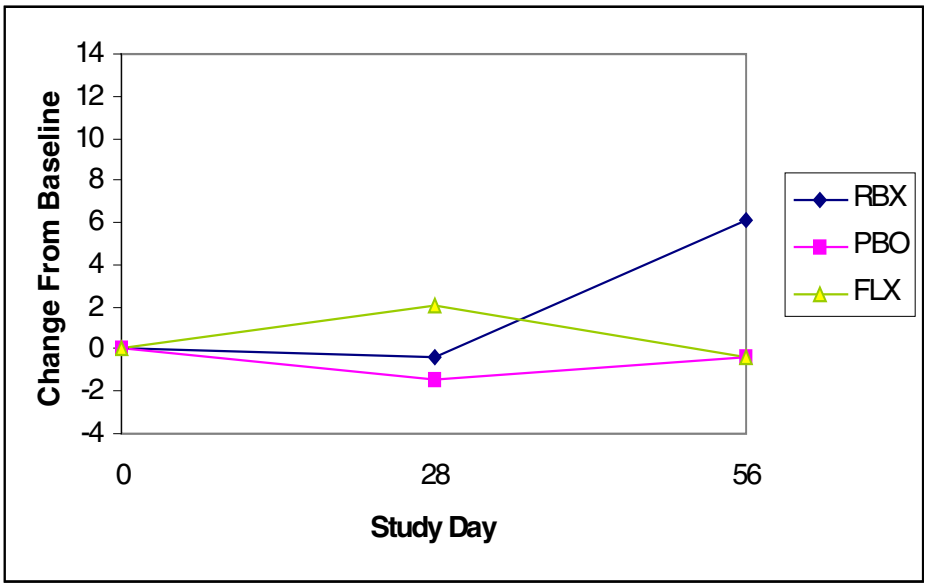
Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

Figure 7. Change in Frequency of Patients Reporting No Masturbation (%) (LOCF Analysis)



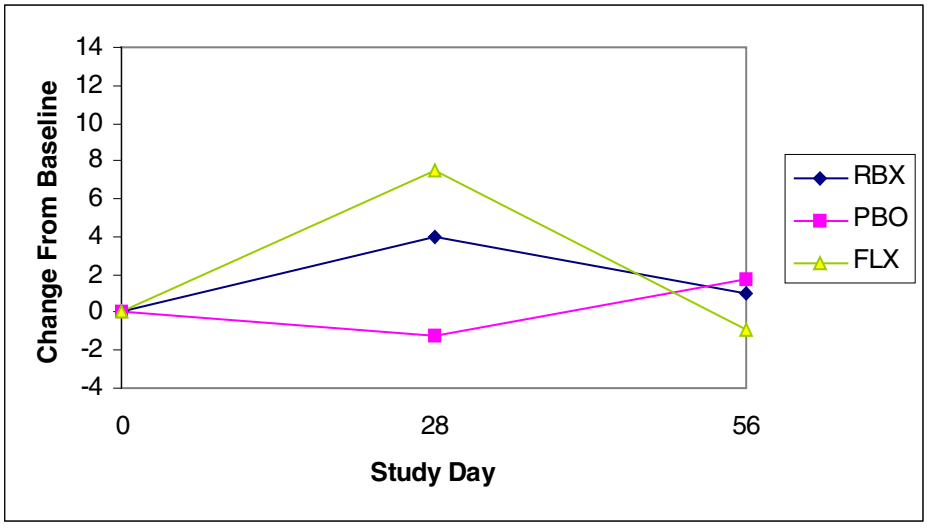
Source: Section 14, Table 3.25A

Figure 8. Change in Frequency of Patients Reporting No Oral Sex (%) (LOCF Analysis)



Source: Section 14, Table 3.26A

Figure 9. Change in Frequency of Patients Reporting No Intercourse (%) (LOCF Analysis)



Source: Section 14, Table 3.27A

10.3.2.9.3 Gender-specific Yes/No Questions

The RSI contained 16 female- and 23 male-specific dichotomous (yes/no) questions. For the female-specific questions, statistically significant differences were observed among treatment groups in the mean changes from baseline to days 28 and 56 for both the LOCF and OC analyses for the item concerning the inability to achieve orgasm. The fluoxetine-treated group was significantly worse than the placebo-treated group on the in ability to achieve orgasm on day 56 (LOCF analysis; p=0.02). The reboxetine-treated group was similar to the placebo-treated group and significantly better than the fluoxetine-treated group on the item concerning the inability to achieve orgasm on day 56 (LOCF analysis; p=0.03). Higher percentages of female patients in both the reboxetine- and placebo-treatment groups were able to achieve orgasm on days 28 and 56 compared with those in the fluoxetine-treatment group. At baseline, 76.6% of female patients in the reboxetine group (LOCF analysis) were able to achieve orgasm (72 of 94), as were 71.4% in the placebo group (60 of 84) and 80.2% in the fluoxetine group (77 of 96); these data were not statistically significantly different. By day 28, the percentage of female patients able to achieve orgasm increased in the reboxetine and placebo groups (86.5%, 64 of 74; and 90.3%, 65 of 72, respectively), but decreased in the fluoxetine group (75.0%, 60 of 80). By day 56, 89.7% of the women in the reboxetine-treatment group (70 of 78) were able to achieve orgasm, as were 89.3% in the placebo-treatment group (67 of 75), compared with 74.4% of the women in the fluoxetine-treatment group (61 of 82). Compared with baseline data, the percentage of female patients able to achieve orgasm increased during the study period for those in the reboxetine- and placebo-treatment groups, but decreased for female patients in the fluoxetine-treatment group. Large changes were observed during the first 28 days of treatment; these remained fairly constant throughout the remainder of the treatment period.

The data from the 16 female- specific questions are summarized in Table 40 for the LOCF analysis and in Table 41 for the OC analysis; statistically significant differences among treatment groups are highlighted. The item concerning inability to achieve orgasm, for which a statistically significant difference was noted among treatment groups on both days 28 and 56, is shown in more detail for baseline and day 56 in Table 44.

For 6 of the 23 male-specific questions, a statistically significant difference was noted among treatment groups. Four of the questions concerned erectile function issues (ie, difficulty getting an erection when sexually stimulated, requiring more stimuli than usual to achieve an erection, decreased fullness of erection, and painful orgasm/ejaculation). The 2 remaining male-specific questions concerned orgasm without erection and genital pain during sexual contact.

For the question concerning difficulty getting an erection when sexually stimulated, at baseline, the percentages of patients responding negatively (ie, did not have difficulty getting an erection when sexually stimulated) was approximately the same across treatment groups. On day 56, the percentage of patients responding negatively decreased in the reboxetine group (ie, greater percentage of patients in the reboxetine group had difficulty getting an erection on day 56 compared with baseline), whereas the percentages remained

approximately the same in each of the other 2 treatment groups. Similar observations can be made from the data from the 3 remaining questions concerning erectile function (eg, requiring more stimuli than usual to achieve an erection, decreased fullness of erection, and painful orgasm/ejaculation). Although statistically significant differences were noted among treatment groups for the questions about orgasm without erection and genital pain during orgasm, statistically significant differences were not noted between any 2 of the treatment groups. The data for male patients are summarized in Table 42 for the LOCF analysis and in Table 43 for the OC analysis; statistically significant differences among treatment groups are highlighted. The results of those items for which statistically significant differences were noted among treatment groups on day 56 in the LOCF analysis are shown in greater detail in Table 44.

Whereas the 4 erectile function questions noted above are of concern, it not known what level of significance these data hold in terms of overall male sexual function. From these data, the percentage of males in the reboxetine-treatment group with erectile function difficulties increased during the study period; however, the degree to which sexual functioning was affected (if at all) is unknown since it did not produce an increased difficulty in maintaining an erection sufficient to complete the sexual act nor did it result in delayed orgasm. If this were a widespread or common problem of physiological origin, one would expect to see difficulty in maintaining an erection, decrease in morning erection, and delayed orgasm; however, in this study, none of the results of a purely physiological problem were observed. The discrepancies in the observations should be the basis of additional discussion, and possibly, of further study.

Table 40. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Females (LOCF Analysis)

LOCF Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
1. Increased Sensitivity, Other Than Pain, in Breasts Upon Physical Contact (No)							
Baseline	80/94	85.1	77/97	79.4	73/87	83.9	0.6297
Day 56	69/78	88.5	78/84	92.9	68/76	89.5	0.3013
2. Increased Sensitivity of Genitals, Other Than Pain, Upon Physical Contact (No)							
Baseline	81/94	86.2	84/96	87.5	77/87	88.5	0.9585
Day 56	69/78	88.5	76/84	90.5	70/76	92.1	0.7911
3. Pain in Breasts Upon Physical Contact (No)							
Baseline	86/94	91.5	85/97	87.6	77/87	88.5	0.7270
Day 56	75/78	96.2	78/84	92.9	70/76	92.1	0.7087
4. Pain in Genitals Upon Physical Contact (No)							
Baseline	87/93	93.5	93/97	95.9	81/87	93.1	0.7326
Day 56	76/78	97.4	83/84	98.8	74/76	97.4	0.4866
5. Decreased Sensitivity in Breasts Upon Physical Contact (No)							
Baseline	85/94	90.4	74/86	86.0	88/97	90.7	0.6590
Day 56	77/78	98.7	80/83	96.4	72/76	94.7	0.6621
6. Decreased Sensitivity in Genitals Upon Physical Contact (No)							
Baseline	84/94	89.4	87/97	89.7	76/86	88.4	0.9830
Day 56	74/78	94.9	77/83	92.8	71/76	93.4	0.6973

Source: section 14, Tables 3.66A-3.81A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 40. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Females (LOCF Analysis)

LOCF Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
7. Inadequate Swelling or Vaginal Lubrication During Sexual Contact (No)							
Baseline	76/93	81.7	82/96	85.4	71/85	83.5	0.8539
Day 56	71/78	91.0	74/83	89.2	66/75	88.0	0.9707
8. Orgasm (Yes)							
Baseline	36/94	38.3	49/97	50.5	37/86	43.0	0.2849
Day 56	41/78	52.6	37/83	44.6	34/76	44.7	0.4406
9. Multiple Orgasm (Yes)							
Baseline	19/92	20.7	14/95	14.7	9/85	10.6	0.1422
Day 56	11/78	14.1	14/83	16.9	12/76	15.8	0.9643
10. Difficulty Achieving Orgasm, But Eventually Being Able To (No)							
Baseline	72/94	76.6	61/96	63.5	59/85	69.4	0.1178
Day 56	61/78	78.2	59/82	72.0	60/75	80.0	0.2958
11. Inability to Achieve Orgasm (No)							
Baseline	72/94	76.6	77/96	80.2	60/84	71.4	0.3602
Day 56	70/78	89.7	61/82	74.4	67/75	89.3	**0.0253**
12. Experiencing Orgasm Without Sexual Provocation (No)							
Baseline	92/94	97.9	94/96	97.9	84/86	97.7	0.9875
Day 56	76/78	97.4	82/83	98.8	74/75	98.7	0.8878
13. Painful Orgasm (No)							
Baseline	90/94	95.7	95/96	99.0	85/85	100.0	0.0728
Day 56	78/78	100.0	81/82	98.8	75/75	100.0	0.2636

Source: section 14, Tables 3.66A-3.81A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

Table 40. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Females (LOCF Analysis)

LOCF Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
14.Decreased Intensity of Orgasm (No)							
Baseline	71/93	76.3	75/94	79.8	63/85	74.1	0.8478
Day 56	63/77	81.8	71/83				
15.Involuntary Contractions That Prevent Vaginal Penetration (No)							
Baseline	83/91	91.2	92/96	95.8	81/85	95.3	0.4446
Day 56	75/78	96.2	78/82	95.1	75/75	100.0	0.1121
16.Physical Pain During Sexual Activity (No)							
Baseline	86/93	92.5	87/96	90.6	75/84	89.3	0.7926
Day 56	74/78	94.9	76/82	92.7	70/75	93.3	0.8425

Source: section 14, Tables 3.66A-3.81A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 41. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Females (OC Analysis)

OC Analysis	RBX		FLX		PBO		P-Value
Item	n/N	%	n/N	%	n/N	%	
1. Increased Sensitivity, Other Than Pain, in Breasts Upon Physical Contact (No)							
Baseline	80/94	85.1	77/97	79.4	73/87	83.9	0.6297
Day 56	53/60	88.3	63/68	92.6	48/55	87.3	0.3027
2. Increased Sensitivity of Genitals, Other Than Pain, Upon Physical Contact (No)							
Baseline	81/94	86.2	84/96	87.5	77/87	88.5	0.9585
Day 56	54/60	90.0	61/68	89.7	49/54	90.7	0.9895
3. Pain in Breasts Upon Physical Contact (No)							
Baseline	86/94	91.5	85/97	87.6	77/87	88.5	0.7270
Day 56	57/60	95.0	51/54	94.4	63/68	92.6	0.8166
4. Pain in Genitals Upon Physical Contact (No)							
Baseline	87/93	93.5	93/97	95.9	81/87	93.1	0.7326
Day 56	58/60	96.7	67/68	98.5	53/55	96.4	0.4713
5. Decreased Sensitivity in Breasts Upon Physical Contact (No)							
Baseline	85/94	90.4	74/86	86.0	88/97	90.7	0.6590
Day 56	59/60	98.3	66/68	97.1	53/55	96.4	0.9767
6. Decreased Sensitivity in Genitals Upon Physical Contact (No)							
Baseline	84/94	89.4	87/97	89.7	76/86	88.4	0.9830
Day 56	56/60	93.3	63/68	92.6	53/55	96.4	0.3442

Source: section 14, Tables 3.66B-3.81B

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 41. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Females (OC Analysis)

OC Analysis	RBX		FLX		PBO		P-Value
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
7. Inadequate Swelling or Vaginal Lubrication During Sexual Contact (No)							
Baseline	76/93	81.7	82/96	85.4	71/85	83.5	0.8539
Day 56	54/60	90.0	61/68	89.7	48/54	88.9	0.9437
8. Orgasm (Yes)							
Baseline	36/94	38.3	49/97	50.5	37/86	43.0	0.2849
Day 56	35/60	58.3	31/68	45.6	27/54	50.0	0.3203
9. Multiple Orgasm (Yes)							
Baseline	19/92	20.7	14/95	14.7	9/85	10.6	0.1422
Day 56	8/60	13.3	11/68	16.2	9/54	16.7	0.9812
10. Difficulty Achieving Orgasm, But Eventually Being Able To (No)							
Baseline	72/94	76.6	61/96	63.5	59/85	69.4	0.1178
Day 56	46/60	76.7	48/67	71.6	44/54	81.5	0.2893
11. Inability to Achieve Orgasm (No)							
Baseline	72/94	76.6	77/96	80.2	60/84	71.4	0.3602
Day 56	54/60	90.0	51/67	76.1	49/54	90.7	**0.0314**
12. Experiencing Orgasm Without Sexual Provocation (No)							
Baseline	92/94	97.9	94/96	97.9	84/86	97.7	0.9875
Day 56	59/60	98.3	67/68	98.5	52/53	98.1	0.9485
13. Painful Orgasm (No)							
Baseline	90/94	95.7	95/96	99.0	85/85	100.0	0.0728
Day 56	60/60	100.0	66/67	98.5	54/54	100.0	0.4724

Source: section 14, Tables 3.66B-3.81B

∗ P-value among treatment groups; highlighted if statistically significant (p≤0.05).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

Table 41. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Females (OC Analysis)

OC Analysis	RBX		FLX		PBO		P-Value
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
14.Decreased Intensity of Orgasm (No)							
Baseline	71/93	76.3	75/94	79.8	63/85	74.1	0.8478
Day 56	49/60	81.7	58/68	85.3	48/54	88.9	0.4856
15.Involuntary Contractions That Prevent Vaginal Penetration (No)							
Baseline	83/91	91.2	92/96	95.8	81/85	95.3	0.4446
Day 56	58/60	96.7	64/67	95.5	54/54	100.0	0.3261
16.Physical Pain During Sexual Activity (No)							
Baseline	86/93	92.5	87/96	90.6	75/84	89.3	0.7926
Day 56	57/60	95.0	62/67	92.5	51/54	94.4	0.7970

Source: section 14, Tables 3.66B-3.81B

∗ P-value among treatment groups; highlighted if statistically significant (p≤0.05).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 42. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Males (LOCF Analysis)

LOCF Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
1. Spontaneous Daytime Erections (No)							
Baseline	31/56	56.4	30/51	60.0	38/60	64.4	0.7128
Day 56	43/50	86.0	36/45	80.0	35/60	72.9	0.0953
2. Painful Erection (No)							
Baseline	55/56	98.2	49/50	98.0	59/59	100.0	0.4925
Day 56	47/50	94.0	45/45	100.0	47/48	97.9	0.1836
3. Erection when Sexually Aroused (Yes)							
Baseline	47/55	85.5	44/50	88.0	47/60	81.0	0.6780
Day 56	43/49	87.8	34/45	75.6	41/48	85.4	0.3129
4. Difficulty Getting an Erection When Sexually Stimulated (No)							
Baseline	47/56	83.9	39/51	76.5	47/60	79.7	0.6557
Day 56	29/49	59.2	35/45	77.8	40/48	83.3	**0.0096**
5. Difficulty Maintaining an Erection to Complete Sexual Act (No)							
Baseline	45/56	80.4	37/49	75.5	43/59	72.9	0.7206
Day 56	34/49	69.4	33/45	73.3	37/48	77.1	0.8032
6. Waking Up From Sleep With an Erection (Yes)							
Baseline	36/56	64.3	34/51	68.0	30/59	50.8	0.0676
Day 56	24/50	50.0	27/45	60.0	26/48	54.2	0.5312

Source: section 14, Tables 3.43A-3.65A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 42. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Males (LOCF Analysis)

LOCF Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
7. Requiring More Stimuli Than Usual to Achieve an Erection (No)							
Baseline	39/56	69.6	36/51	70.6	38/59	64.4	0.7557
Day 56	23/50	46.0	26/45	57.8	38/48	79.2	**0.0066**
8. Requiring More Stimuli Than Usual to Maintain an Erection (No)							
Baseline	41/56	73.2	35/51	68.6	40/59	67.8	0.8013
Day 56	27/50	54.0	29/45	64.4	34/47	72.3	0.4023
9. Decreased Fullness of Erection (No)							
Baseline	41/56	73.2	35/50	70.0	39/59	66.1	0.9151
Day 56	23/50	46.0	31/45	68.9	34/48	70.8	**0.0104**
10. Increased Sensitivity of Genitals Upon Physical Stimulation (No)							
Baseline	47/56	83.9	33/51	64.7	50/59	84.7	**0.0215**
Day 56	41/50	82.0	38/45	84.4	40/48	83.3	0.9860
11. Decreased Sensitivity of Genitals Upon Physical Stimulation (No)							
Baseline	48/56	85.7	43/51	84.3	47/60	79.7	0.3763
Day 56	38/50	76.0	36/45	80.0	42/48	87.5	0.4424
12. Orgasm (Yes)							
Baseline	42/56	75.0	41/51	80.4	44/59	74.6	0.6170
Day 56	39/50	78.0	33/45	73.3	37/48	77.1	0.9410

Source: section 14, Tables 3.43A-3.65A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 42. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Males (LOCF Analysis)

LOCF Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
13.Ejaculation (Yes)							
Baseline	48/56	85.7	42/51	82.4	47/60	79.7	0.8586
Day 56	40/50	80.0	34/45	75.6	36/48	75.0	0.8647
14.Painful Orgasm/Ejaculation (No)							
Baseline	55/56	98.2	50/51	98.0	58/59	98.3	0.4925
Day 56	38/50	76.0	44/45	97.8	46/48	95.8	**0.0013**
15.Orgasm Without Ejaculation (No)							
Baseline	52/56	92.9	46/51	90.2	56/60	94.9	0.5259
Day 56	45/50	90.0	41/45	91.1	44/48	91.7	0.9046
16.Delay in Achieving Orgasm/Ejaculation But Eventually Doing So (No)							
Baseline	39/56	69.6	34/51	66.7	41/59	69.5	0.9232
Day 56	40/49	81.6	33/45	73.3	39/48	81.3	0.6094
17.Inability to Achieve Orgasm/Ejaculation (No)							
Baseline	52/56	92.9	44/51	86.3	47/60	79.7	0.2663
Day 56	43/50	86.0	36/45	80.0	46/48	95.8	0.0730
18.Orgasm Without Erection (No)							
Baseline	54/56	96.4	47/51	92.2	56/59	94.9	0.8068
Day 56	44/50	88.0	44/45	97.8	47/48	97.9	**0.0358**
19.Orgasm During Sleep (No)							
Baseline	52/56	92.9	46/51	90.2	57/60	96.6	0.5200
Day 56	47/50	94.0	44/45	97.8	47/48	97.9	0.5333

Source: section 14, Tables 3.43A-3.65A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 42. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Males (LOCF Analysis)

LOCF Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
20.Genital Pain During Sexual Contact (No)							
Baseline	54/55	98.2	51/51	100.0	59/59	100.0	
Day 56	43/49	87.8	44/45	97.8	44/45	97.8	**0.0299**
21.Orgasm/Ejaculation Occurring Earlier Than Desired (No)							
Baseline	44/56	78.6	35/51	68.6	42/59	71.2	0.4687
Day 56	35/50	70.0	37/45	82.2	38/48	79.2	0.2487
22.Experiencing Orgasm Without Sexual Provocation (No)							
Baseline	54/56	96.4	49/51	96.1	59/59	100.0	0.3876
Day 56	49/50	98.0	44/45	97.8	47/48	97.9	0.9379
23.Generally Decreased Insensitivity of Orgasm (No)							
Baseline	38/56	67.9	36/51	70.6	42/59	71.2	0.8510
Day 56	32/50	64.4	35/45	77.8	42/48	87.5	0.0581

Source: section 14, Tables 3.43A-3.65A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 43. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Males (OC Analysis)

OC Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
1. Spontaneous Daytime Erections (No)							
Baseline	31/55	56.4	30/51	60.0	38/59	64.4	0.7128
Day 56	30/35	85.7	31/35	88.6	30/42	71.4	**0.0130**
2. Painful Erection (No)							
Baseline	55/56	98.2	49/50	98.0	59/59	100.0	0.4925
Day 56	32/34	94.1	35/35	100.0	41/42	97.6	0.5610
3. Erection when Sexually Aroused (Yes)							
Baseline	47/55	85.5	44/50	88.0	47/60	81.0	0.6780
Day 56	33/35	94.3	24/35	68.6	35/42	83.3	**0.0369**
4. Difficulty Getting an Erection When Sexually Stimulated (No)							
Baseline	47/56	83.9	39/51	76.5	47/60	79.7	0.6557
Day 56	21/35	60.0	26/35	74.3	36/42	85.7	**0.0213**
5. Difficulty Maintaining an Erection to Complete Sexual Act (No)							
Baseline	45/56	80.4	37/49	75.5	43/59	72.9	0.7206
Day 56	25/35	71.4	25/35	71.4	34/42	81.0	0.6269
6. Waking Up From Sleep With an Erection (Yes)							
Baseline	36/56	64.3	34/51	68.0	30/59	50.8	0.0676
Day 56	18/35	51.4	21/35	60.0	23/42	54.8	0.7977

Source: section 14, Tables 3.43A-3.65A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 43. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Males (OC Analysis)

OC Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
7. Requiring More Stimuli Than Usual to Achieve an Erection (No)							
Baseline	39/56	69.6	36/51	70.6	38/59	64.4	0.7557
Day 56	16/35	45.7	17/35	48.6	32/42	76.2	**0.0180**
8. Requiring More Stimuli Than Usual to Maintain an Erection (No)							
Baseline	41/56	73.2	35/51	68.6	40/59	67.8	0.8013
Day 56	20/35	57.1	22/35	62.9	30/42	71.4	0.6227
9. Decreased Fullness of Erection (No)							
Baseline	41/56	73.2	35/50	70.0	39/59	66.1	0.9151
Day 56	15/35	42.9	24/35	68.6	30/42	71.4	**0.0076**
10. Increased Sensitivity of Genitals Upon Physical Stimulation (No)							
Baseline	47/56	83.9	33/51	64.7	50/59	84.7	**0.0215**
Day 56	30/35	85.7	30/35	85.7	34/42	81.0	0.8192
11. Decreased Sensitivity of Genitals Upon Physical Stimulation (No)							
Baseline	48/56	85.7	43/51	84.3	47/60	79.7	0.3763
Day 56	27/35	77.1	28/35	80.0	36/42	85.7	0.8385
12. Orgasm (Yes)							
Baseline	42/56	75.0	41/51	80.4	44/59	74.6	0.6170
Day 56	29/35	82.9	26/35	74.3	33/42	78.6	0.9059

Source: section 14, Tables 3.43A-3.65A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 43. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Males (OC Analysis)

OC Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
13.Ejaculation (Yes)							
Baseline	48/56	85.7	42/51	82.4	47/60	79.7	0.8586
Day 56	30/35	85.7	26/35	74.3	31/42	73.8	0.6347
14.Painful Orgasm/Ejaculation (No)							
Baseline	55/56	98.2	50/51	98.0	58/59	98.3	0.4925
Day 56	28/35	80.0	34/35	97.1	40/42	95.2	0.0658
15.Orgasm Without Ejaculation (No)							
Baseline	52/56	92.9	46/51	90.2	56/60	94.9	0.5259
Day 56	33/35	94.3	31/35	88.6	38/42	90.5	0.8516
16.Delay in Achieving Orgasm/Ejaculation But Eventually Doing So (No)							
Baseline	39/56	69.6	34/51	66.7	41/59	69.5	0.9232
Day 56	29/35	82.9	24/35	68.6	35/42	83.3	0.3145
17.Inability to Achieve Orgasm/Ejaculation (No)							
Baseline	52/56	92.9	44/51	86.3	47/60	79.7	0.2663
Day 56	32/35	91.4	27/35	77.1	40/41	97.6	**0.0309**
18.Orgasm Without Erection (No)							
Baseline	54/56	96.4	47/51	92.2	56/59	94.9	0.8068
Day 56	33/35	94.3	34/35	97.1	41/42	97.6	0.0632
19.Orgasm During Sleep (No)							
Baseline	52/56	92.9	46/51	90.2	57/60	96.6	0.5200
Day 56	33/35	94.3	34/35	97.1	41/42	97.6	0.5545

Source: section 14, Tables 3.43A-3.65A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

Table 43. Summary of the Mean Scores (Baseline and Day 56) in the Dichotomous Items for Males (OC Analysis)

OC Analysis	RBX		FLX		PBO		P-Value*
Item	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	
20.Genital Pain During Sexual Contact (No)							
Baseline	54/55	98.2	51/51	100.0	59/59	100.0	
Day 56	31/35	88.6	35/35	100.0	42/42	100.0	0.0745
21.Orgasm/Ejaculation Occurring Earlier Than Desired (No)							
Baseline	44/56	78.6	35/51	68.6	42/59	71.2	0.4687
Day 56	22/35	62.9	28/35	80.0	33/42	78.6	0.1869
22.Experiencing Orgasm Without Sexual Provocation (No)							
Baseline	54/56	96.4	49/51	96.1	59/59	100.0	0.3876
Day 56	35/35	100.0	34/35	97.1	41/42	97.6	0.5769
23.Generally Decreased Insensitivity of Orgasm (No)							
Baseline	38/56	67.9	36/51	70.6	42/59	71.2	0.8510
Day 56	23/35	65.7	27/35	77.1	37/42	88.1	0.2198

Source: section 14, Tables 3.43A-3.65A

* P-value among treatment groups; highlighted if statistically significant ($p \leq 0.05$).

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 44. Selected Items From the Dichotomous Items (LOCF Analysis)

Item	Treatment Group	Baseline				Day 56			
		n/N	%	P-value		n/N	%	P-value	
FEMALE-SPECIFIC									
11. Inability to Achieve Orgasm (No)	RBX	72/94	76.6	among groups	0.3602	70/78	89.7	among groups	**0.0253**
	FLX	77/96	80.2	RBX vs FLX	0.3715	61/82	74.4	RBX vs FLX	**0.0327**
	PBO	60/84	71.4	RBX vs PBO	0.4630	67/75	89.3	RBX vs PBO	0.8264
				FLX vs PBO	0.1374			FLX vs PBO	**0.0213**
MALE-SPECIFIC									
4. Difficulty Getting an Erection When Sexually Stimulated (No)	RBX	47/56	83.9	among groups	0.6557	29/49	59.2	among groups	**0.0096**
	FLX	39/51	76.5	RBX vs FLX	0.4827	35/45	77.8	RBX vs FLX	**0.0164**
	PBO	47/59	79.7	RBX vs PBO	0.8279	40/48	83.3	RBX vs PBO	**0.0171**
				FLX vs PBO	0.5909			FLX vs PBO	0.3421
7. Requiring More Stimuli Than Usual to Achieve an Erection (No)	RBX	39/56	69.6	among groups	0.7557	23/50	46.0	among groups	**0.0066**
	FLX	36/51	70.6	RBX vs FLX	0.6040	26/45	57.8	RBX vs FLX	0.3427
	PBO	38/59	64.4	RBX vs PBO	0.4861	38/48	79.2	RBX vs PBO	**0.0028**
				FLX vs PBO	0.7076			FLX vs PBO	0.0799
9. Decreased Fullness of Erection (No)	RBX	41/56	73.2	among groups	0.9151	23/50	46.0	among groups	**0.0104**
	FLX	35/50	70.0	RBX vs FLX	0.9866	31/45	68.9	RBX vs FLX	**0.0208**
	PBO	39/59	66.1	RBX vs PBO	0.8028	34/48	70.8	RBX vs PBO	**0.0242**
				FLX vs PBO	0.6568			FLX vs PBO	0.6232

Source: section 14, Tables 3.46A, 3.49A, 3.51A, 3.56A, 3.60A, 3.62A, and 3.76A

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine

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Table 44. Selected Items From the Dichotomous Items (LOCF Analysis)

Item	Treatment Group	Baseline				Day 56			
		n/N	%	P-value		n/N	%	P-value	
14. Painful Orgasm/Ejaculation (No)	RBX	55/56	98.2	among groups	0.4924	38/50	76.0	among groups	**0.0013**
	FLX	50/51	98.0	RBX vs FLX	0.6394	44/45	97.8	RBX vs FLX	**0.0049**
	PBO	58/59	98.3	RBX vs PBO	0.3173	46/48	95.8	RBX vs PBO	**0.0072**
				FLX vs PBO	0.3865			FLX vs PBO	0.3613
15. Orgasm Without Erection (No)	RBX	54/56	96.4	among groups	0.8068	44/50	88.0	among groups	**0.0358**
	FLX	47/51	92.2	RBX vs FLX	0.3304	44/45	97.8	RBX vs FLX	0.0522
	PBO	56/59	94.9	RBX vs PBO	0.9842	47/48	97.9	RBX vs PBO	0.0632
				FLX vs PBO	0.8051			FLX vs PBO	0.3173
20. Genital Pain During Sexual Contact (No)	RBX	54/55	98.2	among groups		43/49	87.8	among groups	**0.0299**
	FLX	51/51	100.0	RBX vs FLX		44/45	97.8	RBX vs FLX	**0.0490**
	PBO	59/59	100.0	RBX vs PBO	0.1573	48/48	100.0	RBX vs PBO	**0.0450**
				FLX vs PBO				FLX vs PBO	0.3613

Source: section 14, Tables 3.46A, 3.49A, 3.51A, 3.56A, 3.60A, 3.62A, and 3.76A
Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine
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10.3.3 Efficacy Conclusions

No statistically significant differences were noted between reboxetine and placebo or between fluoxetine and placebo on the primary efficacy endpoint (mean change from baseline in the HAM-D total score on day 56) for either the LOCF or OC analysis. While the primary efficacy endpoint was not attained by patients in either the reboxetine or fluoxetine treatment group, the HAM-D total score decreased over time (corresponding to patient improvement) in each of the 3 treatment groups.

Likewise, this study failed to demonstrate statistically significant differences between reboxetine and placebo or between fluoxetine and placebo on the secondary endpoints of antidepressant efficacy (eg, HAM-D response, remission, anxiety/somatization, cognitive disturbance, and retardation; MADRS; CGI; PGI) on day 56 in either the LOCF or OC analysis. No statistically significant differences in favor of either reboxetine or fluoxetine over placebo were observed in the LOCF analysis at any evaluation time prior to the end of treatment on day 56. Although statistically significant differences in favor of either reboxetine or fluoxetine over placebo were noted occasionally in the OC analysis on days prior to day 56, these were not considered clinically significant. Patients showed improvement over time, regardless of which treatment was administered.

Statistically significant differences were noted among treatment groups in the change from baseline to day 56 in the SF-36 score assessing mental health for both the LOCF and OC analyses. Fluoxetine was superior to either reboxetine or placebo. Reboxetine was superior to placebo in improving the SF-36 patient general health score.

For most assessments in the RSI, treatment with reboxetine was similar to placebo in affecting human sexual function over time; both were generally superior to fluoxetine in this regard. Although the frequency of various sexual activities remained fairly constant throughout the study period for patients in each treatment group, the satisfaction derived from the activities increased for patients in the reboxetine- and placebo-treatment groups, whereas the level of satisfaction for patients in the fluoxetine treatment group decreased. Results of the gender-specific questions showed significantly greater percentages of female patients in the reboxetine- and placebo- treatment groups were able to achieve orgasm compared with those in the fluoxetine-treatment group. The differences among treatment groups were statistically significant on both days 28 and 56, with the differences most notable when comparing data from baseline with those from day 28. Results for the male patients were ambiguous. More difficulties in erectile function were noted for patients in the reboxetine-treatment group compared with the placebo- and fluoxetine-treatment groups on day 56; however, these neither impaired the patient's ability to complete the sexual act nor delayed orgasm. The male-specific data are still under consideration, as these observations of erectile function difficulties are not consistent with those expected from a widespread or common problem of purely physiological origin.

10.4 Safety Results

10.4.1 Treatment-emergent Symptoms

10.4.1.1 Brief Summary of TES

At least 1 TES was reported in similar percentages of patients in the active-treatment groups: 92.0% (138/150) in the reboxetine group and 86.0% (129/150) in the fluoxetine group, whereas at least 1 TES was reported in 78.0% (117/150) of the placebo-treated patients. Drug-related TES were reported in 84.7% (127/150) of the patients in the reboxetine group, in 68.7% (103/150) of the fluoxetine group, and in 50.7% (76/150) of the placebo group. No serious TES was reported in patients in the reboxetine group, whereas a serious TES was reported for 1 patient in the fluoxetine group and for 4 patients in the placebo group. The percentage of patients who discontinued study medication due to TES was highest in the reboxetine group (18.0%, 27/150), and nearly identical between the fluoxetine (6.7%, 10/150) and placebo (8.0%, 12/150) groups. Table 45 presents an overview of the numbers of patients with at least 1 TES.

Table 45. Overall Summary of TES

	RBX N=150		FLX N=150		PBO N=150	
	n	%	n	%	n	%
Patients with at least 1 TES	138	92.0	129	86.0	117	78.0
Drug-Related	127	84.7	103	68.7	76	50.7
Serious	0		1	0.7	4	2.7
Patients who discontinued due to at least 1 TES	27	18.0	10	6.7	12	8.0

Source: section 14, Tables 4.1, 8.1, 9.1, 13.1
Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom

10.4.1.2 TES by Body System

At least 1 TES was reported in 92.0% (138/150) of the patients in the reboxetine group, in 86.0% (129/150) in the fluoxetine group, and in 78.0% (117/150) in the placebo group (section 14, Table 4.1). The frequency of TES is summarized by body system in Table 46.

Table 46. Frequency of TES by Body System

Body System*	RBX N=150		FLX N=150		PBO N=150	
	n	%	n	%	n	%
Patients With At Least 1 TES	138	92.0	129	86.0	117	78.0
Digestive	103	68.7	77	51.3	62	41.3
Nervous	92	61.3	82	54.7	53	35.3
Body	91	60.7	90	60.0	86	57.3
Urogenital	50	33.3	23	15.3	21	14.0
Skin	35	23.3	20	13.3	13	8.7
Cardiovascular	35	23.3	20	13.3	11	7.3
Respiratory	26	17.3	18	12.0	25	16.7
Special Senses	19	12.7	14	9.3	7	4.7
Metabolic and Nutritional	9	6.0	6	4.0	6	4.0
Musculo-Skeletal	3	2.0	8	5.3	10	6.7
Hemic and Lymphatic	1	0.7	0		0	

Source: section 14, Table 4.1

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

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom

Digestive system-related events were the most frequently reported TES in the reboxetine-treatment group, followed by nervous system- and body-as-a-whole system-related events. Body-as-a-whole system-related events were the most frequently reported TES in the fluoxetine-treatment group, followed by nervous system- and digestive system-related events. Body system-related events were the most frequently reported TES in the placebo-treatment group, followed by digestive system- and nervous system-related events.

Section 14, Table 4.1 summarizes all of the TES reported during the study by body system and treatment group. TES are listed by patient (section 14, Table 7.1) and by body system and COSTART term (Table 7.2).

10.4.1.3 TES by COSTART Preferred Term

TES reported in at least 2% of the patients in any treatment group are summarized in Table 47.

Table 47. TES Reported in ≥2% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=150		FLX N=150		PBO N=150	
	n	%	n	%	n	%
BODY	91	60.7	90	60.0	86	57.3
Headache	58	38.7	58	38.7	51	34.0
Infection	26	17.3	23	15.3	16	10.7
Asthenia	12	8.0	13	8.7	11	7.3
Flu Syndrome	12	8.0	6	4.0	4	2.7
Back Pain	10	6.7	3	2.0	9	6.0
Abdominal Pain	9	6.0	8	5.3	13	8.7
Chills	9	6.0	2	1.3	1	0.7
Pain	6	4.0	7	4.7	6	4.0
Accidental Injury	5	3.3	4	2.7	5	3.3
Chest Pain	3	2.0	1	0.7	4	2.7
Neck Pain	2	1.3	0	0.0	5	3.3
Abdomen Enlarged	1	0.7	2	1.3	3	2.0
Fever	1	0.7	3	2.0	2	1.3
CARDIOVASCULAR	35	23.3	20	13.3	11	7.3
Palpitation	14	9.3	5	3.3	5	3.3
Vasodilation	12	8.0	9	6.0	1	0.7
Hypertension	7	4.7	2	1.3	3	2.0
Tachycardia	7	4.7	1	0.7	1	0.7
DIGESTIVE	103	68.7	77	51.3	62	41.3
Dry Mouth	62	41.3	23	15.3	15	10.0
Constipation	41	27.3	11	7.3	15	10.0
Nausea	29	19.3	33	22.0	17	11.3
Anorexia	18	12.0	11	7.3	5	3.3
Dyspepsia	18	12.0	17	11.3	9	6.0
Diarrhea	7	4.7	22	14.7	14	9.3
Flatulence	5	3.3	2	1.3	5	3.3
Rectal Disorder	3	2.0	0	0.0	0	0.0
Tooth Disorder	2	1.3	2	1.3	4	2.7
Vomiting	2	1.3	3	2.0	3	2.0
Increased Appetite	1	0.7	1	0.7	4	2.7

Source: section 14, Table 4.1

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

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom

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Table 47. TES Reported in ≥2% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=150		FLX N=150		PBO N=150	
	n	%	n	%	n	%
METABOLIC AND NUTRITIONAL	9	6.0	6	4.0	6	4.0
Weight Loss	4	2.7	5	3.3	3	2.0
Weight Gain	3	2.0	0	0.0	2	1.3
MUSCULO-SKELETAL	3	2.0	8	5.3	10	6.7
Myalgia	2	1.3	4	2.7	4	2.7
Arthralgia	0	0.0	1	0.7	3	2.0
NERVOUS	92	61.3	82	54.7	53	35.3
Insomnia	45	30.0	32	21.3	14	9.3
Dizziness	23	15.3	15	10.0	9	6.0
Nervousness	16	10.7	14	9.3	7	4.7
Somnolence	14	9.3	21	14.0	10	6.7
Anxiety	13	8.7	17	11.3	11	7.3
Paresthesia	13	8.7	3	2.0	4	2.7
Agitation	6	4.0	3	2.0	2	1.3
Libido Decreased	6	4.0	7	4.7	4	2.7
Akathisia	5	3.3	4	2.7	1	0.7
Abnormal Dreams	2	1.3	3	2.0	0	0.0
Amnesia	3	2.0	5	3.3	1	0.7
Depression	2	1.3	4	2.7	5	3.3
Hypertonia	2	1.3	4	2.7	2	1.3
Thinking Abnormal	2	1.3	3	2.0	2	1.3
Tremor	2	1.3	5	3.3	1	0.7
Sleep Disorder	1	0.7	3	2.0	1	0.7
Apathy	0	0.0	4	2.7	2	1.3
RESPIRATORY	26	17.3	18	12.0	25	16.7
Pharyngitis	12	8.0	6	4.0	6	4.0
Sinusitis	6	4.0	4	2.7	5	3.3
Cough Increased	4	2.7	4	2.7	6	4.0
Rhinitis	4	2.7	1	0.7	6	4.0
Bronchitis	3	2.0	0	0.0	2	1.3
Yawn	1	0.7	4	2.7	0	0.0
Dyspnea	0	0.0	1	0.7	5	3.3

Source: section 14, Table 4.1

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

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom

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Table 47. TES Reported in ≥2% of Patients in Any Treatment Group

COSTART Body System/Preferred Term*	RBX N=150		FLX N=150		PBO N=150	
	n	%	n	%	n	%
SKIN	35	23.3	20	13.3	13	8.7
Sweating	26	17.3	11	7.3	2	1.3
Rash	6	4.0	4	2.7	4	2.7
Hair Disorder	3	2.0	0	0.0	0	0.0
Pruritus	3	2.0	3	2.0	2	1.3
SPECIAL SENSES	19	12.7	14	9.3	7	4.7
Taste Perversion	7	4.7	1	0.7	2	1.3
Abnormality of Accommodation	3	2.0	3	2.0	2	1.3
Otitis Media	3	2.0	0	0.0	0	0.0
Tinnitus	2	1.3	3	2.0	1	0.7
UROGENITAL	50	33.3	23	15.3	21	14.0
Impotence	15	10.0	3	2.0	3	2.0
Abnormal Ejaculation	11	7.3	1	0.7	0	0.0
Urination Impaired	11	7.3	0	0.0	0	0.0
Dysmenorrhea	6	4.0	4	2.7	6	4.0
Urinary Retention	6	4.0	0	0.0	0	0.0
Urinary Frequency	5	3.3	2	1.3	4	2.7
Testis Disorder	4	2.7	0	0.0	1	0.7
Dysuria	3	2.0	0	0.0	1	0.7
Urogenital Disorder	3	2.0	0	0.0	0	0.0
Anorgasmia	1	0.7	5	3.3	0	0.0
Menstrual Disorder	0	0.0	3	2.0	0	0.0

Source: section 14, Table 4.1
*Arranged in decreasing order of frequency based on the reboxetine group.
Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom
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Of the TES reported in at least 5% of reboxetine-treated patients, the following were reported at least twice as frequently in the reboxetine-treated patients as in the placebo-treated patients: flu syndrome, chills, palpitation, vasodilation, dry mouth, constipation, anorexia, dyspepsia, insomnia, dizziness, nervousness, paresthesia, pharyngitis, sweating, impotence, abnormal ejaculation, and impaired urination. Of the TES reported in at least 5% of fluoxetine-treated patients, the following were reported at least twice as frequently in the fluoxetine-treated patients as in the placebo-treated patients: vasodilation, anorexia, insomnia, somnolence, and sweating.

Of the TES reported in at least 5% of reboxetine-treated patients, the following were reported at least twice as frequently in the reboxetine-treated patients as in the fluoxetine-treated patients: flu syndrome, back pain, chills, palpitation, dry mouth, constipation, paresthesia, pharyngitis, sweating, impotence, abnormal ejaculation, and impaired urination. Of the TES reported in at least 5% of fluoxetine-treated patients, diarrhea was reported at least twice as frequently in the fluoxetine-treated patients as in the reboxetine-treated patients.

10.4.1.4 TES by Maximum Intensity

The majority of patients in each treatment group reported TES that were mild to moderate in maximum intensity: 73.3% (110 of 150) in the reboxetine group, 63.3% (95 of 150) in the fluoxetine group, and 69.3% (104 of 150) in the placebo group. At least 1 severe TES was reported in 18.7% (28 of 150) of the patients in the reboxetine group, in 22.7% (34 of 150) of the patients in the fluoxetine group, and in 8.7% (13 of 150) of the patients in the placebo group (section 14, Tables 5.1 and 5.2). All TES are summarized by maximum intensity in section 14, Tables 5.1 and 5.2.

10.4.1.5 TES by Sex

At least 1 TES was reported in 91.5% (86 of 94) of the female reboxetine-treated patients and in 92.9% (52 of 56) of the male reboxetine-treated patients, compared with 88.9% (88 of 99) of the female fluoxetine-treated patients, 80.4% (41 of 51) of the male fluoxetine-treated patients, 84.4% (76 of 90) of the female placebo-treated patients, and 68.3% (41 of 60) of the male placebo-treated patients. Few clinically significant differences were noted in the frequency of TES by sex. TES reported in at least 5% of the patients in any treatment group are summarized by sex in Table 48.

Table 48. TES Reported in at Least 5% of Patients in Any Treatment Group, by Sex

COSTART Body System/ Preferred Term*	Reboxetine		Fluoxetine		Placebo	
	Female N=94	Male N=56	Female N=99	Male N=51	Female N=90	Male N=60
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients With at Least 1 TES	86 (91.5)	52 (92.9)	88 (88.9)	41 (80.4)	76 (84.4)	41 (68.3)
Body						
Headache	41 (43.6)	17 (30.4)	40 (40.4)	18 (35.3)	41 (45.6)	10 (16.7)
Infection	14 (14.9)	12 (21.4)	14 (14.1)	9 (17.6)	8 (8.9)	8 (13.3)
Asthenia	9 (9.6)	3 (5.4)	8 (8.1)	5 (9.8)	8 (8.9)	3 (5.0)
Flu Syndrome	10 (10.6)	2 (3.6)	4 (4.0)	2 (3.9)	2 (2.2)	2 (3.3)
Back Pain	8 (8.5)	2 (3.6)	2 (2.0)	1 (2.0)	4 (4.4)	5 (8.3)
Abdominal Pain	8 (8.5)	1 (1.8)	5 (5.1)	3 (5.9)	8 (8.9)	5 (8.3)
Chills	7 (7.4)	2 (3.6)	1 (1.0)	1 (2.0)	1 (1.1)	0
Pain	5 (5.3)	1 (1.8)	5 (5.1)	2 (3.9)	2 (2.2)	4 (6.7)
Neck Pain	2 (2.1)	0	0	0	2 (2.2)	3 (5.0)
Cardiovascular						
Palpitation	9 (9.6)	5 (8.9)	4 (4.0)	1 (2.0)	4 (4.4)	1 (1.7)
Vasodilation	10 (10.6)	2 (3.6)	4 (4.0)	5 (9.8)	1 (1.1)	0
Hypertension	4 (4.3)	3 (5.4)	2 (2.0)	0	1 (1.1)	2 (3.3)
Tachycardia	6 (6.4)	1 (1.8)	1 (1.0)	0	0	1 (1.7)
Digestive						
Dry Mouth	37 (39.4)	25 (44.6)	17 (17.2)	6 (11.8)	11 (12.2)	4 (6.7)
Constipation	29 (30.4)	12 (21.4)	8 (8.1)	3 (5.9)	10 (11.1)	5 (8.3)
Nausea	21 (22.3)	8 (14.3)	25 (25.3)	8 (15.7)	13 (14.4)	4 (6.7)
Anorexia	12 (12.8)	6 (10.7)	9 (9.1)	2 (3.9)	3 (3.3)	2 (3.3)
Dyspepsia	12 (12.8)	6 (10.7)	12 (12.1)	5 (9.8)	6 (6.7)	3 (5.0)
Diarrhea	6 (6.4)	1 (1.8)	14 (14.1)	8 (15.7)	9 (10.0)	5 (8.3)
Vomiting	0	2 (3.6)	0	3 (5.9)	2 (2.2)	1 (1.7)
Nervous						
Insomnia	33 (35.1)	12 (21.4)	21 (21.2)	11 (21.6)	9 (10.0)	5 (8.3)
Dizziness	14 (14.9)	9 (16.1)	13 (13.1)	2 (3.9)	7 (7.8)	2 (3.3)
Nervousness	11 (11.7)	5 (8.9)	10 (10.1)	4 (7.8)	4 (4.4)	3 (5.0)
Somnolence	10 (10.6)	4 (7.1)	16 (16.2)	5 (9.8)	6 (6.7)	4 (6.7)
Anxiety	8 (8.5)	5 (8.9)	10 (10.1)	7 (13.7)	9 (10.0)	2 (3.3)
Paresthesia	5 (5.3)	8 (14.3)	1 (1.0)	2 (3.9)	2 (2.2)	2 (3.3)
Agitation	5 (5.3)	1 (1.8)	2 (2.0)	1 (2.0)	2 (2.2)	0
Libido Decreased	1 (1.1)	5 (8.9)	1 (1.0)	6 (11.8)	2 (2.2)	2 (3.3)

Source: section 14, Table 6.2

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

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom

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Table 48. TES Reported in at Least 5% of Patients in Any Treatment Group, by Sex

COSTART Body System/ Preferred Term*	Reboxetine		Fluoxetine		Placebo	
	Female N=94	Male N=56	Female N=99	Male N=51	Female N=90	Male N=60
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Depression	2 (2.1)	0	1 (1.0)	3 (5.9)	5 (5.6)	0
Respiratory						
Pharyngitis	8 (8.5)	4 (7.1)	3 (3.0)	3 (5.9)	3 (3.3)	3 (5.0)
Sinusitis	3 (3.2)	3 (5.4)	1 (1.0)	3 (5.9)	4 (4.4)	1 (1.7)
Cough Increased	2 (2.1)	2 (3.6)	3 (3.0)	1 (2.0)	1 (1.1)	5 (8.3)
Rhinitis	1 (1.1)	3 (5.4)	1 (1.0)	0	2 (2.2)	4 (6.7)
Dyspnea	0	0	1 (1.0)	0	5 (5.6)	0
Skin						
Sweating	15 (16.0)	11 (19.6)	7 (7.1)	4 (7.8)	0	2 (3.3)
Rash	3 (3.2)	3 (5.4)	3 (3.0)	1 (2.0)	4 (4.4)	0
Special Senses						
Taste Perversion	3 (3.2)	4 (7.1)	1 (1.0)	0	0	2 (3.3)
Urogenital						
Impotence	0	15 (26.8)	0	3 (5.9)	0	3 (5.0)
Abnormal Ejaculation	0	11 (19.6)	0	1 (2.0)	0	0
Urination Impaired	0	11 (19.6)	0	0	0	0
Dysmenorrhea	6 (6.4)	0	4 (4.0)	0	6 (6.7)	0
Urinary Retention	0	6 (10.7)	0	0	0	0
Urinary Frequency	1 (1.1)	4 (7.1)	1 (1.0)	1 (2.0)	2 (2.2)	2 (3.3)
Testis Disorder	0	4 (7.1)	0	0	0	1 (1.7)
Dysuria	0	3 (5.4)	0	0	0	1 (1.7)

Source: section 14, Table 6.2
*Arranged in decreasing order of frequency based on the reboxetine group.
Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom
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Of the TES reported in at least 5% of female reboxetine-treated patients, the following were reported at least twice as frequently in that group as in the female placebo-treated patients: flu syndrome, chills, pain, palpitation, vasodilation, hypertension, tachycardia, dry mouth, constipation, anorexia, insomnia, nervousness, paresthesia, agitation, pharyngitis, and sweating. Of the TES reported in at least 5% of male reboxetine-treated patients, the following were reported at least twice as frequently in that group as in the male placebo-treated patients: palpitation, vasodilation, dry mouth, constipation, anorexia, dyspepsia, vomiting, insomnia, nervousness, dizziness, anxiety, paresthesia, libido decreased, libido decreased, sinusitis, impotence, abnormal ejaculation, sweating, urination impaired, urinary retention, urinary frequency, testis disorder, and dysuria.

Of the TES reported in at least 5% of female reboxetine-treated patients, the following were reported at least twice as frequently in that group as in the female fluoxetine-treated patients: flu syndrome, chills, palpitation, vasodilation, hypertension, tachycardia, dry mouth, constipation, paresthesia, agitation, pharyngitis, sinusitis, sweating, and taste perversion. Of the TES reported in at least 5% of male reboxetine-treated patients, the following were reported at least twice as frequently in that group as in the male fluoxetine-treated patients: palpitation, hypertension, dry mouth, constipation, paresthesia, rhinitis, sweating, impotence, abnormal ejaculation, urination impaired, urinary retention, urinary frequency, testis disorder, and dysuria.

Of the TES reported in at least 5% of female fluoxetine-treated patients, diarrhea was reported at least twice as frequently in that group as in the female reboxetine-treated patients. Of the TES reported in at least 5% of male fluoxetine-treated patients, the following were reported at least twice as frequently in that group as in the male reboxetine-treated patients: asthenia, abdominal pain, pain, vasodilation, and diarrhea.

Of the TES reported in at least 5% of female reboxetine-treated patients, the following were reported at least twice as frequently in that group as in the male reboxetine-treated patients: flu syndrome, back pain, abdominal pain, chills, pain, vasodilation, tachycardia, and diarrhea. Of the TES reported in at least 5% of male reboxetine-treated patients, the following were reported at least twice as frequently in that group as in the female reboxetine-treated patients: paresthesia, taste perversion, urination impaired, urinary retention, urinary frequency, testis disorder, and dysuria. All TES are found by sex in section 14, Table 6.2.

10.4.1.6 Drug-related TES

TES that were judged by the investigators to have been caused by the investigational medication were reported in 84.7% (127 of 150) of reboxetine-treated patients, in 68.7% (103 of 150) of fluoxetine-treated patients, and in 50.7% (76 of 150) of placebo-treated patients. The drug-related TES reported in at least 5% of patients in any treatment group are summarized in Table 49.

Table 49. Drug-related* TES Reported in ≥5% Patients in Any Treatment Group

COSTART Body System/Preferred Term†	RBX N=150		FLX N=150		PBO N=150	
	n	%	n	%	n	%
Patients With At Least 1 Drug-Related TES	**127**	**84.7**	**103**	**68.7**	**76**	**50.7**
Body						
Headache	37	24.7	33	22.0	30	20.0
Asthenia	9	6.0	9	6.0	7	4.7
Cardiovascular						
Palpitation	12	8.0	3	2.0	3	2.0
Vasodilation	10	6.7	7	4.7	0	‡
Digestive						
Dry Mouth	62	41.3	22	14.7	14	9.3
Constipation	37	24.7	8	5.3	11	7.3
Nausea	27	18.0	23	15.3	13	8.7
Anorexia	17	11.3	9	6.0	3	2.0
Dyspepsia	12	8.0	10	6.7	6	4.0
Diarrhea	5	3.3	12	8.0	11	7.3
Nervous						
Insomnia	38	25.3	23	15.3	13	8.7
Dizziness	21	14.0	10	6.7	6	4.0
Nervousness	13	8.7	11	7.3	5	3.3
Paresthesia	13	8.7	2	1.3	3	2.0
Anxiety	12	8.0	13	8.7	6	4.0
Somnolence	12	8.0	19	12.7	7	4.7
Skin						
Sweating	23	15.3	11	7.3	2	1.3
Urogenital						
Impotence	15	10.0	3	2.0	3	2.0
Abnormal Ejaculation	11	7.3	1	0.7	0	‡
Urination Impaired	10	6.7	0	‡	0	‡

Source: section 14, Table 8.1

* TES 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.

‡ Percent of 0 events.

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom

Of the drug-related TES that were reported in at least 5% of patients in the reboxetine group, the following were reported at least twice as frequently in the reboxetine-treated patients than in the placebo-treated patients: palpitation, vasodilation, dry mouth, constipation, nausea, anorexia, dyspepsia, insomnia, dizziness, nervousness, paresthesia, anxiety, sweating,

impotence, abnormal ejaculation, and urination impaired. Of the drug-related TES that were reported in at least 5% of patients in the fluoxetine group, the following were reported at least twice as frequently in the fluoxetine-treated patients than in the placebo-treated patients: vasodilation, anorexia, nervousness, anxiety, somnolence, and sweating.

All drug-related TES are summarized by COSTART body system and preferred term in section 14, Table 8.1.

10.4.2 Deaths, Serious TES, and Discontinuations Due to TES

10.4.2.1 Deaths

No deaths were reported during this study (section 14, Table 1.3).

10.4.2.2 Serious TES

No serious TES were reported in any of the reboxetine-treated patients. Serious TES were reported in 0.7% (1 of 150) of the fluoxetine-treated patients and in 2.7% (4 of 150) of the placebo-treated patients. None of the serious TES were reported in more than 1 patient in any treatment group. The frequency of patients who experienced serious TES is summarized in Table 50. Narrative summaries for patients who experienced serious TES are provided in section 10.4.2.4.

Table 50. Frequency of Serious TES

COSTART Body System/Preferred Term∗	RBX N=150		FLX N=150		PBO N=150	
	n	%	n	%	n	%
At Least 1 Serious TES	**0**		**1**	**0.7**	**4**	**2.7**
Body	**0**		**1**	**0.7**	**3**	**2.0**
Abdominal Pain	0		0		1	0.7
Back Pain	0		0		1	0.7
Chest Pain	0		1	0.7	0	
Neck Pain	0		0		1	0.7
Suicide Attempt	0		0		1	0.7
Urogenital	**0**		**0**		**1**	**0.7**
Urinary Incontinence	0		0		1	0.7

Source: section 14, Table 13.1

∗Each patient is counted once per body system and once per COSTART term.

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine TES=treatment-emergent symptom

All serious TES are summarized by COSTART body system and preferred term in section 14, Table 13.1. Patients who experienced serious TES are listed in Appendix 15, Table 14.1 (by patient) and Table 14.2 (by body system and preferred term).

10.4.2.3 Discontinuations Due to TES

The proportion of patients who discontinued treatment due to TES was highest for patients in the reboxetine-treatment group, in which 18.0% (27 of 150) discontinued, compared with 6.7% of patients in the fluoxetine treatment group (10 of 150), and 8.0% of patients in the placebo treatment group (12 of 150). Digestive system-related events were the most commonly reported TES that led to discontinuation of reboxetine treatment, followed by nervous system-related events. Nervous system-related events were the most commonly reported TES that led to discontinuation of fluoxetine treatment; the same was true for discontinuation of placebo treatment. The TES that led to discontinuation of treatment in at least 1% the patients in any treatment group are summarized in Table 51.

Table 51. TES Leading to Discontinuation of Treatment in ≥1% of Treated Patients in Any Group

COSTART	RBX N=150		FLX N=150		PBO N=150	
Body System/Preferred Term	n	%	n	%	n	%
At Least 1 TES Leading to Discontinuation	**27**	**18.0**	**10**	**6.7**	**12**	**8.0**
Body	**6**	**4.0**	**2**	**1.3**	**1**	**0.7**
Asthenia	2	1.3	1	0.7	0	*
Headache	2	1.3	1	0.7	1	0.7
Cardiovascular	**8**	**5.3**	**0**	*	**1**	**0.7**
Hypertension	3	2.0	0	*	1	0.7
Tachycardia	3	2.0	0	*	1	0.7
Vasodilation	2	1.3	0	*	0	*
Digestive	**14**	**9.3**	**2**	**1.3**	**3**	**2.0**
Dry Mouth	5	3.3	0	*	0	*
Nausea	5	3.3	0	*	1	0.7
Constipation	3	2.0	1	0.7	0	*
Dyspepsia	2	1.3	0	*	1	0.7
Nervous	**12**	**8.0**	**6**	**4.0**	**7**	**4.7**
Dizziness	4	2.7	0	*	0	*
Insomnia	3	2.0	2	1.3	1	0.7
Agitation	2	1.3	0	*	1	0.7
Somnolence	2	1.3	0	*	0	*
Anxiety	1	0.7	2	1.3	2	1.3
Depression	0	*	1	0.7	5	3.3
Skin	**6**	**4.0**	**1**	**0.7**	**0**	*
Sweating	3	2.0	0	*	0	*
Rash	2	1.3	0	*	0	*
Urogenital	**9**	**6.0**	**1**	**0.7**	**1**	**0.7**
Abnormal Ejaculation	3	2.0	0	*	0	*
Impotence	3	2.0	0	*	1	0.7
Dysuria	2	1.3	0	*	0	*
Urinary Frequency	2	1.3	0	*	0	*
Urinary Retention	2	1.3	0	*	0	*
Urination Impaired	2	1.3	0	*	0	*

Source: section 14, Table 9.1

*Percent of 0 events.

Abbreviations: FLX=fluoxetine, PBO=placebo, RBX=reboxetine, TES=treatment-emergent symptom

10.4.2.4 Narratives

Below are the narratives for patients who experienced serious TES during the study by event (verbatim and by COSTART term). CRFs for these patients are available in Appendix 16.

Fluoxetine Group

Patient number: 1148 (Investigator: Croft—18851)

Events: Chest Pain and Chest Pressure (Chest Pain)

This 37-year-old female patient with a history of major depression entered the study on 27 August 1998 and began taking the study medication on the same date. The investigator did not note a history of cardiac problems. ECGs performed at the screening visit and on day 28 were both normal. The patient experienced severe chest pain/pressure beginning on 15 October 1998, and on that day, she interrupted her dosing schedule by not taking the evening dose of study medication (ie, 2 capsules). She also did not take the morning dose of study medication (ie, 1 capsule) on 16 October 1998. The patient went to the university hospital emergency room on 16 October 1998, where a chest x-ray and ECG were performed. She was subsequently diagnosed with noncardiac chest pain, which continued until 25 October 1998.

The patient resumed the treatment-dosing schedule on the evening of 16 October 1998; she completed study medication treatment on 21 October 1998. During the 56-day visit on 22 October 1998, the patient reported the previously described episode of chest pain and chest pressure to the investigator. The investigator considered these symptoms serious. The patient was maintained on the study and her treatment was not unblinded. The investigator and the medical monitor reported the serious adverse event while the treatment was still blinded.

Both the investigator and the medical monitor indicated that the events were possibly related to treatment with the study medication. The medical monitor indicated that, whereas the etiology of the chest pain and discomfort in this patient is unknown, the conditions that may cause chest pain (eg, angina pectoris) have been previously reported in study medication-treated patients. Concomitant medications taken by the patient during this study included acetaminophen, Rolaids, Tums, and acetaminophen extra-strength. The patient's noncardiac chest pain ended on 25 October 1998, without residual effects. The patient completed the study on 20 November 1998. The patient was scheduled for a 1-week interim follow-up visit.

Placebo Group

Patient number: 1027 (Investigator: Hertzman—11948)

Events: Worsening Back Pain (Back Pain) and Neck Pain (Neck Pain)

This 49-year-old male patient with a history of major depression entered the study on 12 June 1998 and began taking the study medication on the same day. The investigator noted a history of back/neck pain. On 23 July 1998, the patient experienced a worsening of his

back/neck pain, which required hospitalization on 3 August 1998. The patient was continued on the study medication and was discharged from the hospital on 4 August 1998. He continued to have episodic severe neck/back pain. He completed the study-treatment medication on 6 August 1998. This patient did not enter the posttreatment withdrawal phase of this study; he began taking another antidepressant medication on 8 August 1998.

Patient number: 1358 (Investigator: Ferguson—12411)

Event: Suicide Gesture (Suicide Attempt)

This 37-year-old male patient with a history of major depression entered the study on 28 October 1998. On 15 November 1998, he had 1 episode of suicidal gesture, which resolved on the same date, without residual effects. Neither the investigator nor the medical monitor considered this event related to the study medication. On 19 November 1998, based on the clinical judgment of the investigator, this patient was discontinued from the study medication. Rescue treatment was begun the same day. The patient did not complete the study.

Patient number: 1376 (Investigator: Ferguson—12411)

Event: Abdominal Pain (Abdominal Pain)

This 27-year-old female patient with a history of major depression entered the study on 3 November 1998 and began taking the study medication on the same date. The investigator noted a history of diarrhea and abdominal pain. On 23 November 1998, she began experiencing severe abdominal pain and was hospitalized on 24 November 1998 for an increase in pain intensity. The study medication was discontinued on 25 November 1998. This patient did not complete the study medication and her abdominal pain was not resolved. Neither the investigator nor the medical monitor judged this serious adverse event related to the study medication.

Patient number: 1211 (Investigator: Richter—13961)

Event: Urinary Stress Incontinence (Urinary Incontinence)

This 58-year-old female patient with a history of major depression entered the study on 31 August 1998 and began taking the study medication on the same date. The investigator noted a history of urinary stress incontinence. On 29 September 1998, the patient was hospitalized for bladder suspension surgery. The hospitalization was the basis of the serious adverse event. The study medication was not interrupted and the patient was discharged from the hospital on 1 October 1998. The patient had an unremarkable recovery. She completed the study medication on 25 October 1998 and completed the study on 20 November 1998. Neither the investigator nor the medical monitor judged this serious adverse event related to the study medication.

10.4.3 Clinical Laboratory Evaluation

10.4.3.1 Hematology

10.4.3.1.1 Mean Change from Baseline

No statistically significant differences were noted among the treatment groups in the mean change from baseline on days 28 or 56 for basophils, eosinophils, MCV, or monocytes. Statistically significant differences were noted among treatment groups in the mean change from baseline on both days 28 and 56 for erythrocytes, leukocytes, lymphocytes, neutrophils, and platelet count; on day 28 for hemoglobin, reticulocytes, and absolute reticulocytes; and on day 56 for hematocrit. With few exceptions, the differences resulted from the comparison between reboxetine and placebo rather than from fluoxetine and placebo. These data are summarized in section 14, Table 18.1.

For erythrocytes, hematocrit, hemoglobin, leukocytes, neutrophils, platelets, and reticulocytes (day 28 only), placebo treatment was associated with slight mean decreases in values on days 28 and 56 compared with those from baseline. Reboxetine treatment was associated with smaller mean decreases on the same days compared with baseline values, which resulted in statistically significant differences between reboxetine and placebo. However, the magnitude of these changes was small and was not clinically relevant. For erythrocytes, hematocrit, hemoglobin, leukocytes, lymphocytes, platelets, reticulocytes, and absolute reticulocytes, the mean values on days 28 and 56 were in the normal range following treatment with reboxetine, placebo, or fluoxetine.

For lymphocytes on day 56, placebo treatment was associated with slight mean increases compared with baseline values. Reboxetine treatment was associated with smaller mean increases on the same day compared with baseline values, which resulted in a statistically significant difference between reboxetine and placebo. However, the magnitude of the changes in either treatment group was small and was not clinically relevant.

10.4.3.1.2 Values Outside of Predefined Normal Ranges

The majority of patients in each treatment group had postbaseline hematology values that were within the predefined normal ranges (Appendix 15, Table 19.1). There was no evidence of a treatment-related effect on any hematologic assay.

The distribution of patients with hematology assay values outside of the predefined normal ranges is summarized in section 14, Table 19.1. Patients with hematology assay values outside of the predefined normal ranges are listed in Appendix 15, Table 20.1.

10.4.3.2 Serum Chemistry

10.4.3.2.1 Mean Change from Baseline

No statistically significant differences were noted among treatment groups in the mean change from baseline on days 28 or 56 for ALT, AST, BUN, total bilirubin, carbon dioxide, creatinine, glucose, potassium, or urea. Statistically significant differences were noted

among treatment groups in the mean changes from baseline on day 28 for alkaline phosphotase and chloride, as well as on day 56 for sodium and uric acid. section 14, Table 18.2, provides summary statistics for each serum chemistry assay.

For alkaline phosphotase, placebo treatment was associated with a slight mean decrease on day 28 compared with the baseline value, whereas reboxetine was associated with a slight mean increase compared with the baseline value, which resulted in a statistically significant difference between reboxetine and placebo. For chloride, placebo treatment was associated with a slight mean increase on day 28 compared with the baseline value, whereas reboxetine was associated with a slight mean decrease compared with the baseline value, which resulted in a statistically significant difference between reboxetine and placebo. For both alkaline phosphatase and chloride, the magnitudes of the changes from baseline to day 28 were small and were not clinically relevant. The mean values for both alkaline phosphatase and chloride on day 28 were within the normal range. On day 56, no statistically significant differences were noted among treatment groups.

For sodium, there was no statistically significant difference between reboxetine and placebo or between fluoxetine and placebo on day 56. For uric acid, there was no statistically significant difference between reboxetine and placebo on day 56, but there was a statistically significant difference between fluoxetine and placebo. The magnitudes of the changes from baseline for any of the treatment groups were not clinically relevant.

10.4.3.2.2 Values Outside of Predefined Normal Ranges

The majority of patients in each treatment group had postbaseline serum chemistry values that were within the predefined normal ranges (section 14, Table 19.2). The percentages of patients who had liver or renal function tests that were normal at baseline but above the predefined normal limits postbaseline are summarized in Table 52. The percentages of patients with an abnormal postbaseline value were similar among treatment groups. There was no evidence of a treatment-related effect.

Table 52. Patients With at Least 1 Postbaseline Value Above the Predefined Normal Limits* for Liver or Renal Function Tests

Test*	RBX		FLX		PBO	
	N†	n (%)‡	N†	n (%)‡	N†	n (%)‡
Alkaline Phosphatase	122	10 (8.2)	116	4 (3.4)	118	3 (2.5)
Total Bilirubin	128	2 (1.6)	132	4 (3.0)	121	6 (5.0)
AST	124	18 (14.5)	122	12 (9.8)	113	7 (6.2)
ALT	114	16 (14.0)	120	13 (10.8)	103	10 (9.7)
Creatinine	92	26 (28.3)	82	30 (36.6)	91	20 (22.0)
Urea nitrogen	129	4 (3.1)	135	4 (3.0)	126	2 (1.6)

Source: section 14, Table 19.2

* Predefined normal limits: alkaline phosphatase 81-482 U/L, depending on sex and age of patient; total bilirubin 0.1-1.1 mg/dL; AST 12-31 U/L; ALT 10-45 U/L for males and 9-29 U/L for females; creatinine 0.8-1.2 mg/dL for males and 0.6-0.9 mg/dL for females; and urea nitrogen 17-51 mg/dL for males and 13-4 mg/dL for females.

† Number of patients with a normal baseline value and at least 1 postbaseline measurement.

‡ Percent (%) of patients with a normal baseline value and at least 1 postbaseline value exceeding the predefined normal limits.

Abbreviations: RBX=reboxetine, FLX=fluoxetine, PBO=placebo

The distribution of patients with serum chemistry assay values outside of the predefined normal ranges is summarized in section 14, Table 19.2. Patients with serum chemistry assay values outside of the predefined normal ranges are listed in Appendix 15, Table 20.2.

10.4.3.3 Urine Drug Screen

The majority of patients in each treatment group had urine drug screen values at the end of the treatment period (day 56) that were within the predefined normal ranges. The distribution of patients with urine drug screen values outside of the predefined normal ranges is summarized in section 14, Table 19.3. For each of the assays, similar percentages of patients among the 3 treatment groups had values outside of normal ranges. Patients with urine drug screen values outside of the predefined normal ranges are listed in Appendix 15, Table 20.3.

10.4.4 Vital Signs

10.4.4.1 Mean Change from Baseline

No statistically significant differences were observed among treatment groups in the mean change from baseline in systolic blood pressure at any evaluation (section 14, Table 15.1).

Statistically significant differences were observed among treatment groups in the mean change from baseline in the diastolic blood pressure on days 28, 35, 49, and 56 (section 14,

Table 15.2). Statistically significant differences were observed between the reboxetine- and placebo-treatment groups in the mean change from baseline in the diastolic blood pressure on days 35, 49, and 56. Increases in mean diastolic blood pressure observed for patients in the reboxetine-treatment group were 2.8, 3.3, and 2.4 mm Hg on days 35, 49, and 56, respectively. Changes in the mean diastolic blood pressure observed for patients in the placebo-treatment group were 0.0, +0.6, and –0.6 mm Hg on days 35, 49, and 56, respectively. The increases in blood pressure observed for patients in the reboxetine treatment group were small and did not continue to increase as a function of time; they were not clinically relevant.

Statistically significant differences were observed among treatment groups in the mean change from baseline in the sitting pulse rate on all evaluations from day 7 through day 70 (section 14, Table 15.3). On days 7 through 70 for the reboxetine treatment group, the mean change varied between +6.1 and +9.4 beats per minute, whereas for the fluoxetine treatment, the mean change in the number of beats per minute varied between –0.7 and –3.3, and for the placebo group, the mean change in the number of beats per minute varied between +2.1 and -0.5. These data are summarized in Table 53.

Table 53. Mean Change in Sitting Pulse Rate

Visit Day	Mean Change From Baseline (beats/minute)					
	RBX N=150		FLX N=150		PBO N=150	
	n	Mean Change	n	Mean Change	n	Mean Change
7	143	6.1*	137	-1.8	135	0.3
14	128	6.1*	129	-2.0	123	0.3
21	112	6.9*	124	-1.7	122	-0.5
28	106	7.1*	123	-3.3*	115	-0.2
35	103	7.8*	113	-0.7	107	0.5
42	90	9.4*	106	-2.0*	100	1.0
49	94	8.2*	103	-2.3*	90	2.1
56	94	8.1*	108	-1.9	90	0.3
70	73	6.8*	77	-1.0	69	0.4
84	54	1.3	62	-0.8	58	1.3

Source: section 14, Table 15.3
*P-values versus placebo <0.05.

Statistically significant differences were observed among treatment groups in the mean change from baseline body weight at study days 49, 56, 70, and 84 (section 14, Table 15.4).

Statistically significant differences between the reboxetine- and placebo-treated groups were noted at days 49, 56, 70, and 84 and between the fluoxetine- and placebo-treated groups at days 49, 56, and 70. For the above days, the mean weight loss of patients in the reboxetine-treatment group varied between 2.1 and 4.1 lbs, whereas during the same period, the mean weight change for patients in the fluoxetine-treatment group varied between a loss of 1.5 lbs and a gain of 0.2 lbs, and for the placebo group, the mean weight gain varied between 1.6 and 2.9 lbs. Although statistically significant, the observed differences were not clinically important.

10.4.4.2 Values Outside of Predefined Limits

Fewer than 5% of the patients in any treatment group had a postbaseline vital sign that was outside of the predefined limits. Greater numbers of patients in the reboxetine group than in either the fluoxetine or placebo group had at least 1 postbaseline value for blood pressure and/or pulse that was outside of the predefined normal limits (section 14, Table 16.1). These data are summarized in Table 54.

Table 54. Patients With Postbaseline Vital Signs Outside of the Predefined Limits

Variable	Predefined Limit	RBX		FLX		PBO	
		N*	n (%)†	N*	n (%)†	N*	n (%)†
Systolic BP	≥180 mm Hg	144	2 (1.4)	144	0	142	0
	≤90 mm Hg	144	6 (4.2)	144	2 (1.4)	142	6 (4.2)
Diastolic BP	≥105 mm Hg	141	5 (3.5)	143	1 (0.7)	144	0
	≤50 mm Hg	141	4 (2.8)	143	3 (2.1)	144	1 (0.7)
Pulse	≥120 beats/min	144	4 (2.8)	145	1 (0.7)	144	1 (0.7)
	≤50 beats/min	144	0	145	1 (0.7)	144	3 (2.1)

Source: section 14, Table 16.1

* Number of patients with a normal baseline value and at least 1 postbaseline measurement.

† Percent (%) of patients with a normal baseline value and at least 1 postbaseline value exceeding the predefined normal limits.

Abbreviations: BP=blood pressure, FLX=fluoxetine, PBO=placebo, RBX=reboxetine

Two of the 144 patients (1.4%) for whom data were available in the reboxetine group had high values for systolic blood pressure (greater than or equal to 180 mm Hg), whereas none of the patients in either the fluoxetine or placebo groups had high values for systolic blood pressure. Low values for systolic blood pressure (less than or equal to 90 mm Hg) were noted for 4.2% of the patients in both the reboxetine (6 of 144) and placebo (6 of 142) groups, whereas 1.4% (2 of 144) of the fluoxetine-treated patients had low values for systolic blood pressure. For diastolic blood pressure, 3.5% (5 of 141) of patients in the reboxetine group had high values (greater than or equal to 105 mm Hg), whereas 0.7% (1 of 143) of patients in the fluoxetine group and none in the placebo group had high values; 2.8% (4 of

141) of patients in the reboxetine group had low values for diastolic blood pressure (less than or equal to 50 mm Hg), compared with 2.1% (3 of 143) of patients in the fluoxetine group and 0.7% (1 of 144) in the placebo group.

Four of 144 patients (2.8%) in the reboxetine group had high values for pulse (greater than or equal to 120 beats per minute), whereas 1 patient in each of the other 2 treatment groups (0.7%) had a high value for pulse. None of the patients in the reboxetine group had low values for pulse (less than or equal to 50 beats per minute), whereas 0.7% (1 of 145) of the patients in the fluoxetine group and 2.1% (3 of 144) of the patients in the placebo group had a low value for pulse.

The patients who had values outside the predefined limits for systolic or diastolic blood pressure and/or pulse rate are listed in Appendix 15, Table 17.1. There were no clinically relevant differences among treatment groups in the frequency of patients who had vital sign values outside of the predefined limits. The majority of the patients in each treatment group with a postbaseline vital sign outside of a predefined limit had only a single abnormal vital sign value. There was no apparent pattern in the occurrence of the abnormalities in any group, and the majority of the patients in each treatment group had values that were within the predefined limits at the end of the study.

10.4.5 Electrocardiograms

10.4.5.1 Treatment-emergent Abnormalities

Of the reboxetine-treated patients, 18.3% (24 of 131) of those with a normal ECG at baseline had an abnormal ECG at the end of the study, whereas 21.5% (29 of 137) of the fluoxetine-treated patients had an abnormal end-of-study ECG after having had a normal baseline ECG. These abnormalities occurred more frequently in the active-treatment group patients than in the placebo-treated patients, for whom an abnormal end-of-study ECG was reported following a normal baseline ECG in 10.2% (13 of 137). The ECG shifts from baseline to the end of the study are summarized in section 14, Table 22.1.

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

10.4.5.2.1 Mean Change from Baseline

Statistically significant differences were observed among treatment groups in the mean change from baseline at day 56 (end of treatment period) in QRS and QT intervals (section 14, Table 21.1). However, statistically significant differences between patients in the reboxetine- and placebo-treatment groups or between patients in the fluoxetine- and placebo-treatment groups in the mean change from baseline at day were noted only for the QT interval. Mean changes in the QRS interval were –0.7, 1.3, and 0.2 msec for patients in the reboxetine-, fluoxetine-, and placebo-treatment groups, respectively. Mean changes in the QT interval were –20.7, 4.2, and –3.4 msec for patients in the reboxetine-, fluoxetine-, and placebo-treatment groups, respectively. When the QT intervals were corrected for heart rate

using either the Bazett or Fridericia correction formula, no statistically significant differences were observed among treatment groups for the corrected QT interval (QTc).

Statistically significant differences were observed among treatment groups in the mean change from baseline at day 56 (ie, the end of the treatment period) in heart rate, as measured with ECG. Statistically significant differences between patients in the reboxetine- and placebo-treatment groups and between patients in the fluoxetine- and placebo-treatment groups were observed. There was a mean change of +12.3, –0.2, and +3.2 beats per minute for patients in the reboxetine-, fluoxetine-, and placebo-treatment groups, respectively.

10.4.5.2.2 Values Outside of Predefined Limits

Few patients with normal baseline values for ECG parameters had a clinically significant abnormal postbaseline ECG value. Table 55 summarizes the frequency of patients with values outside of the predefined limits for ECG parameters (eg, PR, QRS, QT, or QTc intervals) based upon the numbers of patients with normal baseline values and at least 1 clinically abnormal postbaseline ECG value. These data are listed by patient in Appendix 15, Tables 24.1 and 25.1.

Table 55. Patients With at Least 1 Postbaseline ECG Value Exceeding the Predefined Limits

Parameter	Limit	RBX		FLX		PBO	
		N*	n (%)†	N*	n (%)†	N*	n (%)†
Bradycardia	≤50 beats/min	122	1 (0.8)	133	5 (3.8)	121	1 (0.8)
Tachycardia	≥120 beats/min	122	1 (0.8)	133	0	121	0
PR Interval	≤110 msec	124	2 (1.6)	131	1 (0.8)	123	1 (0.8)
	≥210 msec	124	0	131	0	123	3 (2.4)
QRS Interval	≤30 msec	125	0	132	0	126	0
	≥110 msec	125	0	132	0	126	2 (1.6)
QT Interval	≥470 msec	128	0	134	1 (0.7)	125	0
QTc Interval	≥450 msec (males) ≥470 msec (females)	127	2 (1.6)	134	0	126	1 (0.8)

Source: section 14, Table 23.1

* Number of patients with a normal baseline value and at least 1 postbaseline measurement.

† Percent (%) of patients with a normal baseline value and at least 1 clinically significant abnormal postbaseline ECG.

Abbreviations: RBX=reboxetine, FLX=fluoxetine, PBO=placebo

10.4.6 Exposure In Utero

Despite the fact that patients who were pregnant were excluded from this study and that clear instructions were given to the patients to practice effective contraception, 3 pregnancies occurred among the 450 treated patients in this study. All 3 patients had been randomized to the fluoxetine-treatment group. One patient underwent an induced abortion; no anomalies were observed or detected in the fetus. Each of the other 2 patients delivered a single live-birth infant; no abnormalities were observed or detected in either infant. CRFs for these patients are available in Appendix 17. Available information for each case is summarized below:

Fluoxetine Group

Patient number: 1422 (Investigator: Davidson– 11670)

Event: Pregnancy (Unintended Pregnancy)

This 26-year-old female patient with a history of major depression entered the study on 3 February 1999 and began taking the study medication on the same date. The serum pregnancy test performed at the screening visit (25 January 1999) was negative. The patient completed the study according to the protocol. Her last dose of study medication was taken on 31 March 1999. Due to inadequate response to the study medication, the patient did not complete the posttreatment follow-up period. However, in June 1999 an " Exposure in Utero" follow-up report form was received. This report indicated that the patient underwent an induced abortion on 16 April 1999. No fetal anomalies were observed/detected. This was not a multiple gestation pregnancy. No other information is available.

Patient number: 1306 (Investigator: Ferguson– 12411)

Event: Pregnancy (Unintended Pregnancy)

This 36-year-old female patient with a history of major depression entered the study on 11 February 1999 and began taking the study medication on the same date. The serum pregnancy test performed at the screening visit (8 February 1999) was negative. On 24 February 1999, the patient discontinued the study medication, reporting that she was pregnant. An early termination serum pregnancy test performed on 26 February 1999 was negative. This patient's expected delivery date was estimated as 28 October 1999. In November 1999, an "Exposure in Utero" form was received, which reported a single live birth on 28 October 1999. No infant abnormalities were observed or detected. No other information is available.

Patient number: 1199 (Investigator: Ferguson– 12411)

Event: Pregnancy (Unintended Pregnancy)

This 22-year-old female patient with a history of major depression entered the study on 2 September 1998 and began taking the study medication on the same date. On 27 October 1998 (day 56), the patient completed taking the study medication. The termination serum pregnancy test performed on 3 November 1998 was positive. In November 1999, an "Exposure in Utero" form was received, which reported a single live birth on 29 June 1999. No infant abnormalities were observed or detected. No other information is available.

10.4.7 Discontinuation-emergent Symptoms

10.4.7.1 Brief Summary of DES

At least 1 DES was reported in similar percentages of patients in each of the 3 treatment groups: 58.3% (49/84) in the reboxetine group, 62.4% (53/85) in the fluoxetine group, and 58.8% (40/68) in the placebo group. Drug-related DES were reported in 15.5% (13/84) of the patients in the reboxetine group, in 10.6% (9/85) of the patients in the fluoxetine group, and in 14.7% (10/68) of the patients in the placebo group. Serious DES were reported in 2.4% (2/84) of the patients in the reboxetine group and in 1.2% (1/85) of the patients in the fluoxetine group, whereas none were reported in patients in the placebo group. The percentages of patients discontinuing due to a DES were 3.6% (3/84) in the reboxetine group and 2.4% (2/85) in the fluoxetine group, whereas none of the patients in the placebo group discontinued due to a DES. Table 56 presents an overview of the numbers of patients with at least 1 DES.

Table 56. Overall Summary of DES

	RBX N∗=84		FLX N∗=85		PBO N∗=68	
	n	%	n	%	n	%
Patients with at least 1 DES	49	58.3	53	62.4	40	58.8
Drug-Related	13	15.5	9	10.6	10	14.7
Serious	2	2.4	1	1.2	0	
Patients who discontinued due to at least 1 DES	3	3.6	2	2.4	0	

Source: section 14, Tables 4.1F, 8.1F, 9.1F, and 13.1F

∗ N = number of ITT patients entering the posttreatment follow-up period.

Abbreviations: DES=discontinuation-emergent symptom; FLX=fluoxetine, PBO=placebo, RBX=reboxetine,

10.4.7.2 DES by Body System

The frequency of reported DES was similar among treatment groups. At least 1 DES was reported in 58.3% (49/84) of the patients in the reboxetine group, by 62.4% (53/85) of the patients in the fluoxetine group, and for 58.8% (40/68) of the patients in the placebo group (section 14, Table 4.1F). The frequency of DES is summarized by body system in Table 57.

Table 57. Frequency of DES by Body System

Body System†	RBX N=84*		FLX N=85*		PBO N=68*	
	n	%	n	%	n	%
Patients With At Least 1 DES	**49**	**58.3**	**53**	**62.4**	**40**	**58.8**
Nervous	24	28.6	25	29.4	16	23.5
Body	20	23.8	23	27.1	21	30.9
Digestive	9	10.7	9	10.6	0	
Skin	2	2.4	2	2.4	1	1.5
Respiratory	3	3.6	3	3.5	3	4.4
Cardiovascular	5	6.0	2	2.4	1	1.5
Urogenital	3	3.6	3	3.5	2	2.9
Special Senses	2	2.4	1	1.2	0	
Musculo-Skeletal	1	1.2	4	4.7	3	4.4
Metabolic and Nutritional	1	1.2	1	1.2	3	4.4
Endocrine	0		1	1.2	0	

Source: section 14, Table 4.1F

* N= Number of ITT patients who entered follow-up.

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

Abbreviations: DES=discontinuation-emergent symptom, FLX=fluoxetine, PBO=placebo, RBX=reboxetine

Nervous system-related events were the most frequently reported events in each active-treatment group, followed by body system- and digestive system-related events. Body-system related events were the most frequently reported in the placebo group, followed by nervous system-related events; no digestive-system related events were reported in patients in the placebo group. DES related to the digestive, cardiovascular, and special senses body systems were reported at least 2 times more frequently in the reboxetine group than in the placebo group, whereas DES related to the digestive body systems were reported at least 2 times more frequently in the fluoxetine group than in the placebo group.

Cardiovascular and special senses system-related DES were reported at least 2 times more frequently in patients in the reboxetine group than in patients in the fluoxetine group. Musculo-skeletal and endocrine system-related events were reported at least 2 times more frequently in patients in the fluoxetine group than in patients in the reboxetine group.

section 14, Table 4.1F summarizes all of the DES that were reported during the study by body system and treatment group. The patients who reported DES are listed in Appendix 15, Table 7.1F (by patient) and Table 7.2F (by body system and COSTART term).

10.4.7.3 DES by COSTART Preferred Term

The DES that were reported in ≥2% or more of the patients in any treatment group are summarized in Table 58.

Table 58. DES Reported in ≥ 2% of Patients in Any Treatment Group

COSTART	RBX N†=84		FLX N†=85		PBO N†=68	
Body System/Preferred Term*	n	%	n	%	n	%
NERVOUS	**24**	**28.6**	**25**	**29.4**	**16**	**23.5**
Depression	13	15.5	13	15.3	9	13.2
Somnolence	5	6.0	0		0	
Nervousness	3	3.6	4	4.7	0	
Anxiety	2	2.4	3	3.5	1	1.5
Apathy	2	2.4	2	2.4	0	
Insomnia	2	2.4	6	7.1	5	7.4
BODY	**20**	**23.8**	**23**	**27.1**	**21**	**30.9**
Headache	9	10.7	14	16.5	8	11.8
Infection	6	7.1	0		5	7.4
Malaise	2	2.4	0		1	1.5
Asthenia	1	1.2	2	2.4	3	4.4
Back Pain	1	1.2	2	2.4	1	1.5
Accidental Injury	0		0		4	5.9
Flu Syndrome	0		2	2.4	1	1.5
DIGESTIVE	**9**	**10.7**	**9**	**10.6**	**0**	
Nausea	3	3.6	2	2.4	0	
Diarrhea	1	1.2	3	3.5	0	
SKIN	**2**	**2.4**	**2**	**2.4**	**1**	**1.5**
Skin Disorder	0		2	2.4	0	
RESPIRATORY	**3**	**3.6**	**3**	**3.5**	**3**	**4.4**
Sinusitis	2	2.4	2	2.4	2	2.9
CARDIOVASCULAR	**5**	**6.0**	**1**	**1.5**	**2**	**2.4**
Hypertension	2	2.4	0		0	
Tachycardia	2	2.4	0		0	
Palpitation			2	2.4	1	1.5
UROGENITAL	**3**	**3.6**	**3**	**3.5**	**2**	**2.9**
Urinary Tract Infection	2	2.4	2	2.4	0	
MUSCULO-SKELETAL	**1**	**1.2**	**4**	**4.7**	**3**	**4.4**
Myalgia	1	1.2	4	4.7	2	2.9
METABOLIC AND NUTRITIONAL	**1**	**1.2**	**1**	**1.2**	**3**	**4.4**
SGPT Increased	1	1.2	0		2	2.9

Source: section 14, Table 4.1F

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

† Number of ITT patients who entered the posttreatment follow-up period.

Abbreviations: DES=discontinuation-emergent symptom; FLX=fluoxetine; PBO=placebo; RBX=reboxetine

Within the reboxetine-treatment group, the most common DES (reported in at least 5% of patients) were depression, somnolence, headache, and infection. Within the fluoxetine-treatment group, the most common DES (reported in at least 5% of patients) were depression, insomnia, and headache. Within the placebo-treatment group, the most common DES (reported in at least 5% of patients) were depression, insomnia, headache, infection, and accidental injury.

Of the DES that were reported in at least 5% of reboxetine-treated patients, somnolence was reported at least 2 times more frequently in reboxetine-treated patients than in placebo-treated patients. Of the DES that were reported in at least 5% of fluoxetine-treated patients, none were reported at least 2 times more frequently in fluoxetine-treated patients than in placebo-treated patients.

The following DES were reported at least 2 times more frequently in reboxetine-treated patients than in fluoxetine-treated patients: somnolence, infection, malaise, hypertension, and tachycardia. Insomnia, asthenia, back pain, flu syndrome, diarrhea, skin disorder, palpitation, and myalgia were DES that were reported at least 2 times more frequently in fluoxetine-treated patients than in reboxetine-treated patients.

10.4.7.4 DES by Maximum Intensity

The majority of DES reported in patients in each treatment group were mild to moderate in maximum intensity: 88% (43/49) of the patients in the reboxetine group, 87% (46/53) of the patients in the fluoxetine group, and 95% (38/40) of the patients in the placebo group experienced at least 1 DES of mild or moderate intensity. Severe DES were reported in 12% (6/49) of the patients in the reboxetine group for whom at least 1 DES was reported, in 13% (7/53) of the patients in the fluoxetine group, and in 5% (2/40) of the patients in the placebo group.

Depression was the only DES reported as severe in at least 2 patients in any treatment group (1/84, 1% of reboxetine-treated patients who entered follow-up; 3/85, 4% of fluoxetine-treated patients who entered follow-up; and 2/68, 3% of placebo-treated patients who entered follow-up). All DES are summarized by maximum intensity in section 14, Tables 5.1F and 5.2F.

10.4.7.5 DES by Sex

At least 1 DES was reported in 64% (37/58) of the female reboxetine-treated patients and in 46% (12/26) of the male reboxetine-treated patients, compared with 71% (41/58) of the female fluoxetine-treated patients and 44% (12/27) of the male fluoxetine-treated patients. Within the placebo treatment group, 64% (28/44) of females and 50% (12/24) of males reported at least 1 DES. The DES reported in at least 5% of the patients in any treatment group are summarized by sex in Table 59.

Table 59. DES Reported in ≥5% of Patients in Any Treatment Group, by Sex

COSTART Body System/ Preferred Term	Reboxetine				Fluoxetine				Placebo			
	Female N=58		Male N=26		Female N=58		Male N=27		Female N=44		Male N=24	
	n	%	n	%	n	%	n	%	n	%	n	%
Patients With At Least 1 DES	**37**	**63.8**	**12**	**46.2**	**41**	**70.7**	**12**	**44.4**	**28**	**63.6**	**12**	**50.0**
BODY	**14**	**24.1**	**6**	**23.1**	**20**	**34.5**	**3**	**11.1**	**16**	**36.4**	**5**	**20.8**
Headache	4	6.9	5	19.2	12	20.7	2	7.4	7	15.9	1	4.2
Infection	3	5.2	3	11.5	0		0		4	9.1	1	4.2
Accidental Injury	0		0		0		0		2	4.5	2	8.3
DIGESTIVE	**7**	**12.1**	**2**	**7.7**	**8**	**13.8**	**1**	**3.7**	**0**		**0**	
Diarrhea	1	1.7	0		3	5.2	0		0		0	
MUSCULO-SKELETAL	**1**	**1.7**	**0**		**4**	**6.9**	**0**		**2**	**4.5**	**1**	**4.2**
Myalgia	1	1.7	0		4	6.9	0		1	2.3	1	4.2
NERVOUS	**21**	**36.2**	**3**	**11.5**	**18**	**31.0**	**7**	**25.9**	**8**	**18.2**	**8**	**33.3**
Depression	10	17.2	3	11.5	10	17.2	3	11.1	4	9.1	5	20.8
Somnolence	5	8.6	0		0		0		0		0	
Nervousness	3	5.2	0		4	6.9	0		0		0	
Insomnia	2	3.4	0		5	8.6	1	3.7	2	4.5	3	12.5

Source: section 14, Table 6.2F
Abbreviations: DES=discontinuation-emergent symptom; FLX=fluoxetine; PBO=placebo; RBX=reboxetine

Of the DES that were reported in at least 5% of reboxetine-treated patients, somnolence and insomnia were reported at least 2 times more frequently in the reboxetine-treated female patients than in the reboxetine-treated male patients, whereas headache and infection were reported at least 2 times more frequently in the reboxetine-treated male patients than in the reboxetine-treated female patients. Of the DES that were reported in at least 5% of fluoxetine-treated patients, headache, myalgia, diarrhea, and insomnia were reported at least 2 times more frequently in the fluoxetine-treated female patients than in the fluoxetine-treated male patients, whereas none of the DES were reported at least 2 times more frequently in the fluoxetine-treated male patients than in the fluoxetine-treated female patients. Of the DES that were reported in at least 5% of placebo-treated patients, headache and infection were reported at least 2 times more frequently in the placebo-treated female patients than in the placebo-treated male patients, whereas depression and insomnia were reported at least 2

times more frequently in the placebo-treated male patients than in the placebo-treated female patients. All DES are summarized by sex in section 14, Table 6.2F.

10.4.7.6 Drug-related DES

DES that were judged by the investigators to have been related to the investigational medication were reported in 15.5% (13/84) of the reboxetine-treated patients, in 10.6% (9/85) of the fluoxetine-treated patients, and in 14.7% (10/68) of the placebo-treated patients. The only drug-related DES occurring in at least 5% of the patients in any treatment groups was headache, which was reported in 3.6% (3/84) of the reboxetine-treated patients, in 5.9% (5/85) of the fluoxetine-treated patients, and in 5.9% (4/68) of the placebo-treated patients. A summary of drug-related DES is available in section 14, Table 8.1F.

10.4.7.7 Discontinuations Due to DES

The proportion of patients who discontinued the study due to DES was similar between the active treatment groups: 3.6% (3/84) of the patients in the reboxetine group and 2.4% (2/85) of the patients in the fluoxetine group, whereas none in the placebo group discontinued due to DES. The DES that led to discontinuation are summarized in Table 60.

Table 60. DES Leading to Termination in ≥1% of Treated Patients

COSTART Body System/Preferred Term∗	RBX N=84†		FLX N=85†		PBO N=68†	
	n	%	n	%	n	%
Patients With At Least 1 DES Leading to Termination	**3**	**3.6**	**2**	**2.4**	**0**	
Body	**2**	**2.4**	**0**		**0**	
Abdominal Pain	1	1.2	0		0	
Lab Test Abnormal	1	1.2	0		0	
Malaise	1	1.2	0		0	
Digestive	**1**	**1.2**	**1**	**1.2**	**0**	
Nausea	1	1.2	0		0	
Cholecystitis	0		1	1.2	0	
Nervous	**2**	**2.4**	**1**	**1.2**	**0**	
Depression	1	1.2	0		0	
Paresthesia	1	1.2	0		0	
Thinking Abnormal	1	1.2	0		0	
Anxiety	0		1	1.2	0	
Skin	**1**	**1.2**	**0**		**0**	
Priritus	1	1.2	0		0	

Source: section 14, Table 9.1F

∗Each patient is counted once per body system and once per COSTART term.

† N=number of ITT patients entering follow-up.

Abbreviations: DES=discontinuation-emergent symptom, FLX=fluoxetine, PBO=placebo, RBX=reboxetine

10.4.7.8 Serious DES

Two serious DES were reported in reboxetine-treated patients (2.4%, 2 of 84): 1 was an abnormal laboratory test (body system related)* and the other was depression (nervous system related). The only serious DES reported in a fluoxetine-treated patient (1.2%, 1 of 85) was 1 case of cholecystitis (digestive system related). The frequency of serious DES is provided in Table 61. Narrative summaries for patients who experienced serious DES are provided in section 10.4.7.9.

* Subsequent to database closure, the investigator revised the adverse event report to indicate that this was not a serious adverse event.

Table 61. Frequency of Serious DES

COSTART Body System/Preferred Term∗	RBX N=84†		FLX N=85†		PBO N=68†	
	n	%	n	%	n	%
At Least 1 Serious DES	**2**	**2.4**	**1**	**1.2**		
Body	**1**	**1.2**				
Lab Test Abnormal	1	1.2				
Digestive			**1**	**1.2**		
Cholecystitis			1	1.2		
Nervous	**1**	**1.2**				
Depression	1	1.2				

Source: section 14, Table 13.1F

∗Each patient is counted once per body system and once per COSTART term.

† N=number of ITT patients entering follow-up.

Abbreviations: DES=discontinuation-emergent symptom, FLX=fluoxetine, PBO=placebo, RBX=reboxetine

10.4.7.9 Narratives

Below are narratives for patients who experienced serious DES during the follow-up period by event verbatim (and by COSTART term). CRFs for these patients are available in Appendix 17.

Reboxetine Group

Patient number: 1161 (Investigator: Kennedy—14377)

Events: Positive Urine Benzodiazepines (Lab Test Abnormal)

This 43-year-old female patient with a history of major depression entered the study on 12 August 1998 and began taking the study medication on the same date. The patient completed the treatment phase of the study on 6 October 1998. The required laboratory tests, which included a urine drug screen, were performed on 7 October 1998. The urine drug screen detected a level of benzodiazepines exceeding the normal limits. Following an evaluation by the investigator on day 70 (19 October 1998) during the posttreatment phase of the study, this patient was discontinued due to the reemergence of depressive symptoms.

The investigator considered the positive urine screen for benzodiazepines at the treatment completion to be serious. The investigator did not judge this event as related to the study medication. Subsequent to database closure, the investigator revised the adverse event report to indicate that this was not a serious adverse event. This event was not life-threatening, did

not require hospitalization, or lead to persistent/significant disability/incapacity. Because the event was listed as a serious adverse event at the time of the database closure, this narrative was retained in the study report for completeness.

Patient number: 1238 (Investigator: Delgado—18800)

Events: Suicide Ideation (Depression)

This 24-year-old male patient with a history of major depression entered the study on 9 November 1998 and began taking the study medication on the same date. He completed the treatment phase of the study on 3 January 1999. On 7 January 1999, the patient was seen in the clinic and reported the return of some mild symptoms of depression, but denied having suicidal thoughts. On 8 January 1999, 5 days after withdrawal of the study medication (during the posttreatment phase of the study), the patient developed suicidal ideation and threatened to kill himself. He was seen in the emergency room and was hospitalized for observation. It was learned that the patient had experienced an emotional crisis in his personal life, which had worsened just before his admission to the hospital. The day after the hospital admission, the patient reported feeling much better. The date of discharge and the outcome of this patient are unknown. Daily administration of Prozac 20 mg began on 15 January 1999. The investigator judged this event as possibly related to withdrawal of the study medication.

Fluoxetine Group

Patient number: 1050 (Investigator: Delgado—18800)

Events: Cholecystitis (Cholecystitis)

This 24-year-old female patient with a history of major depression entered the study on 22 July 1998 and began taking the study medication on the same date. The investigator noted a patient history of right-sided abdominal pain. The patient reported taking the last dose of study medication on the morning of 1 September 1998. On 2 September 1998, the patient complained of right-lower quadrant pain, developed acute distress, and was hospitalized for cholecystitis. Subsequently, gall bladder surgery was performed, with hospital discharge on 4 September 1998. Recovery was normal, without residual effects. This patient did not complete the study. Neither the investigator nor the medical monitor considered this event study-medication related.

10.4.8 Safety Conclusions

TES were reported in 92.0% (138 of 150) of the patients in the reboxetine group, in 86.0% (129/150) in the fluoxetine group, and in 78.0% of the placebo group. Drug-related TES were reported in 84.7% (127 of 150) of the patients in the reboxetine group, in 68.7% (103 of

150) of the fluoxetine group, and in 50.7% (76 of 150) of the placebo group. No serious TES was reported in patients in the reboxetine group, whereas a serious TES was reported for 1 patient in the fluoxetine group and for 4 patients in the placebo group. The percentage of patients who discontinued study medication due to TES was highest in the reboxetine group (18.0%, 27 of 150), and nearly identical between the fluoxetine (6.7%, 10 of 150) and placebo (8.0%, 12 of 150) groups. A greater proportion of patients who were treated with reboxetine in the short-term, controlled, US studies (19.5%; 50 of 256), including this study, discontinued study medication because of 1 or more treatment-emergent adverse events compared with reboxetine-treated patients in the short-term, controlled, non-US studies (11.9%, 125 of 1048) ***[ref].*** It is possible that factors other than drug effect, such as current clinical trial behaviors in the United States, are responsible for the higher reporting rates. The majority of the reboxetine clinical studies were conducted in the mid- 1980s outside of the United States. Patient and/or investigator behavior in the late 1990s may represent a variable that accounts for the differcne. It should be noted that the 18.0% discontinuation rate for reboxetine in this study is within the ranges that have been reported for some of the newer antidepressant medications, such as paroxetine (with a discontinuation rate of 20%), citalopram (with a discontinuation rate of 16%), and vanlataxine (with a discontinuation rate of 19%). ***[ref]*** No clinically relevant differences among treatment groups were noted in the frequency of patients who had vital sign values outside of the predefined limits.

Of the reboxetine-treated patients, 18.3% (24 of 131) of those with a normal ECG at baseline had an abnormal ECG at the end of the study, whereas 21.5% (29 of 137) of the fluoxetine-treated patients had an abnormal end-of-study ECG after having had a normal baseline ECG. ECG abnormalities occurred approximately twice as frequently in the active treatment group patients than in the placebo-treated patients, for whom an abnormal end-of-study ECG was reported following a normal baseline ECG in 10.2% (13 of 137). Whereas statistically significant differences were observed among treatment groups in the mean change from baseline to the end of the treatment period in QRS and QT intervals, the magnitude of the changes was small; additionally, when changes in the QT intervals were corrected for heart rate, no statistically significant differences were observed among treatment groups. Few patients with normal ECGs at baseline developed clinically significant ECG abnormalities postbaseline.

At least 1 DES was reported in similar percentages of patients in each of the 3 treatment groups: 58.3% (49 of 84) in the reboxetine group, 62.4% (53 of 85) in the fluoxetine group, and 58.8% (40 of 68) in the placebo group. Drug-related DES were reported in 15.5% (13 of 84) of the patients in the reboxetine group, in 10.6% (9 of 85) of the patients in the fluoxetine group, and in 14.7% (10 of 68) of the patients in the placebo group. Serious DES were reported in 2.4% (2 of 84) of the reboxetine group and in 1.2% (1 of 85) of the fluoxetine group, whereas none were reported in the placebo group. The percentages of patients discontinuing the study due to a serious DES were 3.6% (3 of 84) in the reboxetine group and 2.4% (2 of 85) in the fluoxetine group, whereas none of the patients in the placebo group discontinued due to a DES.

11 DISCUSSION AND OVERALL CONCLUSIONS

This study failed to demonstrate statistically significant differences between reboxetine and placebo or between fluoxetine and placebo on the primary efficacy endpoint (mean change from baseline in the HAM-D total score on day 56) for either the LOCF or OC analyses. Whereas the primary efficacy endpoint was not attained by patients in either the reboxetine or fluoxetine treatment group, the HAM-D total score decreased over time (corresponding to patient improvement) in each treatment group, including the placebo group. Likewise, this study failed to demonstrate statistically significant differences between reboxetine and placebo or between fluoxetine and placebo on the secondary endpoints of antidepressant efficacy on day 56 in either the LOCF or OC analysis. The scores of the secondary efficacy endpoints changed in the appropriate direction, indicating patient improvement.

This study was one of the first large multicenter, placebo-controlled studies to evaluate sexual function and sexual satisfaction in major depressive disorder. For most assessments in the RSI, treatment with reboxetine was comparable to treatment with placebo. Reboxetine was significantly superior to fluoxetine in analyses of overall degree of sexual satisfaction and ability to become sexually excited. Fluoxetine was significantly inferior to placebo in analyses of overall degree of sexual satisfaction, ability to become sexually excited, frequency of pleasurable sexual thoughts, and the frequency of desire to initiate sexual activity. The frequency of various sexual activities remained fairly stable throughout the 56-day treatment period, with no significant differences among treatment groups; however, greater percentages of patients in the reboxetine- and placebo-treatment groups were satisfied with their overall sexual function and desire compared with the percentages of patients in the fluoxetine-treatment group. Statistically significant differences were noted among treatment groups in the ability of female patients to achieve orgasm on days 28 and 56, favoring reboxetine and placebo over fluoxetine. Statistically significant differences were noted for 6 male-specific questions. Of these, 4 were related to erectile function (eg, difficulty in getting an erection when sexually stimulated, requiring more stimuli than usual to achieve an erection, decreased fullness of erection, and painful orgasm/ejaculation); however, these problems did not produce the differences among treatment groups (concerning the ability to maintain an erection sufficient for completing the sexual act, morning erection, or delay in orgasm) that would have been expected from a widespread or common problem of purely physiological origin. The adverse effect profile on sexual function from treatment with reboxetine is similar to that of placebo, and significantly better than that of fluoxetine.

TES were reported slightly more frequently in patients treated with reboxetine compared with patients treated with fluoxetine or placebo; however, no serious TES were reported in reboxetine-treated patients, whereas, 1 serious TES was reported in fluoxetine-treated patients and 4 in placebo-treated patients. No clinically relevant differences among treatment groups were noted in the frequency of patients who had vital sign values outside of the predefined limits. ECG abnormalities occurred approximately twice as frequently in the active treatment group patients as in the placebo-treated patients.

DES were reported in few patients in any of the 3 treatment groups. At least 1 DES was reported in similar percentages of patients in each of the 3 treatment groups; the same was true for drug-related DES. Although serious DES were reported in a higher percentage of patients in the reboxetine group than in the fluoxetine or placebo groups, nonetheless, there were very few patients in any group with a serious DES: 2 patients in the reboxetine group, 1 in the fluoxetine group, and none in the placebo group.

In evaluating why this study failed to show efficacy of reboxetine compared with fluoxetine and placebo, it is important to note several potential problems that were considered, but that did not seem to account for the failure of this study. The possibility that the treatment groups were different at baseline was considered. However, the patients were similarly matched among treatment groups at baseline with regard to demographic variables, factors relating to previous history of depression, and the use of concomitant medications. If patients were not taking the study medication correctly, this could obviously result in study failure. However, based on the mean daily dosing data, patients in the active treatment groups were taking reboxetine or fluoxetine as specified in the protocol. Finally, if patients were taking concomitant psychoactive medications that could treat depression, despite prohibition of such medications in the study protocol, this could result in study failure, especially if there was disproportionate use in the placebo group. However, in reviewing the concomitant medication records for this study, it was noted that the proportion of patients who took disallowed psychoactive medications was quite low and similar across the treatment groups.

There may be several reasons for the failure of the active treatments to show significant differences from placebo on the primary efficacy measure at day 56. Over 30% of the patients in each treatment group dropped out prior to the end of the 8-week study, largely due to nonserious TES or lost to follow-up. Many of the dropouts due to TES were within the first 14 days of the study. Early dropouts such as these impair the ability to distinguish between the active treatments and the placebo, since these patients typically have not had sufficient time to respond to active medication and, consequently, their relatively high HAM-D total scores would have been carried forward in the LOCF analysis.

A relatively high placebo effect was seen in this study, and this may also have contributed to the inability to distinguish the active treatments from placebo. The placebo response rate was 44.1% in the LOCF analysis and 56.2% in the OC analysis at day 56. High placebo response rates are poorly understood, but are not unexpected in clinical trials of antidepressants.

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