Studie 045

(95-CRBX-045)

Studienbericht

PNU-155950E/Reboxetine CLINICAL RESEARCH 95-CRBX-045 Issued 09 November 1999; Amended 26 May 2000 and 23 March 2001

Comparison of Placebo and Three Fixed Doses of Reboxetine in a Population of Patients with Major Depression.

A phase II, double-blind, randomized, parallel group, multicenter study of 3 fixed doses of reboxetine or placebo, given orally twice daily to adult patients with Major Depressive Disorder

Final Report of the Trial
95-CRBX-045

Previous Reports of the Trial:
Final Report Originally Issued 09 November 1999;
Amended 26 May 2000 and 23 March 2001

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

Trial Initiation Date	17 July 1997
Trial Completion Date	08 July 1999
Sponsor's Responsible Medical Officer	Mark T Brown, MD CNS Development Pharmacia & Upjohn Kalamazoo, MI, USA
Development Phase of Trial	II

1 SIGNATURE PAGE

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

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2 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: Comparison of Placebo and Three Fixed Doses of Reboxetine in a Population of Patients with Major Depressive Disorder.

Protocol Number: 95-CRBX-045

Investigator(s): 48 investigators. The list of investigators can be found in Appendix 6.

Study Center(s): Multinational, Multicenter (Belgium, France, Germany, Italy, Netherlands, Russia, and Sweden).

Publication (reference): None

Studied period (years): **Phase of development:** II
17 July 1997
08 July 1999

Objectives: To assess the risk/benefit ratio of 3 fixed dose levels of reboxetine (RBX) compared to placebo (PBO), with the aim of establishing among these doses, the lowest dose maximally effective in patients suffering from a Major Depressive Disorder.

To determine the population pharmacokinetics of RBX enantiomers at steady state, to assess possible factors affecting enantiomer pharmacokinetics, and to assess the possible relationship between plasma enantiomer concentrations and therapeutic/untoward effects. Pharmacokinetic results will be reported in a separate study report.

Methodology: This phase II, multicenter, multinational, double-blind, randomized, parallel group study evaluated RBX in patients suffering from Major Depressive Disorder. Treatment groups consisted of placebo, RBX 2 mg/day, RBX 4 mg/day and RBX 8 mg/day. Adult patients were selected from the population under inpatient care or attending outpatient or day-hospital clinics; if necessary, they were hospitalized for the first 2 treatment weeks.

Before entry in this 6-week study, patients must not have taken antidepressants for a period ranging from 4 days to 2 weeks, depending on the class of psychotropic drugs, (ie, washout duration was 4 days for tricyclic antidepressants [TCAs], 14 days for monoamine oxidase inhibitors [MAOIs] and for fluoxetine, and 1 week for other selective serotonin reuptake inhibitors [SSRI]). Patients who satisfied the study entry criteria were randomized to receive treatment with RBX (2 mg, 4 mg, or 8 mg/day) or placebo.

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Number Of Patients (Planned And Analyzed): The plan was to enroll 80 patients per treatment group. However, since dropout rate was higher (30% versus planned 20%), a total of 365 patients were targeted for enrollment instead of the originally planned 320 patients.

Diagnosis And Main Criteria For Inclusion: Patients of either sex, of any race, aged 18 to 65 years with a diagnosis of Major Depressive Disorder (DSM-IV F32 - F33.0, F33.1) without psychotic features, and a total score ≥ 22 and <35 in the 21-item HAM-D were eligible for enrollment in the study.

Test Product, Dose And Mode Of Administration, Batch Number: Reboxetine (RBX) 2 mg/day [Batch No. C06G22], RBX 4 mg/day [Batch No. C06G16], and RBX 8 mg/day [Batch No. C06G23] was administered twice daily (BID) as an oral capsule. Study medication was administered in the morning and in the evening at a fixed time (8 to 9 am and 5 to 6 pm).

Duration of Treatment: 42 days; extension of treatment thereafter for another 16 weeks was optional.

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo (PBO), orally administered BID [Batch No. C06G12] in the morning and in the evening at a fixed time (8 to 9 am and 5 to 6 pm).

Criteria for Evaluation:

Efficacy: Patients who received at least one dose of medication and who had at least one efficacy evaluation after baseline were included in the efficacy analyses (intent-to-treat [ITT] efficacy population). The primary efficacy measure was the mean change from baseline on the HAM-D total score. The Clinical Global Impression (CGI) scale, the Montgomery-Asberg Depression Rating Scale (MADRS), Patient Global Impression (PGI), individual items of HAM-D, as well as response/remission rates, and time to response/remission served as measures for secondary efficacy.

Safety: Patients who received at least one dose of study medication or PBO were included in the safety analyses (intent-to-treat safety population). Safety evaluations included treatment-emergent symptoms (TES), vital signs, laboratory assays, and ECGs.

Statistical Methods: Categorical variables were summarized using frequency counts. Comparability among treatment groups at baseline was assessed using a one-way analysis of variance (ANOVA) for continuous variables and a chi-square test for categorical variables. Two types of efficacy analyses were performed: 1) last observation carried forward (LOCF) in which the last valid assessment was used as an estimate for all subsequent missing values, and 2) observed case (OC) in which missing data were not replaced. Continuous variables (eg, mean change from baseline in the HAM-D total score) were analyzed

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Statistical Methods: continued

using a two-way analysis of variance (ANOVA), with treatment, investigator, and treatment-by-investigator as factors. The intent-to-treat data set using the LOCF technique is the primary analysis and the OC analysis is included as a secondary analysis. Summary statistics (mean, mean change from baseline, median change from baseline, and standard deviation) were calculated for clinical laboratory tests, vital signs, and ECGs. Differences among treatment groups in the mean change from baseline at each post-baseline evaluation were analyzed using a one-way ANOVA.

SUMMARY – CONCLUSIONS

Patient Disposition and Demographics:

The treatment groups were comparable for demographic and psychiatric characteristics at baseline.

The study completion rate was 67.8% (59/87) in the RBX 2-mg group, 59.8% (52/87) in the RBX 4-mg group, 69.7% (62/89) in the RBX 8-mg group, 77% (67/87) in the PBO group. The primary reasons for study discontinuation in each group were due to lack of efficacy (11.5% [10/87] RBX 2-mg group; 18.4% [16/87] RBX 4-mg group; 4.5% [4/89] RBX 8-mg group; 8% [7/87] PBO group) and due to nonserious **AE**s (10.3% [9/87] for both RBX 2 mg and RBX 4-mg group; 14.6% [13/89] RBX 8-mg group, and 8% [7/87] in the PBO group).

EFFICACY RESULTS:

Primary Efficacy Variable

At each follow-up evaluation, no statistically significant differences were observed among treatment groups for the HAM-D total score by the LOCF or by the OC analysis. At Day 42, the mean decrease in the HAM-D total score by the LOCF analysis was –10.0 for the RBX 2-mg group, –8.6 for the RBX 4-mg group, –10.5 for the RBX 8-mg group, and –11.3 for the PBO group. By the OC analysis, the mean decrease in the HAM-D score on Day 42 was –13.2 for the RBX 2-mg group, –13.0 for the RBX 4-mg group, –13.6 for the RBX 8-mg group, and –13.9 for the PBO group. The mean changes in the HAM-D total score were higher for the PBO group than for any of the RBX groups, for both the LOCF and the OC analyses, demonstrating a high placebo response in this study.

Secondary Efficacy Variables:

No statistically significant differences were observed either in the LOCF or the OC analyses between the RBX treatment groups and PBO group for the CGI-Improvement rate or the CGI-Severity of Illness score through 42 days of treatment. For the CGI-Efficacy Index, no significant treatment group differences were seen for either the LOCF or the OC analysis.

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For the MADRS score, the mean change from baseline at each post-baseline evaluation for both the LOCF and OC analyses was not significantly different between treatment groups.

For the HAM-D response rate by the LOCF analysis, no statistically significant differences were seen between any of the RBX treatment groups and PBO during the study period except at Day 7. By Day 42, 38.4% (33/86) of patients in the RBX 2-mg group, 36% (31/86) of patients in the RBX 4-mg group, 43.2% (38/88) of patients in the RBX 8-mg group, and 45.3% (39/86) of patients in the PBO group were classified as responders. For the OC analysis, no statistically significant differences were seen in the response rate between any of the RBX treatment groups and PBO during the study period except at Day 7. By Day 42, 49.2% (30/61) of patients in the RBX 2-mg group, 54.5% (30/55) in the RBX 4-mg group, 54.7% (35/64) in the RBX 8-mg group, and 57.4% (39/68) in the PBO group were classified as responders.

The PGI score did not achieve statistical significance between treatment groups for the LOCF or the OC analyses.

SAFETY RESULTS:

Treatment-emergent AEs were reported at similar frequencies between treatment groups (67.8% in the RBX 2-mg group, 67.8% in the RBX 4-mg group, 76.4% in the RBX 8-mg group, and 59.8% in the PBO group). While the active treatment groups had slightly higher rates of treatment-emergent AEs than the placebo group, no dose-dependent trend toward higher rates of these AEs with increasing reboxetine dose was observed. No deaths were reported in this study. The frequencies of SAEs were similar between the RBX-treated patients and patients in the PBO group. The SAEs were considered unrelated to reboxetine in 6 of the 10 (60%) reboxetine-treated patients who experienced an SAE. No dose-dependent trend toward a higher incidence of SAEs with increasing RBX dose was observed. A total of 65 events led to discontinuation in the RBX-treatment groups; most (approximately 62% [40/65]) of these events were mild or moderate in severity with recovery noted for a majority (approximately 69% [45/65]) of these events. Five of 263 (1.9%) reboxetine-treated patients discontinued the study due to SAEs. Three of 5 of these patients had SAEs that were considered by the investigator as unrelated to study medication. No dose-dependent trend toward discontinuation from the study due of SAEs was observed. There was some increase in discontinuations due to nonserious AEs as the reboxetine dose increased.

The most common AEs were those that would be expected from an agent with noradrenergic activity. Among the AEs that were reported by at least 2% of patients in the RBX treatment groups, tachycardia, dry mouth, constipation, nausea, sweating, insomnia, and impaired urination were reported at least twice as frequently by patients in the RBX treatment groups compared to the PBO group. The incidence of AEs in general did not show a clear relationship to reboxetine dose. A trend toward increasing incidence of abdominal pain, palpitation, nausea, pharyngitis, rhinitis, and urination impairment with increasing RBX dose was observed (though for several of these, the numbers of AEs are small).

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A trend toward decreasing incidence of headache, dizziness, paresthesia, and sleep disorder with increasing RBX dose was observed (though for several of these, the numbers of AEs are small). For all other AEs, (ie, for the majority of the AEs) there was no trend between AE incidence and RBX dose. Most AEs were evenly distributed among the RBX treatment groups. The follow-up AE data for patients who continued treatment beyond the study defined treatment period (Day 42) are consistent with the data obtained during the study. However, due to the small sample size, conclusions in the follow-up group are limited.

No clinically significant changes among treatment groups or dose-dependent mean changes in systolic or diastolic blood pressure were seen. Statistically significant changes from baseline were noted in the pulse rate throughout the study among treatment groups and between each RBX group and PBO group. The median mean increase in the pulse rate for all RBX-treatment groups during the course of the study was 5.9 beats per minute. There was no dose-dependent relationship between RBX dose and mean pulse rate increase. The pulse rate increase was seen on Day 7 and persisted with little change through Day 42 for each RBX treatment group. Overall, no clinically important mean changes from baseline to Day 28 or Day 42 were observed for any of the hematology or serum chemistry parameters. A small number of patients (13.7% in the RBX 2-mg group, 10.8% in the RBX 4-mg group, 5.8% in the RBX 8-mg group, and 1.4% in the PBO group) had ECG findings that shifted from normal at baseline to abnormal at the end of study. Most of these changes occurred in the RBX-treated patients, although a dose-dependent difference was not seen. The most frequent treatment-emergent ECG abnormality was sinus tachycardia (6 patients in the RBX 2-mg group, 4 patients in the RBX 4-mg group, and 1 patient in the RBX 8-mg group). Analysis of the ECG results indicates that RBX does not cause a clinically significant prolongation of the QTc interval. In addition, no dose-related effect of RBX on QTc intervals was observed.

CONCLUSION:
The high placebo response in this study is the main reason that RBX failed to show a significant difference when compared to PBO. In fact, in this study, the improvement in the PBO group was greater than any active treatment group for the HAM-D, the primary efficacy measure. The high placebo response precluded a statistically significant comparison in favor of RBX. The study demonstrated that reboxetine was a safe treatment for patients with major depressive disorder. In general, there was no dose-dependent relationship for incidence of treatment emergent AEs, SAEs, or discontinuation due to SAEs. The AEs reported were characteristic of a medication with noradrenergic activity. No unexpected AEs occurred in this study and most of the SAEs that occurred in the RBX-treated patients were considered by the investigator to be unrelated to study medication.

In conclusion, this study failed to distinguish significant differences between RBX and PBO and failed to identify the minimal effective dose of RBX for the treatment of major depressive disorder.

Date of the report: Issued 09 November 1999; Amended 26 May 2000 and 23 March 2001

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4 ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are used in this report:

AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
BID	Twice daily
CGI	Clinical Global Impression
CNS	Central nervous system
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
FU	Follow-Up
GI	Gastrointestinal
HAM-D	Hamilton Rating Scale for Depression
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LOCF	Last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine oxidase inhibitor
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Hemoglobin Volume
PBO	Placebo
PGI	Patient Global Impression
RBX	Reboxetine
REM	Rapid eye movement
SAE	Serious adverse event
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressant
TES	Treatment-emergent symptom
T_4	Thyroxine (tetra-iodo-thyronine)
TSH	Thyroid stimulating hormone
WBC	White blood cell

5 ETHICS

5.1 Independent Ethics Committee (IEC/IRB)

The protocol (and all amendments) and informed consent form were reviewed by each investigator's independent ethics committee (IEC) or institutional review board (IRB), according to the institutional and national regulations and the requirements of the individual countries. Other than modifications for safety, no changes to the protocol were allowed once the study had started, without specific written agreement of the investigators, the IEC or IRB, and the study monitor. A list of all IECs/IRBs consulted can be found in Appendix 4.

A copy of the protocol and amendments are included in Appendix 2, and a sample case report form (CRF) is included in Appendix 3.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the ethical principles that have their rights and origins in the Declaration of Helsinki, Finland 1964 and later revisions.

5.3 Patient Information and Consent

Prior to enrolling in the study, each investigator was required to give full and understandable verbal and written information as to the nature, purpose, and potential risk of the study medication, as well as the action of the study medication to all patients, who were also informed that they may withdraw from the study at any time. Written patient information was given to the patient before enrollment and was not to be changed without prior discussion with P&U. Informed consent forms, which were to be approved by the investigator's IEC or IRB, were to be signed by all patients (or patients nearest of kin). A sample of the informed consent form is included in Appendix 5.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigative Sites

A total of 48 investigators in 7 countries were recruited to perform the study and receive study medication supplies. Of these, 40 investigators in 6 countries enrolled patients into the study. The investigators in Netherlands did not enroll any patients. The list of investigators and sites can be found in Appendix 6.

6.2 Central Laboratory

Laboratory assays (hematology, serum chemistry) were performed by Covance Central Laboratory Services, Indianapolis, IN.

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]. The social and occupational impairment associated with depression has been reported to be equivalent to or greater than that associated with such chronic and recurrent disorders as diabetes, hypertension, arthritis, gastrointestinal (GI) disturbances, lung disturbances, bronchitis, emphysema, and back problems [4, 5]. A 15% mortality rate in association with suicide alone has been reported for patients whose depression is severe enough to require hospitalization [6].

Although specific pharmacologic and psychotherapeutic interventions have been found to be effective in treating major depression, fewer than half of individuals with depression currently receive such treatments [7]. This under treatment is 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 or an adequate duration of therapy [7].

Tricyclic antidepressants (TCAs) are frequently used to treat depression and are effective in 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) are comparable to the TCAs in efficacy but offer distinct advantages over the TCAs 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 (AE), eg, diarrhea and nausea, as well as with some central nervous system (CNS) AEs (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 methanesulphonate (reboxetine mesylate; hereafter referred to as RBX) is a specific noradrenaline reuptake inhibitor, which has been shown to be highly potent in rodent models that are predictive of antidepressant activity in humans (eg, reserpine antagonism, clonidine effects prevention, rapid eye movement [REM] sleep latency increase) [8]. RBX has no relevant affinity for the serotonin or dopamine uptake sites or for the muscarinic or adrenergic receptors [9]. On the basis of RBX potency in the animal models that are predictive of antidepressant activity and on the relative absence of the properties that are reportedly responsible for the side-effects of the classical antidepressant agents, the clinical evaluation of RBX for the treatment of patients with depressive disorders was implemented.

In a phase I pharmacodynamic study in which single, oral doses of RBX over the range of 0.2 to 5 mg were administered to healthy volunteers [10], administration of the 5-mg dose was associated with orthostatic hypotension and tachycardia. In a second PBO-and imipramine-controlled pharmacodynamics study, single 1- and 3-mg doses of RBX induced dose-related modifications in electroencephalogram (EEG) power bands and in psychometric performance, which were suggestive of psychostimulating properties, whereas the 75-mg dose of imipramine produced changes which were consistent with its known sedative activity [11]. In healthy volunteers, the average peak levels of RBX were observed at 2 hours after oral administration, with levels appearing stable for 1 to 6 hours after administration [12]. The plasma half-life of RBX was estimated to be 13.2 hours; 73% of the area under the concentration-time curve (AUC) following an oral dose was accounted for by unchanged RBX. Doses of up to 10 mg/day of RBX were shown to be well tolerated in an early phase II, 4-week, open-label, multicenter study in which 98 depressed patients were treated with RBX over the range of 4 to 12 mg [13].

Several studies [14, 15, 16, 17, 18] have confirmed the efficacy profile of RBX (8-mg dose for adults and 4-6 mg for elderly patients) in the acute treatment of Major Depressive Episodes. This dose comparison study was initiated to assess the risk/benefit ratio of 2, 4, and 8 mg doses of RBX compared to placebo, with the aim of establishing among these doses, the lowest dose maximally effective in patients suffering from a Major Depressive Disorder.

8 OBJECTIVES

To assess the risk/benefit ratio of 3 fixed dose levels of RBX compared to placebo, with the aim of establishing among these doses, the lowest dose maximally effective in patients suffering from a Major Depressive Disorder.

To determine the population pharmacokinetics of RBX enantiomers at steady state, assess possible factors affecting enantiomer pharmacokinetics, and to assess the possible relationship between plasma enantiomer concentrations and therapeutic/untoward effects. Pharmacokinetic results will be reported in a separate study report.

9 METHODS

9.1 Overall Study Design and Plan

This phase II, multicenter, multinational, double-blind, randomized, parallel group study of RBX was conducted in patients suffering from Major Depressive Disorder. Treatment groups consisted of placebo, RBX 2 mg/day, RBX 4 mg/day, and RBX 8 mg/day. Adult patients were selected from the population under inpatient care or attending outpatient or day-hospital clinics; if necessary, they were hospitalized for the first 2 treatment weeks.

Before entry in this 6-week study, patients must not have taken antidepressants for a period ranging from 4 days to 2 weeks,[†] depending on the class of psychotropic drugs (eg, 4 days for tricyclic antidepressants [TCAs], 2 weeks for monoamine oxidase inhibitors [MAOIs] and for fluoxetine, and 1 week for other selective serotonin reuptake inhibitors [SSRIs]. Patients who satisfied the study entry criteria and the washout period of 4 days to 2 weeks (depending on the class of psychotropic drug previously used) underwent the screening laboratory, standardized psychopathological evaluations, and ECG assessments prior to randomization to one of the 4 treatment groups. Patients received 1 capsule twice daily (BID) orally from Day 1 to Day 42. Study medication was administered in the morning and in the evening at a fixed time (8 to 9 am and 5 to 6 pm).

The Hamilton Rating Scale for Depression (HAM-D) [19], the Clinical Global Impression (CGI) scale [20], the Montgomery-Asberg Depression Rating Scale (MADRS) [21], and the Patient Global Impression (PGI) scale were used to assess the efficacy of the study medications. The safety of the study medications was assessed by evaluation of newly-observed symptoms, vital signs, laboratory tests, and electrocardiograms (ECG).

The primary efficacy measure was the mean change from baseline on the HAM-D total score. The secondary efficacy measures were Clinical Global Improvement (CGI) Response Rate, the CGI-Severity of Illness scale, CGI-Efficacy Index, the mean change from baseline in the Montgomery-Asberg Depression Rating total score (MADRS), response/remission rates using HAM-D 21 item scale, as well as Patient Global Impression Scale (PGI). A decrease of at least 50% in the total HAM-D score vs baseline was considered the definition of response whereas total HAM-D score of 10 or less was considered the definition of remission.

[†] As per Amendment 1, Section 9.8.1

9.2 Discussion of Study Design

The double-blind, randomized, parallel group study design is generally recognized as one which provides an unbiased assessment of the efficacy and safety of an investigational drug. Placebo was chosen as a comparator for the different doses of RBX used in this study. The 6-week treatment period encompasses the period that is needed to detect clinically relevant differences between treatment groups.

9.3 Study Population

9.3.1 Inclusion Criteria

Patients had to satisfy the following criteria to qualify for inclusion in the study:

- Diagnosis of Major Depressive Disorder (DSM-IV F32 - F33.0, F33.1 [22]) without psychotic features (as per Amendment 1, Section 9.8.1)
- Male or female of any race, aged 18 to 65 years
- A total score $\geq$ 22 and <35 on the 21-item HAM-D (at screen and confirmed at Day 0)
- Written informed consent

9.3.2 Exclusion Criteria

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

- History of DSM-IV diagnosis of dysthymia (F34.1), cyclothymia (F34.0), bipolar (F30 - F31), schizophrenia (F 20.xx) (as per Amendment 1, Section 9.8.1).
- Resistance to antidepressive treatment (lack of response to at least 2 courses of previous antidepressants given at full doses (ie, those recommended by the manufacturer) for more than 1 month.
- Current use of high dose of benzodiazepines or chronic therapy with carbamazepine, valproate, lithium, etc. (as per Amendment 1, Section 9.8.1).
- History of Major Depressive Disorders associated with endocrine disorders: hypo- and hyperthyroidism tested by levels of TSH and T4, hypo- and hypercorticosteroidism, etc.
- Positive pregnancy test (as per Amendment 1, Section 9.8.1).
- Refusal by female patients of potential child-bearing age to use efficient contraceptives during the study period
- Participation in any clinical study with an investigational compound in the 3 months preceding this study
- A DSM-IV diagnosis of substance abuse disorder or dependence, presently or in the 6 months preceding the study (as per Amendment 1, Section 9.8.1).

- History or presence of gastrointestinal, liver, or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, and excretion of drugs
- History of seizures or brain injury, current evidence of clinically important hematopoietic, respiratory, or cardiovascular diseases. Current evidence of urinary retention, or glaucoma
- Any important clinical illness in the 4 weeks preceding the study which might interfere with the conduct of the trial
- Clinically relevant abnormal findings at admission in the physical examination, laboratory tests, or electrocardiogram (ECG)
- Electroconvulsive therapy (ECT) within the previous 6 months
- Major risk of suicide (as judged by the investigator [HAM-D Item 3 score>2]) or history of attempted suicide attempt during the current depressive episode (as per Amendment 8, Section 9.8.1).
- Current use of known inhibitors of drug metabolizing enzymes (with the exception of CYP2D6), such as azole antifungals, macrolide antibiotics, or fluvoxamine (refer to Amendment 11, Section 9.8.1).

9.3.3 Removal of Patients from Therapy or Assessment

Patients could withdraw from the study treatment if, in the opinion of the investigator, it was medically necessary, or if the patient wished to do so for other reasons. Termination of treatment prior to completion of the 6-week treatment period was considered under the following circumstances.

- Unacceptable toxicity: defined as the occurrence of a serious adverse event (SAE, see Section 9.5.3).
- Lack of efficacy: applied to patients who after at least 2 weeks of treatment showed deterioration (worsening of the CGI), or no change, and if according to investigator's judgment this exposed the patients to an unacceptable risk.
- Switch to mania
- Increased risk of suicide

The above mentioned conditions were not to be considered as protocol violations.

In case of treatment discontinuation, the reasons for the withdrawal were to be clearly described and the patient was to be examined whenever possible, irrespective of the reason for withdrawal. All of the efficacy and safety evaluations that were scheduled for the final visit were to be conducted at the time of discontinuation.

9.4 Treatments

9.4.1 Treatments Administered

Eligible patients were randomized to 1 of the 4 treatment groups. Patients received 1 capsule orally twice daily (BID) from Day 1 to Day 42. Study medication was to be administered in the morning and in the evening at a fixed time (8 to 9 am and 5 to 6 pm).

Certain investigators were permitted to continue treatment beyond 42 days for an additional 16 weeks, still in the double-blind mode, to those patients who benefited from the treatment. Patients had to fulfill certain conditions outlined in Amendment 2 or 4 (Section 9.8.1) to continue the follow-up treatment.

If deemed appropriate by the investigator, for safety reasons, the daily dose could be reduced for a period not exceeding 7 consecutive days by omitting 1 capsule per day, while treatment discontinuation could not last longer than 4 days. If this period was exceeded, the patient was to be taken off the study. If the treatment was resumed nonetheless, this was to be considered a protocol violation (Amendment 7, Section 9.8.1).

9.4.2 Identity of Investigational Product

For each patient, 6 bottles labeled with the patient number and the indication "Week 1" to "Week 6" were prepared. Each bottle contained the medication necessary for 1 week plus 2 capsules for possible losses, prepared according to the BID regimen, with 1 capsule for the "morning" and 1 capsule for the "evening" dose. Indistinguishable capsules containing RBX 1 mg (1 mg x 2), 2 mg (2 mg x 2), 4 mg (4 mg x 2), plus excipients or excipients only (placebo) were used.

Supplies of study medications were to be stored at room temperature. Information relating to the study medications is summarized in Table 1.

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

Study Medication	Capsule Strength	Supplier	Batch Number
Reboxetine	1 mg	P&U	C06G22
Reboxetine	2 mg	P&U	C06G16
Reboxetine	4 mg	P&U	C06G23
Placebo	-	P&U	C06G12

9.4.3 Method of Assigning Patients to Treatment Groups

The main investigator allocated the patients to treatment groups at baseline, sequentially at the center[†], on the basis of the patient's temporal entry into the study. Patients were randomized evenly between groups to receive RBX 2 mg, 4 mg, 8 mg, or placebo.

9.4.4 Selection of Doses in the Study

The 2, 4, and 8-mg doses for reboxetine corresponded to a standard dose-doubling design frequently used in dose-range finding trials.

9.4.5 Selection and Timing of Dose for Each Patient

Patients were randomized to receive 1 capsule BID of RBX (2 mg, 4 mg or 8-mg daily dose) or placebo from Day 1 to Day 42. Treatment was to be administered in the morning between 8 and 9 am and in the evening between 5 and 6 pm.

9.4.6 Blinding

Study medications were supplied as identically appearing capsules in bottles labeled with the patient number. The investigator was given individual sealed envelopes containing the information on each patient's treatment. These envelopes were to be opened only in case of an emergency necessitating treatment identification; the investigator was to immediately (within 24 hours) inform the study monitor and justify the reasons for opening the code in the CRF (Adverse Event Form). The sealed individual codes were then returned to Pharmacia & Upjohn at the end of the study.

9.4.7 Prior and Concomitant Therapy

Patients received standard psychological support; specific cognitive-behavior therapy, however, was not allowed[†]. No concomitant psychotropic medications other than hypnotics listed in the study protocol (lorazepam, oxazepam, temazepam), if required, were allowed during the study period. In order to overcome acute, disabling anxiety episodes that may arise during the study, a single course of the protocol-specified benzodiazepines at doses recommended by the manufacturer, and for a period not exceeding 3 consecutive days was permitted. Prolonged administration (longer than 3 consecutive days) was considered a protocol violation (refer to Amendment 7, Section 9.8). The administration of other concomitant psychotropic drugs was considered as a protocol violation and the patient was excluded from the study.

Other therapy considered necessary for the patient's welfare was allowed at the discretion of the investigator. All such therapy was to be recorded in the Case Report Form (CRF). No other drug under investigation was to be used concomitantly with the study medication. The

[†] As per Amendment 1, Section 9.8.1

patients were not allowed to participate concurrently in any other clinical study. Contraceptives were allowed in order to satisfy the inclusion/exclusion criteria in female patients. Over the counter (OTC) and herbal medicines were allowed, if required, as a symptomatic treatment; these medicines were to be recorded in the relevant form along with the AE requiring the treatment.

9.4.8 Treatment Compliance

Study medication was dispensed to the patient at each visit; a bottle of the previous supply of study medication was to be returned by the patient at this time. Compliance was to be strictly monitored. Capsules dispensed and returned were to be recorded on the Medication Record Form. Acceptable patient compliance was defined as an overall drug intake of at least 90% of the prescribed amount. Reduction in dose was permitted for safety reasons, while treatment discontinuation was not to exceed 4 days and a 50% reduction was not to exceed 7 days (refer to Amendment 7, Section 9.8.1).

9.5 Efficacy and Safety Variables

9.5.1 Study Schedule

The schedule of activities is presented in Table 2.

Table 2. Schedule of Activities

Evaluation	Study Day [Visit]							
	≥-14 [SCR]*	0 [1]	7 [2]	14 [3]	21 [4]	28 [5]	35 [6]	42 [7]†
Informed Consent	X							
Medical history; clinical and physical exam; history of mental disorder	X							
History of anti-depressant medications	X							
Rating Scales (HAM-D, CGI, MADRS, PGI)‡	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X
Biochemistry and Hematology§	X					X		X
PK Samples			X	X		X		X
12-Lead ECG	X							X
Blood Pressure and Pulse	X	X	X	X	X	X	X	X

* Screening visit must take place within 2 weeks prior to baseline.
† Or at end of treatment for any patient who withdrew from the study prior to Visit 7.
‡ HAM-D and CGI evaluated at screen; HAM-D, CGI, and MADRS evaluated at baseline.
§ Any clinically significant abnormal laboratory assay values were to be repeated
HAM-D = Hamilton Depression Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale, CGI = Clinical Global Impressions, PGI = Patient Global Impressions, SCR = Screen, PK = Pharmacokinetics, ECG = Electrocardiograms

For follow-up activities beyond Day 42, the visits were to occur every 4 weeks and were to include vital signs, HAM-D, MADRS, CGI, tolerance (every AE was to be reported), concomitant therapy, and a record of delivered and returned study medication (refer to Amendments 2 and 4, Section 9.8.1).

9.5.2 Efficacy Variables

The primary efficacy measure was the mean change from baseline on the HAM-D total score. The secondary efficacy measures were the mean change from baseline in total score of the CGI-Severity of Illness, the CGI Global Improvement, the CGI-Efficacy Index, and the CGI Global Improvement Responder status (a responder is defined as having Clinical Global

Impression ≤2 as very much improved or much improved), as well as response/remission rates, and time to response/remission. A decrease of at least 50% in the total HAM-D score vs baseline was considered the definition of response, whereas total HAM-D score of 10 or less was considered the definition of remission. The mean change from baseline in the total score of the MADRS scale and the Patient Global Impression scale were also secondary efficacy measures.

9.5.2.1 Hamilton Rating Scale for Depression

The severity of depression was quantified using the 21-item HAM-D scale [19] at the screening evaluation, at baseline, and on Days 7, 14, 21, 28, 35, and 42. The investigator was to rate each item on the HAM-D on a scale from 0 to 2 or 0 to 4, to denote whether the symptom was absent or, if present, of mild, moderate, or severe intensity. The scores for each of the 21 items were to be totaled to give the HAM-D total score, which provided a global judgment of the severity of the patient's depression. Patients were to have a total score of at least 22 on the HAM-D at baseline. The 21 items of the HAM-D and the scoring range for each are summarized in Table 3.

Table 3. 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	0-4
21. Obsessional and Compulsive Symptoms	0-2

Source: Hamilton 1967 [19].

9.5.2.2 Clinical Global Impression

The CGI rating scale [20] consists of 3 subscales: Severity of Illness, Global Improvement, and Efficacy Index. In this study, all 3 subscales were used to assess the severity of the patient's illness on Days 7, 14, 21, 28, 35, and 42. Severity of illness was the only scale used at Baseline. The Efficacy Index was a rating system where the efficacy outcome was ranked against the tolerability (ie, side effects) outcome. A low score indicated a marked outcome (ie, vast improvement) and no drug tolerability, while a high score indicated that the patient's condition was unchanged or worse and the tolerability outweighed the therapeutic effect. The Severity of Illness and Global Improvement scales are defined in Table 4.

Table 4. Clinical Global Impression Scale

Severity of Illness	Global Improvement
Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?	Compared to the patient's condition at baseline (Day 0), how much has the patient changed?
1. Normal, not at all ill	1. Very much improved
2. Borderline mentally ill	2. Much improved
3. Mildly ill	3. Minimally improved
4. Moderately ill	4. No change
5. Markedly ill	5. Minimally worse
6. Severely ill	6. Much worse
7. Among the most extremely ill patients	7. Very much worse

Source: Guy W 1976 [20]

9.5.2.3 Montgomery-Asberg Depression Rating Scale

The investigator completed the MADRS [21] at baseline and on Days 7, 14, 21, 28, 35, and 42. The MADRS rating scale is based on a clinical interview and consists of 10 depression-related items: 1) apparent sadness, 2) reported sadness, 3) inner tension, 4) reduced sleep, 5) reduced appetite, 6) concentration difficulties, 7) lassitude, 8) inability to feel, 9) pessimistic thoughts, and 10) suicidal thoughts. For each item, a score of 0 would signify the absence of the symptom and a score of 6 would signify the most extreme form of the symptom (range is 0-60). The total score was calculated by adding the score for each individual item.

9.5.2.4 Patient's Global Impression

The PGI was completed on Days 7, 14, 21, 28, 35, and 42. The PGI was a 10-point visual analogue scale where patients rated their general condition since the start of the study. On the 10-point scale, a score of 0 denoted worst condition, 5 denoted unchanged condition, and 10 denoted best condition.

9.5.3 Safety Variables

A medical history was obtained at screening, along with a clinical and physical examination. Vital sign measurements, including blood pressure and pulse were measured at screening, baseline, and at each subsequent visit. Adverse events and clinical laboratory assay values were also monitored during the study as described below.

9.5.3.1 Adverse Events

An adverse event was any undesirable clinical event occurring in a patient during a clinical trial, whether or not it was related to the investigational product. All AEs that occurred during the study were to be recorded on the CRF and reported to P&U, regardless of whether or not the events were related to the study medication. The definitions of events and reporting procedures are provided in the study protocol. The investigator assessed the type of event, severity of the AE (ie, mild, moderate, or severe), the seriousness of the event (ie, serious or nonserious), outcome, and the possible relationship between the AE and the study medication and any concomitant medications. Adverse events were also to be reported to P&U up to 1 month after the study ended, if in the judgment of the investigator, there might be an association between the event and the previous use of the study medication. A pre-existing condition (ie, if the onset of the event was prior to the first dose of study medication [baseline symptoms] and the event does not increase in severity after initiation of study medication) was not to be reported as an AE.

In this study, a SAE included death, life-threatening event (ie, immediate risk of death), in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, permanent impairment of function or permanent damage to a body structure or requiring intervention to prevent permanent impairment damage, cancer, congenital anomaly/birth defect, and overdose (refer to Amendment 3, Section 9.8). Serious AEs were to be reported within 1 working day by the investigator to the monitor or medical staff at P&U, regardless of the time that may have elapsed from the time that the event occurred to when the investigator first learnt of it. An event was not to be reported as serious if the investigator considered it as a relapse or an expected change or progression of the condition for which the patient was being treated by study medication, without any symptoms or signs than those present before treatment.

9.5.3.2 Exposure in Utero

Investigators were required to report any pregnancy that occurred during treatment and the outcome of the pregnancy.

9.5.3.3 Laboratory Tests

Hematology (Hb, hematocrit, RBC, WBC, MCV, MCH, MCHC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and RBC morphology) and serum chemistry assays (for Na^+, K^+, CL^-, creatinine, AST, ALT, pregnancy test, T_4, and TSH [screen only- as per Amendment 8, Section 9.8]) were performed at screen, Day 28, Day 42, or End of

Treatment. Laboratory tests were conducted by Covance Central Laboratory Services, Indianapolis, IN.

9.5.3.4 Vital Signs

Systolic and diastolic blood pressure and radial pulse rate were measured in the morning (sitting position) at each visit.

9.5.3.5 Electrocardiograms

ECGs were performed at screening and at Day 42 or End of Treatment. The investigator was allowed to seek the advice of the cardiologist if any abnormal ECG tracings were obtained.

9.5.4 Drug Concentration Measurements

Blood was drawn for pharmacokinetic assessments on Days 7, 14, 28, and 42. The results of these assessments will be presented in a separate report.

9.6 Data Quality Assurance

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

- The Sponsor made periodic visits to the study sites to ensure that proper procedures were being followed.
- Data for each patient were collected on standard CRFs.
- Information on the CRFs was verified with source documentation.
- Standard operating procedures of P&U were followed in the creation and quality control of all tables, listings, and analyses.

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

9.7.1 Determination of Sample Size

The adequacy of the sample size was investigated by looking at the power to at least be able to detect the difference between the PBO group and the 8-mg RBX treatment group. In a previously conducted RBX study [23] the difference between PBO and the RBX groups in the mean change from baseline of the 21-item HAM-D total score was 4.7 with the standard deviation of 9.5. Eighty patients per treatment group were necessary in order to provide the test with a power of 88% and alpha=0.05 (two-sided). With 80 patients per arm, 80% power can still be achieved in the observed case analyses if 20% of patients drop out from the study. However, since the actual dropout rate was higher (30% vs planned 20%), a total of 365 patients (about 91 patients per treatment group) were targeted for enrollment instead of the 320 patients originally planned (refer to Amendment 12, Section 9.8.1).

9.7.2 Data Sets Analyzed

The intent-to-treat (ITT) data set, which includes all patients randomized into the trial who received at least one treatment dose with at least one post-baseline efficacy visit was used for the analysis. All analyses were based on the pre-printed study period numbers on the CRF. Two types of analyses were performed for the primary variables: "last observation carried forward" (LOCF) and "observed cases" (OC). The LOCF analysis uses the last valid assessment as an estimate for all subsequent missing values. The OC analysis does not replace missing data. The intent-to-treat data set using the LOCF technique is the primary analysis and the OC analysis is included as a secondary analysis. All reported p-values are based on two-sided tests. Results are reported as statistically significant if the p-value was 0.050 or less.

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

9.7.3 Demographic and Baseline Characteristics

Continuous variables were summarized using treatment group means, standard deviations, and ranges. Categorical variables were summarized using frequency counts. Comparability among treatment groups at baseline was assessed using a one-way analysis of variance (ANOVA) for continuous variables and a chi-square test for categorical variables.

9.7.4 Efficacy Evaluations

For the continuous variables (such as HAM-D total mean change from baseline and MADRS total mean change from baseline), testing for the overall differences among the treatment groups was performed using a two-way analysis of variance (ANOVA) model that included treatment, investigator, treatment-by-investigator terms. Treatment-by-investigator interaction was tested to evaluate poolability of data. If the interaction effect was significant at the 0.10 level ($P<0.10$), the individual investigator results were presented to identify the source of the interactions. Tests of main effects will not be dependent on significance of the interaction term. Orthogonal contrast was used to test for differences between each reboxetine dose and placebo. Also, subset analyses were performed by severity and gender. Patients with illness rated as severe were defined as those patients scoring 5-7 (markedly to severely ill) on the CGI Severity of Illness scale at baseline, while those with a score less than 5 at baseline were considered to have a non-severe illness. Categorical data (such as response and remission) were analyzed by the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.

Means of individual component of the HAMD were displayed by treatment group and by visit to identify any components that may have had a major influence on the HAMD total. 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 that were used by the investigators to identify AEs in the CRFs were translated into COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) terms and then grouped according to COSTART body system and preferred term.

Each AE was counted once according to the date of onset. If the onset was prior to the first dose of study medication and the event did not increase in severity after initiation of study drug, the AE was considered to be a pretreatment AE and was not counted in the adverse-event frequency tables. If the onset was prior to the first dose of study medication and the severity increased after baseline, the event was counted as an AE. This rule is consistent with the treatment-emergent symptom (TES) convention for counting AEs.

The TES incidence was summarized as follows: 1) by body system and preferred term; 2) by maximum severity; 3) by age; 4) by gender; 5) by relationship to study drug; and 6) by seriousness. Drug-related events were defined as those for which the investigator deemed the event related to the study medication. A summary of the AEs that resulted in the termination of the study medication was also prepared.

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 post-baseline evaluation were analyzed using a one-way ANOVA. Differences between each reboxetine treatment group and placebo were analyzed using a paired t-test.

The frequency of patients who had clinically significant values for laboratory assay tests was tabulated, and data for the individual patients were listed. The criteria used to identify patients with clinically significant laboratory values was determined by the central laboratories normal ranges (see Appendix 9).

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 groups in the mean change from baseline at each post-baseline evaluation were analyzed using a one-way ANOVA. Differences between each reboxetine treatment group and placebo were analyzed using a paired t-test.

The frequency of patients who had clinically significant abnormal vital signs was tabulated, and data for the individual patients were listed. The following criteria were used to identify patients with clinically significant values for vital signs:

Variable	Criteria
Heart Rate	≤50 or ≥120 beats/minute
Systolic Blood Pressure	≤90 or ≥180 mmHg
Diastolic Blood Pressure	≤50 or ≥105 mmHg

9.7.5.4 Electrocardiograms

The ECGs were read manually by personnel at Premier Research Worldwide (Philadelphia, PA), and the heart rate, PR, QRS, and QT data were electronically transferred to P&U. The QT interval data were corrected for heart rate using the modified Bazett's formula (by Premier) and using Fridericia's correction formula (by P&U, using the Premier dataset).

A "shift" table was prepared to show the number and percentage of patients who had normal or abnormal ECG findings at the last evaluation versus at the pretreatment assessment. Patients who had abnormal ECG findings were listed.

9.7.6 Rules for Estimation of Missing Data

9.7.6.1 Efficacy Data

In the case of a missing HAM-D or MADRS individual component score at baseline, the total score for the patient at baseline was set to missing in both the LOCF and OC analyses. For missing post-baseline individual component scores, the last observed total score was carried forward to estimate subsequent missing scores in the LOCF analysis. In the OC analysis, the total score for the patient on a particular visit was set to missing if a post-baseline individual component score was missing. In the LOCF analyses, no observations were carried forward if the final valid assessment occurred at baseline.

9.7.6.2 Safety Data

If the onset date for an AE was missing, the study period on the adverse event case report form 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 Changes in the Conduct of the Study

The original protocol was amended 12 times. All relevant changes summarized in this section are reflected in the text of the report. The amendments relevant to this study are presented below:

Amendment 1, 24 April 1997

- The initial washout period ranging from 4 days to 4 weeks was changed to a range of 4 days to 2 weeks because of investigator concerns with the long washout period.

- The period that the patients were to be free of antidepressants before study entry was changed from a range of 4 days to 4 weeks to a range of 4 days to 2 weeks.
- An additional statement was added to the section on "Number of Patients" stating that the centers failing to enroll at least 1 patient in the 3 months following ethical approval and study medication shipment would be closed.
- The classification of Major Depressive Disorder the inclusion criteria was changed from DSM-IV 296.2x-296.3 to DSM-IV F32-F33.0, F-33.1.
- Changes in exclusion criteria were:
    - ♦ Patients were to be excluded if they had dysthymia, cyclothymia as per the original protocol. This was changed to exclude patients with a history of DSM-IV diagnosis of dysthymia (F34.1), cyclothymia (F34.0), bipolar (F30 - F31), and schizophrenia (F 20.xx).
    - ♦ Resistance to full doses of previous antidepressants was specified as being that recommended by the manufacturer.
    - ♦ Patients taking high doses of benzodiazepines or those under chronic therapy with carbamazepine, valproate, lithium, etc. were to be excluded.
    - ♦ All patients who had a positive pregnancy test were to be excluded rather than only those of child-bearing age (as per original protocol).
    - ♦ The exclusion of patients who had DSM-IV diagnosis of substance abuse was extended to reflect the presence of this disorder at enrollment or in the 6 months preceding the study.
    - ♦ The statement about patients who were at risk for suicide was clarified in order to specify the definition using the HAM-D Item 3 score of >2. Patients who had a history of suicide attempts were also to be excluded.
- Patient allocation was to be done at baseline, sequentially by center, and on the basis of patient's temporal entry into the study, and not only by the latter criterion (as per the original protocol).
- An agreement by P&U to provide study medication to those patients who wanted to continue the treatment after the 6-week study period was added to the protocol.
- Allowance was made for patients to receive standard psychological support without specific cognitive-behavior therapy or concomitant psychotropic drugs (other than hypnotics) and not be considered as a violation of the protocol.
- Inter-rater reliability of all psychiatric evaluations was to be investigated.
- Biochemistry assays were to be conducted at Screening, Day 21, Day 42, or End of Treatment. The investigator by this amendment was also allowed to seek the advice of a cardiologist in case of any observed abnormal ECG tracings.

- Patients could also be withdrawn from the study, if after 2 weeks of treatment, they showed deterioration or unchanged CGI score, and if in the investigator's judgment this exposed the patient to an unacceptable risk.

Amendment 2, 6 June 1997

This amendment allowed the French investigators to continue the treatment of patients, who benefited from the medications for 16 weeks beyond the study period (42 days), still in double-blind mode.

Certain conditions were to be met for patients to continue treatment:

- Protocol specifications were to be duly fulfilled
- The visit on Day 42 should have been completed
- The patient was willing to complete the treatment and the investigator expected to see benefits with the follow-up treatment.
- Patient compliance was good during the study
- Patients accepted the follow-up constraints

These visits were to occur every 4 weeks and were to include: vital signs, HAM-D, MADRS (as per Amendment 4 below), CGI, tolerance (every AE was to be reported), concomitant therapy, and record of delivered and returned study medication.

Amendment 3, 9 June 1997

In this amendment, the definition of a SAE was expanded to include permanent impairment of function or permanent damage to a body structure, cancer, and overdose.

Amendment 4, 21 July 1997

This amendment was written to allow the Italian investigators to continue the treatment of patients who benefited from the medications for 20 weeks beyond the study period (42 days), still in double-blind mode.

The Patient Information Sheet was amended to exclude women who were pregnant. Women of child-bearing potential were required to use an efficient contraceptive method while on the study. Information that placebo could improve clinical status in about 30% of depressed patients, that the study would not be undertaken until approval was obtained from the appropriate IEC/IRB, and that patients had a right to receive a copy of the Patient Information Sheet was also added.

Amendments 5 (22 October 1997), 6 (23 December 1997), and 9 (16 July 1998)

These amendments list additional centers and names of investigators. The lists can be found in Appendix 6.

Amendment 7, 4 February 1998

A dose reduction statement was added to the compliance section. If deemed appropriate by the investigator, for safety reasons, the daily dose could be reduced for a period not exceeding 7 consecutive days by omitting 1 capsule per day, while treatment discontinuation could not last longer than 4 days. If this period was exceeded, the patient was to be taken off the study. If the treatment was resumed nonetheless, this was to be considered a protocol violation.

In order to overcome acute, disabling anxiety episodes that may arise during the study, a single course of the benzodiazepines (as listed in Appendix 4 of the study protocol), at doses recommended by the manufacturer, and for a period not exceeding 3 consecutive days was permitted. Prolonged administration (longer than 3 consecutive days) was to be considered a protocol violation.

Amendment 8, 13 May 1998

The exclusion criteria regarding the history of attempted suicide was modified in order to specifically refer to the current depressive episodes. This modification was done after several months of practical experience with this study, and because not every suicide attempt in the past (expressed as actions or words) would necessarily increase the acute risk in the current depressive episode. Since patients who are suicidal still must not be enrolled in the study, this amendment does not increase the risk for the patients in the study.

To exclude patients who suffer from thyroid dysfunction, the levels of T_4 (thyroxin) and TSH (thyroid stimulating hormone) were also measured at screening.

Due to slow accrual, the recruitment period had to be extended from 12 months to 18 months with the new end date being the first quarter of 1999.

Amendment 10, 1 October 1998

This amendment specified that the last inclusion date was to be 31 December 1998. A list of additional supplementary centers in 3 additional countries (Sweden, Russia, and Netherlands) is also contained in this amendment (see Appendix 6).

Amendment 11, 20 October 1998

Since the metabolism and interaction potential for reboxetine are poorly characterized, an additional criterion was added to the exclusion criteria: Patients currently taking known inhibitors of drug metabolizing enzymes (with the exception of CYP2D6), such as azole antifungals, macrolide antibiotics or fluvoxamine were to be excluded from the study.

Amendment 12, 8 December 1998

This amendment extended the inclusion period and increased the sample size. Since the actual dropout rate was higher (30% vs planned 20%), a total of 365 patients were targeted

for enrollment instead of the 320 patients originally planned. Therefore, the last inclusion date for The Netherlands, Russia, and Sweden was extended to 28 February 1999. The last inclusion date for France, Germany, and Italy was to remain as 31 December 1998 (due to the earlier expiration date [28 February 1999] of the drug).

9.8.2 Changes in Planned Analyses

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

All patients randomized into the study had ECGs read by Premier Research Worldwide (Philadelphia, PA). This reading was performed by a single cardiologist who measured PR, QRS, and QT intervals as well as calculated QTc intervals using modified Bazett's formula. PNU calculated Fridericia's formula from Premier's data set.

Since there were no statistically significant differences in the primary efficacy variables, the following analyses were not completed: orthogonal contrast and regression analyses to assess the relationship between dose and response, ninety percent confidence intervals on the differences between the treatment group with the highest reduction in the HAMD total score and other reboxetine treatment groups, and time to response/remission.

10 RESULTS

Key data displays are included in the text. Detailed, supportive statistical tables and patient listings are included in Section 14 and Appendices 10 to 13, respectively. References to these tables are included in the text.

The protocol was amended (see Section 9.8.1, Amendments 2 and 4) to allow the French and Italian investigators to continue the treatment of patients, who benefited from the medications for 16 weeks in France and for 20 weeks in Italy beyond the study period (42 days), still in double-blind mode. Sixteen patients continued treatment beyond Day 42. The patient disposition, demographics, and safety data, hereafter called follow-up data for these patients are also included in this report.

10.1 Study Patients

(Section 14, Table 1.1)

10.1.1 Disposition of Patients During the Study

(Section 14, Table 1.3; Appendix 10, Table 1.4)

The number of patients either completing or discontinuing the study and reasons for discontinuation are shown in Table 5. The patients who discontinued are listed in Appendix 10 (Table 1.4).

Table 5. Summary of Patient Disposition

Disposition	RBX 2-mg n (%)	RBX 4-mg n (%)	RBX 8-mg n (%)	PBO n (%)
Randomized Patients	87 (100.0)	87 (100.0)	89 (100.0)	87 (100.0)
Intent-to-Treat Patients	87 (100.0)	87 (100.0)	89 (100.0)	87 (100.0)
Patients who Completed	59 (67.8)	52 (59.8)	62 (69.7)	67 (77.0)
Patients who Discontinued	28 (32.2)	35 (40.2)	27 (30.3)	20 (23.0)
Reasons for Discontinuation				
Lack of Efficacy	10 (11.5)	16 (18.4)	4 (4.5)	7 (8.0)
Adverse Events				
Serious	0 (0)	3 (3.4)	2 (2.2)	0 (0)
Nonserious	9 (10.3)	9 (10.3)	13 (14.6)†	7 (8.0)
Administrative				
Ineligible	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)
Protocol Noncompliance	1 (1.1)	-	1 (1.1)	1 (1.1)
Patient Request	3 (3.4)	3 (3.4)	4 (4.5)	3 (3.4)
Lost to Follow-up	4 (4.6)	3 (3.4)	2 (2.2)†	0 (0)
Other	0 (0)	0 (0)	0 (0)	1 (1.1)

† Patient # 1089 was included in the lost to follow-up category rather than in the AE (nonserious) category. Therefore, the data in these categories have been modified to account for this discrepancy and does not match the source tables.
RBX = reboxetine; PBO = placebo
Source: Section 14, Table 1.3

A total of 350 patients were enrolled in the study and randomized to receive treatment with RBX 2 mg (87 patients), RBX 4 mg (87 patients), RBX 8 mg (89 patients), and PBO (87 patients). Fifty-nine (67.8%) of the patients in the RBX 2-mg group, 52 (59.8%) of the patients in the RBX 4-mg group, 62 (69.7%) of the patients in the RBX 8-mg group, and 67 (77%) of the patients in the PBO group completed the study. The primary reasons for study discontinuation in each group were due to lack of efficacy (11.5% [10/87] RBX 2-mg group; 18.4% [16/87] RBX 4-mg group; 4.5% [4/89] RBX 8-mg group; 8% [7/87] PBO group) and due to nonserious AEs (10.3% each [9/87] for both RBX 2-mg and RBX 4-mg group; 14.6% [13/89] RBX 8-mg group, and 8% [7/87] in the PBO group).

10.1.2 Disposition of Patients During Follow-Up

(Section 14, Table 1.3 FU)

Table 6 summarizes patient disposition for 16 patients who continued to be treated with study medication after Day 42.

Table 6. Summary of Patient Disposition (FU)

Disposition	RBX 2-mg n	RBX 4-mg n	RBX 8-mg n	PBO n
Randomized Patients	6	2	3	5
Intent-to-Treat Patients	6	2	3	5
Patients who Completed	3	1	0	2
Patients who Discontinued	2	1	3	3
Reasons for Discontinuation				
Lack of Efficacy	0	0	0	1
Improvement	1	0	0	0
Adverse events				
Non-Serious	0	1	1	0
Administrative				
Protocol Noncompliance	0	0	1	0
Patient Request	0	0	1	1
Lost to Follow-up	1	0	0	1

RBX = reboxetine; PBO = placebo
Source: Section 14, Table 1.3 FU

10.1.3 Protocol Deviations

(Appendix 11, Table 26.1)

Lorazepam, oxazepam or temazepam were the protocol-specified psychotropic medications that patients were allowed to take (for not more than 3 consecutive days - see Section 9.4.7). A total of 68 patients (22 in the RBX 2-mg group, 13 in the RBX 4-mg group, 16 in the RBX 8-mg group, and 17 in the PBO group) who took lorazepam, temazepam, or oxazepam for anxiety, tension, anguish, or inner tension for more than 3 consecutive days, or some other psychotropic drug were considered as protocol deviations. In addition, 2 patients in the RBX 8-mg group were considered protocol deviations for failing to meet the entry criteria (HAM-D baseline score <22). A full listing of these patients can be found in (Appendix 11, Table 26.1). None of these patients were excluded from the efficacy or safety analyses.

10.1.4 Demographic and Other Baseline Characteristics

10.1.4.1 Demographic Characteristics of Patients at Baseline

(Section 14, Tables 2.1, 2.2)

Table 7 below summarizes demographic data for the ITT patients at baseline.

Table 7. Patient Demographics

Variable	RBX - mg N=87	RBX 4-mg N=87	RBX 8-mg N=89	PBO N=87	P-value
Age (years)					
Mean±SD	42.3±10.9	40.8±10.0	41.6±10.6	40.5±11.2	0.6634*
Range	18 – 62	22 – 61	18 – 65	18 – 65	
Weight (lb)					
Mean±SD	149±28.4	156±35.7	158±32.1	156±39.6	0.3512*
Range	104 – 238	98.1 – 287	94.8 – 287	90.4 – 340	
Not Reported	0	0	1	0	
Height (in)					
Mean±SD	66.2±3.4	65.7±3.4	66.6±3.6	65.7±3.3	0.1976*
Range	59.1 – 76.4	58.7 – 74.0	59.1 – 77.2	57.1 – 73.2	
Not Reported	2	0	3	1	
Sex (No. and %)					
Male	26 (29.9%)	32 (36.8%)	33 (37.1%)	26 (29.9%)	0.5820†
Female	61 (70.1%)	55 (63.2%)	56 (62.9%)	61 (70.1%)	
Race (No. and %)					
Caucasian	85 (97.7%)	83 (95.4%)	87 (97.8%)	82 (94.3%)	0.9159†
Black	1 (1.1%)	2 (2.3%)	0	2 (2.3%)	
Asian	0	1 (1.1)	1 (1.1)	1 (1.1)	
Other	1 (1.1)	1 (1.1)	1 (1.1)	2 (2.3)	

* p-values are based on one-way ANOVA with treatment as the main effect
† p-values are based on chi-square test
% are based on number of patients in each group
RBX = reboxetine; PBO = placebo, SD = standard deviation
Source: Section 14, Tables 2.1, 2.2

No statistically significant differences among treatment groups were observed in the demographic characteristics (ie, age, weight, height, sex, and race). Patients ranged in age from 18 to 65 years.

10.1.4.2 Demographics of Patients at Follow-Up

(Section 14, Tables 2.1FU, 2.2FU)

Table 8 summarizes the demographics for the patients who continued treatment beyond Day 42. Considering the small sample size, the treatment groups were balanced for all variables.

Table 8. Patient Demographics (FU)

Variable	RBX 2-mg N= 6	RBX 4-mg N= 2	RBX 8-mg N= 3	PBO N= 5	P-Value
Age (years)					
Mean±SD	40.7±14.1	40.5±0.7	38.3±2.1	47.4±9.3	0.6326*
Range	18–58	40–41	36–40	37–59	
Weight (lb)					
Mean±SD	140±19.2	151±20.2	126±30.9	155±37.7	0.5385*
Range	104–154	137–165	104–161	122–213	
Height (in)					
Mean±SD	66.1±3.15	65.0±2.76	62.2±0.80	65.3±3.96	0.4184*
Range	61.8–70.1	63.0–66.9	61.4–63.0	61.0–69.3	
Sex (No. and %)					
Male	2	1	0	3	0.3828†
Female	4	1	3	2	
Race (No. and %)					
Caucasian	6	2	3	5	-
Inpatient/Outpatient					
Outpatient	6	2	3	5	-

* p-values are based on a one-way ANOVA with treatment as the main effect
† p-values are based on chi-square test (chi-square test may not be valid)
RBX = reboxetine; PBO = placebo
Source: Tables 2.1FU, 2.2FU

10.1.4.3 Psychiatric History

10.1.4.3.1 Previous History of Depression

(Section 14, Table 2.4)

A summary of the prior history of depression is presented in Table 9.

Table 9. Previous History of Depression

Variable	RBX 2-mg N=87	RBX 4-mg N=87	RBX 8-mg N=89	PBO N=87	P-Value*
Age (years) at Onset of Major Depression					
No. of Patients Reporting	87	87	88	87	
Mean ± SD	36.0±10.8	33.4±10.7	35.2±12.2	34.3±11.1	0.4696
Range	13-60	14-58	2-65	8-62	
No. of Previous Episodes					
No. of Patients Reporting	77	76	79	77	
Mean ± SD	2.3±3.7	2.4±3.0	2.5±3.0	4.0±11.2	0.2890
Range	0-25	0-17	0-15	0-80	
Approximate Duration of Last Episode (weeks)					
No. of Patients Reporting	58	64	60	62	
Mean ± SD	26.2±25.6	21.4±26.1	36.9±77.2	23.3±29.6	0.2307
Range	0-104	0-156	0-581	0-156	

* p-values are based on a one-way ANOVA with treatment as the main effect
RBX = reboxetine; PBO = placebo; SD = standard deviation
Source: Section 14, Table 2.4

No statistically significant differences were observed among treatment groups in the prior history of depression based on mean age at onset of depression, the mean number of previous episodes, or the mean duration of the last episode.

10.1.4.3.2 Characteristics of Present Depressive Episode

(Section 14, Tables 2.4, 2.5)

Table 10 summarizes the baseline characteristics for the present depressive episode.

Table 10. Characteristics of the Present Depressive Episode

Variable	RBX 2-mg N=87	RBX 4-mg N=87	RBX 8-mg N=89	PBO N=87	P-Value
Approximate Duration (wk)					
No. of Patients Reporting	86	87	89	87	
Mean ± SD	37.9±84.7	18.0±22.2	25.1±48.8	22.3±37.7	0.0850*
Range	2-593	1-156	1-318	1-260	
Best Characterized as (No. and %):					
Exacerbation of chronic condition	4 (4.6)	8 (9.2)	10 (11.2)	6 (6.9)	0.8751†
Recurrence of similar previous conditions	49 (56.3)	44 (50.6)	44 (49.4)	47 (54.0)	
Significantly different from any previous conditions	6 (6.9)	7 (8.0)	4 (4.5)	7 (8.0)	
First occurrence, no previous psychiatric diagnosis	28 (32.2)	28 (32.2)	31 (34.8)	27 (31.0)	
Precipitating External Stress (No. and %):					
Absent	30 (34.5)	29 (33.3)	33 (37.1)	27 (31.0)	0.8235†
Probably present	29 (33.3)	33 (37.9)	28 (31.5)	37 (42.5)	
Definitely present	28 (32.2)	25 (28.7)	28 (31.5)	23 (26.4)	

* p-values are based on a one-way ANOVA with treatment as the main effect
† p-values are based on chi-square test
% are based on ITT patients
RBX = reboxetine; PBO = placebo
Source: Section 14, Tables 2.4, 2.5

The approximate duration of the present depressive episode ranged from 1 to 593 weeks across the groups; the mean duration of the present episode was 37.9 weeks in the RBX 2-mg group, 18 weeks in the RBX 4-mg group, 25.1 weeks in the RBX 8-mg group, and 22.3 weeks in the placebo group. For about 50% of the patients in each group, the present episode was judged to be a recurrence of similar previous conditions. For a third of the patients in each group, the present depressive episode was the first occurrence of major depression. Most patients (≥63%) in each group had precipitating stress associated with their present episode. No statistically significant differences among treatment groups were found in the variables assessing the present depressive episode.

10.1.4.3.3 Severity of Depression at Baseline

(Section 14, Table 2.3)

Table 11 summarizes the baseline values for HAM-D, CGI-Severity of Illness, and MADRS scales.

Table 11. Severity of Depression at Baseline

Variable	R BX 2-mg N = 87	RBX 4-mg N = 87	RBX 8-mg N = 89	PBO N = 87	P-Value*
HAM-D					
Mean Total Score ± STD	26.3±2.5	26.2±2.7	26.4±2.6	26.4±2.6	0.8934
Range	22-32	22-33	18-32	22-33	
CGI—Severity of Illness†					
Mean Score ± STD	4.8±0.7	4.7±0.7	4.8 ± 0.8	4.7±0.6	0.3623
Range	4-6	3-6	3 - 6	3-6	
MADRS					
Mean Total Score ± STD	31.5±4.5	30.8±5.1	32.2±5.3	32.2±5.1	0.2453
Range	20-39	19-43	16-46	21-44	

* p-values are based on a one-way ANOVA with treatment as the main effect
† 7-point scale: 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = among the most extremely ill patients
RBX = reboxetine; PBO = placebo, STD = standard deviation, HAM-D = Hamilton Rating Scale for Depression, CGI = Clinical Global Impression, MADRS = Montgomery-Asberg Depression Rating Total Score
Source: Section 14, Table 2.3

No statistically significant differences among treatment groups were observed in the severity of depression at baseline as judged by the mean HAM-D total score, the mean CGI-Severity of Illness score, or the mean MADRS score.

10.1.4.3.4 Other Baseline Evaluations

(Section 14, Tables 2.1, 2.2, 2.6, 2.7)

No statistically significant differences among treatment groups were observed in systolic or diastolic blood pressure, pulse rate, cigarette smoking, consumption of caffeinated beverages per day, and in/outpatient status (Section 14, Tables 2.1, 2.2). Similarly, no statistically significant differences among treatment groups were observed in the proportion of patients who had normal or abnormal physical examination (Section 14, Table 2.6) or any significant differences in patient medical histories (Section 14, Table 2.7).

10.1.5 Concomitant Medications

10.1.5.1 Prior to Study

(Section 14, Table 2.9)

At the screening evaluation, 51.7% (45/87) of patients in the RBX 2-mg group, 52.9% (46/87) of patients in the RBX 4-mg group, 51.7% (46/89) of patients in the RBX 8-mg group, and 54% (47/87) of patients in the PBO group were taking at least one medication.

Concomitant medications taken most frequently (≥5% in each treatment group) at pretreatment included antianxiety medications (mostly lorazepam and oxazepam), estrogens, or oral contraceptives. A detailed summary of concomitant medications can be found in Section 14, Table 2.9.

10.1.5.2 During the Study Period

(Section 14, Table 2.10)

Noninvestigational medications were taken concomitantly with the study medication by 69% (60/87) of patients each in the RBX 2-mg group and RBX 4-mg group, 70.1% (61/87) of patients in the PBO group, and by 73% (65/89) of patients in the RBX 8-mg group. Acetaminophen (mostly paracetamol), antianxiety medications (mostly lorazepam or oxazepam), estrogens, nonbarbiturates sedatives and hypnotics, and oral contraceptives were taken by ≥5% of patients in each group. A detailed summary of concomitant medications can be found in Section 14, Table 2.10.

10.2 Dosage Information

10.2.1.1 Extent of Exposure

(Section 14, Table 2.8)

Table 12 summarizes the mean daily dose, ie, the average dose that was taken over a specified treatment interval.

Table 12. Mean Daily Dose By Visit†

	RBX 2-mg N = 87		RBX 4-mg N = 87		RBX 8-mg N = 89	
Study Day	n‡	Mean Dose (mg/d)	n‡	Mean Dose (mg/d)	n‡	Mean Dose (mg/d)
7	84	2.02	85	3.89	88	7.74
14	82	2.01	80	3.97	84	7.83
21	70	2.02	76	3.97	80	7.94
28	68	2.02	65	3.78	76	7.96
35	63	1.98	62	3.98	69	8.02
42	60	2.02	54	4.14	62	7.98

† Average dose for all patients who took study medication during the corresponding week
‡ Number of patients with dosing information at the specified visit
RBX = reboxetine; PBO = placebo
Source: Section 14, Table 2.8

Patients in the RBX 2-mg group, RBX 4-mg, RBX 8-mg were to receive 1 capsule (1, 2 or 4 mg each) BID from Day 1 to Day 42 in the morning and evening at a fixed time. If deemed appropriate by the investigator, the daily dose could be reduced for a period not exceeding 7 consecutive days by omitting 1 capsule a day, while treatment discontinuation could not

last longer than 4 days. The mean dosing data at each visit suggests that most patients in each treatment group complied with the protocol-specified dosing regimen.

10.2.2 Measurement of Treatment Compliance

(Appendix 12, Table 27.1)

Listings of mean daily dose were examined by reviewing each individual record (Case Report Form dispensing/return records) of patients with <75% of prescribed dose for any treatment week. This identified patients who discontinued study medication for more than 4 days or who took less than 50% of the prescribed dose for 7 days, in violation of Amendment 7. Seven patients were identified as noncompliant with treatment as per the above specifications. The listing of patients can be found in Appendix 12 (Table 27.1).

Investigator No	Patient No	Treatment Group	Deviation
14634	1061	RBX 2mg	Took < 50% of weekly dose
18261	2190	RBX 4 mg	Missed medication for 1 week
19900	2175	RBX 4 mg	Took < 50% of weekly dose
19907	3076	RBX 4 mg	Missed medication for 6 days
18249	2017	RBX 8 mg	Missed medication for 6 days
18261	2191	RBX 8 mg	Missed medication for 7 days
19901	5033	RBX 8 mg	Missed medication for 6 days

10.3 Efficacy Results

The efficacy analyses were based on the intent-to-treat patient (ITT) population, which included patients who received at least one dose of study medication and who had at least one post-baseline visit. All of the 350 patients randomized into the study (87 in the RBX 2-mg group, 87 in the RBX 4-mg group, 89 in the RBX 8-mg group, and 87 in these PBO group) satisfied this criterion and were therefore included in the ITT efficacy analyses.

10.3.1 Primary Efficacy Variable

The primary efficacy variable was the mean change from baseline on the HAM-D total score. Two types of analyses were performed for the primary variables: “Last 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 intent-to-treat data set using the LOCF technique was the primary analysis and the OC analysis was the secondary analysis.

10.3.1.1 HAM-D Total Score During the Study

(Section 14, Tables 2.3, 3.1A, 3.1B, 3.14, 3.15)

Table 13 summarizes the mean change from baseline in the HAM-D total score at each post-baseline evaluation for both the LOCF and OC analyses. At each evaluation (Day 7, 14, 21, 28, 35, and 42), no statistically significant differences were observed among treatment groups

by the LOCF or by the OC analysis. At Day 42, the mean decrease in the HAM-D total score was –10.0 for the RBX 2-mg group, –8.6 for the RBX 4-mg group, –10.5 for the RBX 8-mg group, and –11.3 for the PBO group by the LOCF analysis. By the OC analysis, the mean decrease in the HAM-D score on Day 42 was –13.2 for the RBX 2-mg group, –13.0 for the RBX 4-mg group, –13.6 for the RBX 8-mg group, and –13.9 for the PBO group. The mean changes in the HAM-D total score were higher for the PBO group than for any of the RBX groups for both the LOCF and the OC analyses, demonstrating a high placebo response in this study. Mean change from baseline to Day 42 on the HAM-D total score by gender and severity did not show a statistical significance when comparing RBX-treated patients with patients in the PBO group (Section 14, Tables 3.14, 3.15).

Table 13. Mean Change From Baseline in Hamilton Rating Scale (HAM-D) Total Score

Analysis	Group	Baseline		Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
		n	Mean	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	RBX 2mg	87	26.3	85	-3.6	86	-5.9	86	-7.8	86	-8.5	86	-9.7	86	-10.0
	RBX 4-mg	87	26.2	86	-2.2	86	-5.7	86	-7.3	86	-7.5	86	-7.9	86	-8.6
	RBX 8-mg	89	26.4	87	-2.0	88	-4.8	88	-8.5	88	-9.7	88	-9.8	88	-10.5
	PBO	87	26.4	84	-3.3	85	-5.9	85	-8.8	86	-10.4	86	-10.6	86	-11.3
P-value*	Among Treatment Groups	NA		0.0796		0.5436		0.7777		0.1933		0.3455		0.3589	
OC	RBX 2-mg	87	26.3	85	-3.6	82	-6.1	69	-9.0	67	-10.3	64	-12.1	61	-13.2
	RBX 4-mg	87	26.2	86	-2.2	80	-6.0	76	-8.1	66	-9.4	62	-10.2	55	-13.0
	RBX 8mg	89	26.4	87	-2.0	84	-5.5	81	-9.4	78	-11.3	70	-12.2	64	-13.6
	PBO	87	26.4	84	-3.3	82	-6.1	78	-9.5	75	-11.7	69	-12.7	68	-13.9
P-value*	Among Treatment Groups	NA		0.0796		0.8101		0.8430		0.7687		0.9383		0.9029	

* P-values are based on a 2-way analysis of variance (ANOVA)

† mean change from baseline

RBX = reboxetine; PBO = placebo; LOCF = Last Observation Carried Forward; OC = Observed Case; NA = not applicable

Source: Section 14, Tables 2.3, 3.1A, 3.1B

10.3.1.2 HAM-D Total Score During Follow-Up

(Section 14, Table 3.1B FU)

Table 14 summarizes the mean change from baseline in the HAM-D total score for the patients who continued treatment after Day 42.

Only 12 of 248 (4.8%) patients completing 42 days treatment continued follow-up treatment. Five patients were treated with RBX 2 mg/day; 1 was treated with RBX 4 mg/day; 3 were treated with RBX 8 mg/day, and 3 were treated with PBO. The small sample size in the follow-up treatment groups precludes meaningful comparisons.

In general, antidepressant efficacy for patients entering the follow-up treatment phase was maintained during the follow-up period.

Table 14. Mean Change From Baseline in Hamilton Rating Scale (HAM-D) Total Score (FU)

		Baseline		Day 42		Week 4†		Week 8†		Week 12†		Week 16†		Week 20†	
Analysis	Group	n	Mean	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
OC	RBX 2-mg	87	26.3	61	-13.2	5	-22.6	5	-22.4	5	-19.4	4	-21.5	1	-16.0
	RBX 4-mg	87	26.2	55	-13.0	1	-26.0	1	-26.0	1	-27.0	1	-24.0	1	-17.0
	RBX 8-mg	89	26.4	64	-13.6	3	-18.0	1	-19.0	1	-7.0	-	-	1	-6.0
	PBO	87	26.4	68	-13.9	3	-19.0	3	-20.3	2	-21.0	2	-22.0	-	-

† Week after Day 42
RBX = reboxetine; PBO = placebo
Source: Section 14, Tables 2.3 FU, 3.1B FU

10.3.2 Secondary Efficacy Variable(s)

The secondary efficacy measures were Clinical Global Improvement (CGI), CGI-Response Rate, the CGI-Severity of Illness scale, CGI-Efficacy Index, the mean change from baseline in the Montgomery-Asberg Depression Rating total score (MADRS), response/remission rates using HAM-D 21 item scale, as well as Patient Global Impression Scale (PGI).

10.3.2.1 Clinical Global Impression Scales

Clinical Global Impression scale is comprised of the Clinical Global Improvement (CGI), CGI-Response Rate, CGI-Severity of Illness scale, and CGI-Efficacy Index.

10.3.2.1.1 Clinical Global Improvement

(Section 14, Tables 3.4A, 3.4B)

The distribution of responses on the CGI-Global Improvement scale (eg, “very much improved,” “much improved,” “minimally improved,” “no change,” and “minimally worse”) are summarized in Section 14, Tables 3.4A and 3.4B, for the LOCF and OC analyses, respectively. Except for Day 42, where the among treatment groups overall p-value was 0.0453 for LOCF (pairwise comparison of RBX 2 mg versus PBO p-value=0.0385 in favor of the PBO group), no other significant differences among treatment groups were observed (Section 14, Tables 3.4A, 3.4B).

10.3.2.1.2 Clinical Global Improvement-Response Rate

(Section 14, Tables 3.6A, 3.6B)

Table 15 summarizes the CGI-Global Improvement responder status (a measure of improvement) at each post-baseline visit for both the LOCF and OC analyses. A responder was defined as a patient with a global improvement score of 1 (very much improved) or 2 (much improved). Section 14, Tables 3.6A and 3.6B provide additional information, including the p-values for the least square mean change for the LOCF and OC analyses, respectively. No statistically significant differences were seen among treatment groups over the study period either by the LOCF or by the OC analysis.

Table 15. Clinical Global Impression (CGI)-Global Improvement Responder Status†

Analysis	Group	Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
		n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
LOCF	RBX 2-mg	11/ 85	12.9	17/86	19.8	26/86	30.2	30/86	34.9	37/86	43.0	37/86	43.0
	RBX 4-mg	9/86	10.5	25/86	29.1	26/86	30.2	27/86	31.4	32/86	37.2	35/86	40.7
	RBX 8-mg	6/87	6.9	18/88	20.5	31/88	35.2	42/88	47.7	44/88	50.0	46/88	52.3
	PBO	10/84	11.9	21/85	24.7	29/85	34.1	34/86	39.5	36/86	41.9	42/86	48.8
P-value*	Among Treatment Groups	0.4565		0.3728		0.8961		0.1627		0.3905		0.3587	
OC	RBX 2-mg	11/85	12.9	17/82	20.7	25/70	35.7	28/67	41.8	35/64	54.7	35/61	57.4
	RBX 4-mg	9/86	10.5	25/80	31.3	26/76	34.2	27/66	40.9	31/62	50.0	33/55	60.0
	RBX 8mg	6/87	6.9	18/84	21.4	31/80	38.8	42/78	53.8	44/70	62.9	44/64	68.8
	PBO	10/84	11.9	21/83	25.3	28/78	35.9	33/76	43.4	35/69	50.7	41/68	60.3
P-value*	Among Treatment Groups	0.4565		0.2918		0.9843		0.4153		0.4779		0.4880	

* P-values are based on a Cochran-Mantel-Haenszel test

† CGI-Global Impression Score of 1 (very much improved) or 2 (much improved)

N = number of patients with data reported, n = number of responders,

RBX = reboxetine; PBO = placebo; LOCF = Last Observation Carried Forward, OC = Observed Case

Source: Section 14, Tables 3.6A, 3.6B

10.3.2.1.3 Clinical Global Impression-Severity of Illness

(Section 14, Tables 2.3, 3.10A, 3.10B)

Table 16 summarizes the mean change from baseline in the CGI-Severity of Illness scores for the RBX treatment groups and Placebo group. No statistically significant differences in the mean change from baseline were observed among treatment groups over the study period. At Day 42, the mean decrease of the CGI-Severity of Illness score was –1.3 in the RBX 2-mg group, -1.0 in the RBX 4-mg group, -1.4 in the RBX 8-mg group, and –1.3 in the PBO group for the LOCF analysis. In the OC analysis, at Day 42, the mean decrease in the CGI-Severity of Illness score was –1.8 in the RBX 2-mg group, -1.6 in the RBX 4-mg group, -1.8 in the RBX 8-mg group, and –1.7 in the PBO group. Tables 3.10A and 3.10B (Section 14) provide additional information, including the p-values for the least square mean change for the LOCF and OC analyses. Table 3.11 (Section 14) presents a cross tabulation of the Baseline vs. Endpoint score.

Table 16. Mean Change from Baseline in Clinical Global Impression (CGI)-Severity of Illness Score†

Analysis	Group	Baseline		Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
		N	Mean	n	X‡	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	RBX 2-mg	87	4.8	85	-0.3	86	-0.6	86	-0.8	86	-1.0	86	-1.1	86	-1.3
	RBX 4mg	87	4.7	86	-0.1	86	-0.5	86	-0.7	86	-0.8	86	-0.9	86	-1.0
	RBX 8-mg	89	4.8	87	-0.2	88	-0.5	88	-1.0	88	-1.3	89	-1.2	88	-1.4
	PBO	87	4.7	84	-0.3	85	-0.5	85	-0.9	86	-1.1	86	-1.2	86	-1.3
P-value	Among Treatment Groups	NA		0.1187		0.9032		0.6703		0.2256		0.4858		0.2806	
OC	RBX 2-mg	87	4.8	85	-0.3	82	-0.6	70	-1.0	67	-1.2	64	-1.5	61	-1.8
	RBX 4mg	87	4.7	86	-0.1	80	-0.5	76	-0.9	66	-1.1	62	-1.3	55	-1.6
	RBX 8-mg	89	4.8	87	-0.2	84	-0.6	80	-1.1	78	-1.4	71	-1.5	64	-1.8
	PBO	87	4.7	84	-0.3	83	-0.5	78	-1.0	76	-1.3	69	-1.4	68	-1.7
P-value	Among Treatment Groups	NA		0.1187		0.8923		0.8511		0.6090		0.7733		0.4096	

* P-values are based on a 2-way analysis of variance (ANOVA)

† 7-point scale: 1 = normal, not at all ill, 2 = borderline mentally ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill, 7 = among the most extremely ill patients

‡ Mean change from baseline

RBX = reboxetine; PBO = placebo; LOCF = Last Observation Carried Forward, OC = Observed Case, NA = not applicable

Source: Section 14, Tables 2.3, 3.10A, 3.10B

10.3.2.1.4 Clinical Global Impression-Efficacy Index

(Section 14, Tables 3.9A, 3.9B)

The investigators were asked to weight the therapeutic effect of the study medication against its tolerability for each patient at each evaluation point after baseline.

Table 17 summarizes the mean efficacy index score at each post-baseline evaluation. No statistically significant changes in the mean efficacy index were observed among treatment groups over the period of the study by the LOCF or the OC analysis.

Table 17. Clinical Global Impression Efficacy Index†

Analysis	Group	Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
		n	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
LOCF	RBX 2-mg	85	11.0	86	10.0	86	8.9	86	8.5	86	8.0	86	7.7
	RBX 4mg	86	11.5	86	9.8	86	9.0	86	9.0	86	8.7	86	8.5
	RBX 8mg	87	11.6	88	10.1	88	8.5	88	7.8	89	7.9	88	7.5
	PBO	83	10.7	84	9.3	85	8.2	86	7.8	86	7.9	86	7.6
P-Value*	Among Treatment Groups	0.1355		0.5202		0.6871		0.2331		0.6163		0.4339	
OC	RBX 2mg	85	11.0	82	9.9	70	8.0	67	7.4	64	6.6	61	5.9
	RBX 4-mg	86	11.5	80	9.5	76	8.4	66	7.9	62	7.1	55	6.3
	RBX 8mg	87	11.6	84	9.9	80	8.1	78	6.9	71	6.4	64	5.4
	PBO	83	10.7	82	9.2	78	7.8	76	7.1	69	6.7	68	6.1
P-Value*	Among Treatment Groups	0.1355		0.5576		0.9449		0.8364		0.8619		0.3080	

* p-value are based on two-way ANOVA

† A lower score is indicative of a more positive efficacy index value (range is 1-16)

RBX = reboxetine; PBO = placebo; LOC = Last Observation Carried Forward, OC = Observed Case

Source: Section 14, Tables 3.9A, 3.9B

10.3.2.2 Montgomery-Asberg Depression Rating Scale

(Section 14, Tables 2,3, 3.5A, 3.5B)

The MADRS rating scale, a 10-item scale, was based on a clinical interview with the patient. For each item, a score of 0 would signify the absence of the symptom and a score of 6 would signify the most extreme form of the symptom (range is 0-60). The total score was calculated by adding the score for each individual item.

Table 18 summarizes the mean change from baseline in the MADRS total score at each post-baseline evaluation for both the LOCF and OC analyses. No statistically significant differences among treatment groups were seen during the period of the study. On Day 42, the mean decrease from baseline in the MADRS total score was –12.3 for the RBX 2-mg group, -10.1 for the RBX 4mg group, -13.0 for the RBX 8-mg group, and –13.3 for the PBO group by the LOCF analysis. The mean decrease was slightly greater by the OC analysis (-16.3 in the RBX 2-mg group, -16.5 in the RBX 4-mg group, -16.7 in the RBX 8-mg group, and –16.4 in the PBO group). Section 14, Tables 3.5A and 3.5B provide additional information, including the p-values for the least square mean change and the standard deviation for the mean change, for the LOCF and OC analyses, respectively.

Table 18. Mean Change From Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score‡

Analysis	Group	Baseline		Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
		n	Mean	n	X†	N	X†	n	X†	n	X†	n	X†	n	X†
LOCF	RBX 2-mg	87	31.5	85	-3.7	86	-6.6	86	-9.1	86	-10.3	86	-11.7	86	-12.3
	RBX 4mg	87	30.8	86	-2.6	86	-6.6	86	-8.3	86	-8.3	86	-9.1	86	-10.1
	RBX 8-mg	89	32.2	87	-3.0	88	-6.2	88	-10.3	88	-11.6	89	-12.0	88	-13.0
	PBO	87	32.2	84	-4.1	85	-7.3	85	-10.2	86	-12.2	86	-11.9	86	-13.3
P-Values*	Among Treatment Groups	NA		0.5007		0.7066		0.6966		0.1970		0.3579		0.3306	
OC	RBX 2mg	87	31.5	85	-3.7	82	-7.0	70	-10.8	67	-12.8	64	-14.6	61	-16.3
	RBX 4-mg	87	30.8	86	-2.6	80	-7.3	76	-9.5	66	-11.2	62	-12.9	55	-16.5
	RBX 8mg	89	32.2	87	-3.0	84	-6.6	81	-11.1	78	-13.0	71	-14.8	64	-16.7
	PBO	87	32.2	84	-4.1	83	-7.5	78	-10.9	76	-13.5	69	-14.2	68	-16.4
P-Values*	Among Treatment Groups	NA		0.5007		0.7069		0.9005		0.9999		0.8652		0.5832	

* P-values are based on two-way ANOVA

† Mean change from baseline value

‡ A total of 0 would signify the absence of a system and a score of 6 would signify the most extreme form of the symptom on a 10-item scale (range 0-60).

RBX = reboxetine; PBO = placebo**;** LOCF = Last Observation Carried Forward; OC = Observed Case, NA= not applicable

Source: Section 14, Tables 2.3, 3.5A, 3,5B

10.3.2.3 HAM-D Responder/Remission Status

Response Rate (a decrease of at least 50% in the 21-item HAM-D total score versus baseline was considered a response) and Remission Rate (a 21-item HAM-D total score of 10 or less) were used to rate responder and remission status.

10.3.2.3.1 HAM-D Responder Status

(Section 14, Tables 3.7A, 3.7B, 3.8)

Table 19 summarizes the HAM-D responder status.

For the LOCF analysis, except for Day 7 (among treatment p-value=0.0245), no statistically significant differences were seen in the responder rate among treatment groups during the study period. By Day 42, 38.4% (33/86) of patients in the RBX 2-mg group, 36% (31/86) of patients in the RBX 4-mg group, 43.2% (38/88) of patients in the RBX 8-mg group, and 45.3% (39/86) of patients in the PBO group were classified as responders (Section 14, Tables 3.7A, 3.8).

For the OC analysis, except for Day 7 (among treatment p-value=0.0245), no statistically significant differences were seen in the responder rate among treatment groups during the study period. By Day 42, 49.2% (30/61) of patients in the RBX 2-mg group, 54.5% (30/55) in the RBX 4-mg group, 54.7% (35/64) in the RBX 8-mg group, and 57.4% (39/68) in the PBO group were classified as responders (Section 14, Tables 3.7B, 3.8).

Table 19. HAM-D Responder Status†

Analysis	Group	Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
		n/N	%	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
LOCF	RBX 2-mg	9/85	10.6	16/86	18.6	22/86	25.6	26/86	30.2	36/86	41.9	33/86	38.4
	RBX 4-mg	2/86	2.3	13/86	15.1	19/86	22.1	24/86	27.9	29/86	33.7	31/86	36.0
	RBX 8-mg	3/87	3.4	9/88	10.2	24/88	27.3	31/88	35.2	37/88	42.0	38/88	43.2
	PBO	5/84	6.0	13/85	15.3	28/85	32.9	34/86	39.5	34/86	39.5	39/86	45.3
P-value*	Among Treatment Groups	0.0245**		0.3446		0.5184		0.4335		0.6845		0.6358	
OC	RBX 2-mg	9/85	10.6	15/82	18.3	19/69	27.5	23/67	34.3	33/64	51.6	30/61	49.2
	RBX 4-mg	2/86	2.3	13/80	16.3	19/76	25.0	23/66	34.8	28/62	45.2	30/55	54.5
	RBX 8-mg	3/87	3.4	9/84	10.7	24/81	29.6	31/78	39.7	36/70	51.4	35/64	54.7
	PBO	5/84	6.0	13/82	15.9	28/78	35.9	34/75	45.3	34/69	49.3	39/68	57.4
P-value*	Among Treatment Groups	0.0245**		0.4667		0.5574		0.5354		0.9807		0.6727	

* P-values are based on a Cochran-Mantel-Haenszel test

† A responder is defined as 50% or more decrease from baseline on HAM-D

** p-value <0.05 indicates statistical significance

RBX = reboxetine; PBO = placebo; LOCF = Last Observation Carried Forward, OC = Observed Case

Source: Section 14, Tables 3.7A, 3.7B, 3.8

10.3.2.3.2 HAM-D Remission Status

(Section 14, Tables 3.12A, 3.12B)

For the LOCF analysis, except for Day 7 (among treatment p-value = 0.0135), no statistically significant differences among treatment groups were observed. By Day 42, 27.9% (24/86) in the RBX 2-mg group, 31.4% (27/86) in the RBX 4-mg group, 34.1% (30/88) in the RBX 8-mg group, and 38.4% (33/86) in the PBO group were considered as being in remission (Section 14, Table 3.12A)

For the OC analysis, except for Day 7 (among treatment p-value=0.0135), no other statistically significant differences among treatment groups were observed. By Day 42, 39.3% (24/61) of patients in the RBX 2-mg group, 47.3% (26/55) of patients in the RBX 4-mg group, 42.2% (27/64) of patients in the RBX 8-mg group, and 48.5% (33/68) of patients in the PBO group were considered as being in remission (Section 14, Table 3.12B).

10.3.2.4 Patient Global Impression

(Section 14, Tables 3.13A, 3.13B)

The PGI was a 10-point visual analogue scale where patients rated their general condition since the start of the study. On the 10-point scale, a score of 0 denoted worst condition, 5 denoted unchanged condition, and 10 denoted best condition.

Table 20 summarizes the mean values for PGI. No statistically significant differences among treatment groups were seen by either the LOCF or by the OC analysis.

Table 20. Patient Global Impression†

Analysis	Group	Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
		N	Mean	n	Mean	n	Mean	n	Mean	n	Mean	n	Mean
LOCF	RBX 2-mg	85	5.3	86	5.5	86	5.8	86	5.8	86	6.1	86	6.1
	RBX 4-mg	85	5.1	86	5.6	86	5.7	86	5.7	86	5.9	86	6.1
	RBX 8-mg	87	5.3	88	5.6	88	6.1	88	6.3	89	6.2	88	6.4
	PBO	84	5.4	85	5.5	85	6.1	86	6.2	86	6.0	86	6.3
P-Value*	Among Treatment Groups	0.5208		0.8492		0.2286		0.2810		0.6182		0.4540	
OC	RBX 2-mg	85	5.3	81	5.6	70	6.3	67	6.3	63	6.7	61	6.9
	RBX 4-mg	85	5.1	79	5.7	75	5.9	64	6.3	62	6.5	55	7.1
	RBX 8-mg	87	5.3	84	5.8	80	6.3	76	6.7	69	6.9	64	7.2
	PBO	84	5.4	83	5.5	78	6.2	76	6.4	69	6.4	68	6.7
P-Value	Among Treatment Groups	0.5208		0.6141		0.3462		0.6832		0.4663		0.1160	

* P- values based on two-way ANOVA

† PGI 10-point scale, 0=worst condition, 5=unchanged, and 10=best condition (range 0–10)

RBX = reboxetine; PBO = placebo; LOC = Last Observation Carried Forward, OC = Observed Case

Source: Section 14, Tables 3.13A, 3.13B

10.3.3 Efficacy Conclusions

Overall, at end of treatment (Day 42), no significant differences were observed between any of the RBX treatment groups and PBO for the primary efficacy variable (HAM-D total score) or for the secondary efficacy variables (CGI - Global Improvement Responder Status, CGI-Severity of Illness scale, CGI-Efficacy Index, the mean change from baseline in the MADRS, response/remission rates using HAM-D 21 item scale, or in the PGI). Based on the HAM-D responder status, 38.4% of patients in the RBX 2-mg group, 36% of patients in the RBX 4-mg group, 43.2% of patients in the RBX 8-mg group, and 45.3% in the PBO group were classified as responders for the LOCF analysis. For the OC analysis, 49.2% of patients in the RBX 2-mg group, 54.5% of patients in the RBX 4-mg group, 54.7% of patients in the RBX 8-mg group, and 57.4% of patients in the PBO group were classified as responders. The high placebo response is preventing a statistically significant comparison. In this setting, a judgment regarding the relative merits of one dose's effectiveness over another is not possible.

10.4 Safety Results

All 350 randomized patients (87 each in the RBX 2 mg, RBX 4-mg group, and PBO group, and 89 in the RBX 8-mg group) received at least one dose of study medication and were included in the safety analysis.

10.4.1 Adverse Events (AEs)

10.4.1.1 Brief Summary of Adverse Events During Study

(Section 14, Tables 4.1, 8.1, 9.1, 10.1, 13.1; Appendix 13, Tables 7.1, 7.2)

A listing of all patients who had treatment-emergent AEs and discontinuations due to AEs can be found in Appendix 13.

Table 21 summarizes the treatment-emergent AEs that occurred during the study.

Table 21. Overview of Adverse Events

Patients	RBX 2-mg N = 87 n (%)	RBX 4-mg N = 87 n (%)	RBX 8-mg N = 89 n (%)	PBO N = 87 n (%)
At Least One AE	59 (67.8)	59 (67.8)	68 (76.4)	52 (59.8)
At Least One Drug-Related† AE	50 (57.5)	52 (59.8)	60 (67.4)	40 (46.0)
Serious AEs	0	6 (6.9)	4 (4.5)	4 (4.6)*
Discontinued Due to AEs	9 (10.3)‡	12 (13.8)‡	15 (16.9)‡	7 (8.0)
Discontinuation Due to SAEs	0	3 (3.4)‡	2 (2.2)	0

* Patient #1162 in PBO group is incorrectly listed as having a SAE (event occurred 58 days after last dose). Therefore, the data have been modified to exclude this patient and do not match the source table.

† Based on investigator's opinion; includes events for which the relationship to study medication was given as certain, probable or possible/doubtful.

‡ Two additional patients in the RBX 2-mg group, 1 patient in the RBX 4-mg group, and 1 patient in the RBX 8-mg group discontinued due to AEs, however, for these patients, no AEs led to discontinuation according to the AE form. The data were therefore modified to include these patients and do not match the source tables.

RBX = reboxetine; PBO = placebo

Source: Section 14, Tables 4.1, 8.1, 9.1, 10.1, 13.1

At least one treatment-emergent AE was reported for 67.8% (59/87) of patients in the RBX 2-mg group, 67.8% (59/87) in the RBX 4-mg group, 76.4% (68/89) in the RBX 8-mg group, and 59.8% (52/87) in the PBO group. None of the patients in the RBX 2-mg group had any SAEs; 6.9% (6/87) of patients in the RBX 4-mg group, 4.5% (4/89) of patients in the RBX 8-mg group, and 4.6% (4/87) of patients in the PBO group had SAEs. The percentage of patients who discontinued the study due to AEs was generally higher in the RBX groups compared to the PBO group. Three patients in the RBX 4-mg and 2 patients in the RBX 8-mg group had SAEs that led to study discontinuation. No trend of an increase in SAEs or an increase in discontinuations due to SAEs was observed with increasing RBX dose.

10.4.1.2 Brief Summary of Adverse Events During Follow-Up

(Section 14, Tables 4.1 FU, 8.1 FU, 9.1 FU)

Table 22 summarizes the AEs occurring during follow-up. Adverse events occurred at similar frequencies in all treatment groups. A definitive conclusion cannot be drawn due to the small sample size.

Table 22. Overview of Adverse Events (FU)

Patients	RBX 2-mg N = 6	RBX 4-mg N = 2	RBX 8-mg N = 3	PBO N = 5
At Least One AE	3	1	2	2
At Least One Drug Related AE	3	0	2	0
At Least One AE Leading to Termination	0	1	1	0

RBX = Reboxetine; PBO = Placebo
Source: Section 14, Tables 4.1 FU, 8.1 FU, 9.1 FU

10.4.1.3 All Adverse Events

(Section 14, Table 4.1; Appendix 13, Tables 7.1, 7.2)

Table 23 summarizes all AEs by body system. Safety data listings for each patient can be found in Appendix 13.

Table 23. Summary of Adverse Events by Body System†

Body System	RBX 2-mg N = 87 n (%)	RBX 4-mg N = 87 n (%)	RBX 8-mg N = 89 n (%)	PBO N = 87 n (%)
Patients with at Least One AE	59 (67.8)	59 (67.8)	68 (76.4)	52 (59.8)
Digestive	31 (35.6)	34 (39.1)	39 (43.8)	18 (20.7)
Body	19 (21.8)	19 (21.8)	23 (25.8)	23 (26.4)
Nervous	27 (31.0)	28 (32.2)	22 (24.7)	21 (24.1)
Cardiovascular	18 (20.7)	14 (16.1)	18 (20.2)	14 (16.1)
Urogenital	8 (9.2)	9 (10.3)	12 (13.5)	4 (4.6)
Skin	12 (13.8)	10 (11.5)	11 (12.4)	8 (9.2)
Metabolic and Nutritional	3 (3.4)	3 (3.4)	4 (4.5)	4 (4.6)
Respiratory	0 (0)	2 (2.3)	3 (3.4)	1 (1.1)
Special Senses	3 (3.4)	6 (6.9)	2 (2.2)	1 (1.1)
Musculo-Skeletal	2 (2.3)	1 (1.1)	1 (1.1)	1 (1.1)
Hemic and Lymphatic	0 (0)	1 (1.1)	1 (1.1)	0 (0)

† Arranged in descending order of frequencies based on the RBX 8-mg treatment group
Each patient was counted once per body system
RBX = reboxetine; PBO = placebo
Source: Section 14, Table 4.1

Digestive-related events were the most frequently reported events in each treatment group (35.6% [31/87] in the RBX 2-mg group; 39.1% [34/87] in the RBX 4-mg group; 43.8% [39/89] in the RBX 8-mg group; 20.7% [18/87] in the PBO group) followed by body as a whole (21.8% [19/87] in the RBX 2 mg and 4-mg group; 25.8% [23/89] in the RBX 8-mg group, and 26.4% [23/87] in the PBO group) and the nervous system-related events (31% [27/87] in the RBX 2-mg group; 32.2% [28/87] in the 4-mg group; 24.7% [22/89] in the RBX 8-mg group, and 24.1% [21/87] in the PBO group). Digestive and Urogenital-related

events were reported more frequently by patients in the RBX treatment groups compared to patients in the PBO group with a trend towards a higher incidence with increasing dose of RBX. However, AEs related to the nervous system were reported more frequently by patients in the low dose groups (RBX 2-mg and 4-mg) than in the RBX 8-mg group or in the PBO group. Overall, for the majority of AEs by body system, no dose-dependent trend was observed.

10.4.1.4 Adverse Events Reported by 2% or More of Reboxetine-Treated Patients During the Study

(Section 14, Table 4.1)

Table 24 summarizes the AEs reported by 2% or more RBX-treated patients. A summary of all AEs can be found in Table 4.1 (Section 14).

Table 24. Adverse Events in ≥ 2% of Patients*

Body System/COSTART Term	RBX 2 mg N = 87		RBX 4 mg N = 87		RBX 8 mg N = 89		Placebo N = 87	
	n	%	n	%	n	%	n	%
BODY								
Headache	15	17.2	14	16.1	11	12.4	12	13.8
Abdominal Pain	2	2.3	3	3.4	6	6.7	2	2.3
Fever	1	1.1	0	0	3	3.4	0	0
Reaction Unevaluable	1	1.1	1	1.1	2	2.2	3	3.4
Asthenia	2	2.3	0	0	1	1.1	1	1.1
Flu Syndrome	0	0	1	1.1	1	1.1	4	4.6
CARDIOVASCULAR								
Tachycardia	10	11.5	5	5.7	9	10.1	0	0
Palpitation	1	1.1	4	4.6	7	7.9	2	2.3
Hypotension	2	2.3	1	1.1	3	3.4	3	3.4
Hypertension	3	3.4	1	1.1	2	2.2	6	6.9
Peripheral Vascular Disorder	2	2.3	0	0	0	0	0	0
DIGESTIVE								
Dry Mouth	13	14.9	13	14.9	20	22.5	7	8.0
Constipation	9	10.3	14	16.1	13	14.6	2	2.3
Nausea	9	10.3	10	11.5	11	12.4	5	5.7
Anorexia	2	2.3	2	2.3	3	3.4	0	0
Vomiting	3	3.4	5	5.7	3	3.4	4	4.6
Dyspepsia	1	1.1	4	4.6	1	1.1	1	1.1
Rectal Disorder	0	0	3	3.4	0	0	0	0
METABOLIC AND NUTRITIONAL								
Weight Loss	2	2.3	1	1.1	3	3.4	2	2.3
NERVOUS								
Insomnia	9	10.3	7	8.0	8	9.0	4	4.6
Anxiety	4	4.6	5	5.7	5	5.6	8	9.2
Dizziness	9	10.3	5	5.7	5	5.6	6	6.9
Vertigo	0	0	4	4.6	3	3.4	1	1.1
Agitation	1	1.1	2	2.3	2	2.2	1	1.1
Depression	1	1.1	4	4.6	2	2.2	1	1.1
Nervousness	7	8.0	1	1.1	2	2.2	1	1.1
Hypertonia	0	0	2	2.3	0	0	1	1.1
Paresthesia	2	2.3	1	1.1	0	0	0	0
Tremor	1	1.1	3	3.4	1	1.1	0	0
Sleep Disorder	2	2.3	1	1.1	0	0	0	0
RESPIRATORY								
Pharyngitis	0	0	1	1.1	2	2.2	1	1.1
Rhinitis	0	0	1	1.1	2	2.2	0	0
SKIN								
Sweating	11	12.6	9	10.3	11	12.4	4	4.6
Rash	0	0	1	1.1	1	1.1	2	2.3
Acne	0	0	0	0	0	0	2	2.3
Pruritus	0	0	2	2.3	0	0	1	1.1
SPECIAL SENSES								
Abnormality of Accommodation	0	0	4	4.6	1	1.1	0	0
UROGENITAL								
Abnormal Ejaculation	1	1.1	2	2.3	1	1.1	0	0
Urination Impaired	2	2.3	3	3.4	6	6.7	0	0
Urination Retention	1	1.1	0	0	2	2.2	2	2.3
Impotence	1	1.1	2	2.3	0	0	0	0

* Arranged in decreasing order of frequency based on RBX 8 mg, 4 mg, 2-mg group

RBX = reboxetine; PBO = placebo

Note: Each patient was counted once per Body System/COSTART Term

Source: Section 14, Table 4.1

Among the AEs that were reported in at least 2% of patients in the RBX groups, tachycardia, dry mouth, constipation, nausea, insomnia, sweating, and impaired urination were reported at least twice as frequently in each RBX treatment group compared to the PBO group. The incidence of AEs in general did not show a clear relationship to RBX dose. A trend toward increasing incidence of abdominal pain, palpitation, nausea, pharyngitis, rhinitis, and urination impairment with increasing RBX dose was observed (though for several of these, the numbers of AEs are small). A trend toward decreasing incidence of headache, dizziness, paresthesia, and sleep disorder with increasing RBX dose was observed (though for several of these, the numbers of AEs are small). For all other AEs (ie, for the majority of AEs), there was no trend between AE incidence and RBX dose. Most AEs were evenly distributed among the RBX treatment groups.

10.4.1.5 Adverse Events Reported at Follow-Up

(Section 14, Table 4.1 FU)

Table 25 summarizes the AEs at follow-up. No dose-dependent trend was observed in the frequencies of AEs. Conclusions are limited due to the small sample size.

Table 25. Summary of Adverse Events by Body System (FU)

Body System	RBX 2 mg N = 6 n	RBX 4 mg N = 2 n	RBX 8 mg N = 3 n	PBO N = 5 n
Patients With at Least One AE	3	1	2	2
Body	1	1	1	1
Cardiovascular	2	0	0	1
Digestive	1	0	1	0
Nervous	2	0	1	1
Special Senses	1	0	0	0
Urogenital	1	0	0	0

n = Number of patients reporting a treatment-emergent symptom
Each patient is counted once per body system
Source: Section 14, Table 4.1 FU

10.4.1.6 Adverse Events by Maximum Severity

The majority of patients in each treatment group reported events that were mild (17.2% [15/87] in the RBX 2-mg group, 20.7%[18/87] in the RBX 4-mg group, 21.3% [19/89] in the RBX 8-mg group, and 26.4% [23/87] in the PBO group) to moderate (40.2% [35/87] in the RBX 2-mg group, 27.6% [24/87] in the RBX 4-mg group, 39.3% [35/89] in the RBX 8-mg group, and 19.5% [17/87] in the PBO group). Severe treatment-emergent AEs were reported in 10.3% [9/87] of patients in the RBX 2-mg group, 19.5% [17/87] of patients in the RBX 4-mg group, 15.7% [14/89] of patients in the RBX 8-mg group, and 13.8% [12/87] of patients in the PBO group (Section 14, Tables 5.1, 5.2).

There was a trend toward increasing incidence of mild AEs with increasing RBX dose, but there was no trend toward increasing incidence of moderate or severe AEs with increasing RBX dose.

The severe treatment-emergent AEs that were reported in more than one patient were headache (2 patients each in the RBX 2-mg and in the PBO group), hypertension (2 patients in the PBO group), dry mouth (2 patients in the RBX 8-mg group), vomiting (2 patients in the PBO group), anxiety (3 patients in the RBX 2-mg group, 5 patients in the RBX 4-mg group and 2 patients in the RBX 8-mg group), depression (3 patients in the RBX 4-mg group and 2 patients in the RBX 8-mg group), dizziness (2 patients each in RBX 4 mg, RBX 8-mg group, and PBO group), insomnia (3 patients in the RBX 2-mg group and 2 patients in the RBX 4-mg group). All treatment-emergent AEs are summarized by maximum severity in Tables 5.1 and 5.2 (Section 14).

10.4.1.7 Drug-Related Adverse Events

(Section 14, Table 8.1)

Table 26 summarizes AEs that were considered drug-related. According to the investigator's judgment, 57.5% (50/87) of patients in the RBX 2-mg group, 59.8% (52/87) in the RBX 4-mg group, 67.4% (60/89) in the RBX 8-mg group, and 46% (40/87) in the PBO group experienced at least one drug-related treatment-emergent AEs.

Table 26. Drug-Related* Adverse Events in ≥ 2% of Patients

Body System/COSTART Term	RBX 2 mg N = 87		RBX 4 mg N = 87		RBX 8 mg N = 89		PBO N= 87	
	n	%	n	%	n	%	n	%
Drug-related Adverse Events	**50**	**57.5**	**52**	**59.8**	**60**	**67.4**	**40**	**46.0**
BODY								
Headache	11	12.6	13	14.9	8	9.0	10	11.5
Abdominal Pain	0	0	2	2.3	4	4.5	1	1.1
CARDIOVASCULAR								
Tachycardia	8	9.2	4	4.6	9	10.1	0	0
Palpitation	1	1.1	4	4.6	6	6.7	2	2.3
Hypotension	2	2.3	1	1.1	3	3.4	2	2.3
Hypertension	3	3.4	1	1.1	2	2.2	5	5.7
Peripheral Vascular Disorder	2	2.3	0	0	0	0	0	0
DIGESTIVE								
Dry Mouth	11	12.6	13	14.9	20	22.5	7	8.0
Constipation	7	8.0	14	16.1	12	13.5	2	2.3
Nausea	8	9.2	8	9.2	10	11.2	4	4.6
Anorexia	2	2.3	2	2.3	3	3.4	0	0
Vomiting	2	2.3	4	4.6	2	2.2	3	3.4
Dyspepsia	0	0	3	3.4	0	0	1	1.1
METABOLIC AND NUTRITIONAL								
Weight Loss	1	1.1	1	1.1	3	3.4	2	2.3
NERVOUS								
Insomnia	7	8.0	6	6.9	7	7.9	3	3.4
Dizziness	5	5.7	5	5.7	4	4.5	6	6.9
Agitation	1	1.1	2	2.3	2	2.2	1	1.1
Anxiety	3	3.4	2	2.3	2	2.2	5	5.7
Nervousness	6	6.9	1	1.1	2	2.2	1	1.1
Depression			2	2.3	1	1.1	0	0
Paresthesia	2	2.3	1	1.1	0	0	0	0
Sleep Disorder	2	2.3	1	1.1	0	0	0	0
Tremor	0	0	2	2.3	0	0	0	0
Vertigo	0	0	4	4.6	3	3.4	1	1.1
SKIN								
Sweating	11	12.6	9	10.3	10	11.2	3	3.4
SPECIAL SENSES								
Abnormality of Accommodation	0	0	4	4.6	0	0	0	0
UROGENITAL								
Urination Impaired	2	2.3	2	2.3	6	6.7	0	0
Abnormal Ejaculation	1	1.1	2	2.3	1	1.1	0	0
Urinary Retention	1	1.1	0	0	1	1.1	2	2.3
Impotence	1	1.1	2	2.3	0	0	0	0

* Based on the investigator's judgment; includes events for which the relationship to the study medication was given as certain, probable, or possible/doubtful

n = Number of patients reporting a treatment-emergent symptom considered related

% based on number of intent-to-treat patients

Each patient is counted once per body system

Each patients is counted once per COSTART term

RBX = reboxetine; PBO = placebo

Source: Section 14, Table 8.1

Tachycardia, constipation, nausea, anorexia, insomnia, sweating, urination impairment and abnormal ejaculation were reported as drug-related AEs at least twice as frequently in each RBX group compared to the PBO group. Although there was a trend toward increasing incidence of drug-related AEs for abdominal pain, palpitation, and dry mouth with increasing RBX dose, in general, the incidence of drug-related AEs did not show a clear relationship to RBX dose. Most drug-related AEs were evenly distributed among the RBX treatment groups. A summary of all drug-related AEs can be found in Table 8.1 (Section 14).

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

10.4.2.1 Deaths

There were no deaths during the study.

10.4.2.2 Serious Adverse Events

(Section 14, Table 13; Appendix 13, Tables 14.1, 14.2)

A total of 14 patients (6 patients in the RBX 4-mg group, 4 patients in the RBX 8-mg group, and 4 patients [modified data-1 patient was incorrectly listed as having an SAE that occurred 58 days after last dose] in the PBO group) experienced SAEs (Section 14, Table 13.1). The frequencies of SAEs were similar between the RBX-treated patients and patients in the PBO group. A total of 16 SAEs were reported in these 14 patients. The SAE was considered unrelated to study medication in 6 of 10 (60%) of the RBX-treated patients who experienced an SAE. Details of these SAEs can be found in the SAE narratives (Section 10.4.2.4).

10.4.2.3 Discontinuations Due to Adverse Events

(Section 14, Table 11.1; Appendix 13, Tables 11.1, 11.2, 12.1, 12.2)

Table 27 summarizes patients who had treatment-emergent AEs that led to discontinuation of study medication.

Table 27. Patients Who Discontinued From the Study Due to Adverse Events

Patient No.	Age/ Sex	Treatment	Average Daily Dose (mg/d)	Day of Last Dose	Onset Day	Stop Day	COSTART Event(s)	Nature of Event/Maximum Intensity	Outcome
1129	55/F	RBX 2 mg	1.67	11	11	11	Hypertension	Episodic/Moderate	Recovered
1003	36/M	RBX 2 mg	4.00	5	2	5	Anorexia	Constant/Moderate	Recovered
				5	2	5	Nausea	Constant/Moderate	Recovered
1017	34/F	RBX 2 mg	1.57	36	36	-	Agitation	Constant/Moderate	Continues
				36	36	46	Agitation	Constant/Moderate	Recovered
				36	31	46	Nervousness	Constant/Moderate	Recovered
				36	36	46	Nervousness	Constant/Moderate	Continues
2160	49/F	RBX 2 mg	-	35	36	42	Insomnia	Episodic/Mild	Recovered
2072	48/F	RBX 2 mg	1.86	11	3	12	Headache	Episodic/Mild	Recovered
				11	3	12	Nausea	Constant/Moderate	Recovered
1123	47/F	RBX 2 mg	2.00	10	9	12	Chills	Constant/Severe	Recovered
				10	9	12	Peripheral Vascular Disorder	Constant/Severe	Recovered
1050	30/F	RBX 2 mg	2.33	14	9	-	Hypotension	Episodic/Severe	Continues
1004	43/F	RBX 2 mg	-	25	-	-	Missing	Missing	Missing
4032	56/M	RBX 2 mg	-	5	-	-	Missing	Missing	Missing
5011	24/M	RBX 4 mg	-	19	-	-	Missing	Missing	Missing
5088	59/M	RBX 4 mg	3.00	3	2	4	Nausea	Episodic/Severe	Recovered
				3	3	3	Vomiting	Episodic/Severe	Recovered
				3	2	5	Dizziness	Episodic/Severe	Recovered
				3	2	3	Vertigo	Episodic/Severe	Recovered
				3	2	5	Sweating	Episodic/Severe	Recovered
1058	25/F	RBX 4 mg	4.00	35	1	-	Insomnia	Constant/Severe	Continues

continued

Table 27. Patients Who Discontinued From the Study Due to Adverse Events

Patient No.	Age/ Sex	Treatment	Average Daily Dose (mg/d)	Day of Last Dose	Onset Day	Stop Day	COSTART Event(s)	Nature of Event/Maximum Intensity	Outcome
5008	39/F	RBX 4 mg	5.00	3	3	8	Tachycardia	Episodic/Moderate	Recovered
				3	3	8	Agitation	Episodic/Moderate	Recovered
				3	3	8	Anxiety	Episodic/Severe*	Recovered Residual Effects
				3	3	10	Nervousness	Constant/Moderate	Recovered
5040	45/F	RBX 4 mg	5.00	19	18	21	Dehydration	Episodic/Moderate	Recovered
2036	36/F	RBX 4 mg	4.57	22	20	53	Depression	Episodic/Severe	Recovered Residual Effects
2118	50/F	RBX 4 mg	4.57	40	12	13	Vaginal Hemorrhage	Episodic/Moderate*	Recovered Residual Effects
4027	54/F	RBX 4 mg	3.71	18	11	18	Abdominal Pain	Episodic/Moderate*	Recovered
				18	3	19	Headache	Constant/Mild	Recovered
				18	3	19	Palpitation	Constant/Moderate	Recovered
				18	12	-	Insomnia	Constant/Moderate	Continues
				18	2	19	Menstrual Disorder	Constant/Mild	Recovered
				18	3	19	Urinary Frequency	Constant/Moderate	Recovered
4029	61/M	RBX 4 mg	3.71	9	2	10	Chills	Episodic/Mild	Recovered
				9	2	10	Anorexia	Constant/Mild	Recovered
				9	2	10	Constipation	Chronic/Moderate	Recovered
				9	2	10	Libido Decreased	Constant/Moderate	Recovered
				9	2	10	Sleep Disorder	Constant/Mild	Recovered
				9	2	10	Urination Impaired	Constant/Mild	Recovered
1033	60/F	RBX 4 mg	4.00	12	5	-	Palpitation	Chronic/Severe	Continues
				12	5	-	Anxiety	Chronic/Severe	Continues

continued

Table 27. Patients Who Discontinued From the Study Due to Adverse Events

Patient No.	Age/ Sex	Treatment	Average Daily Dose (mg/d)	Day of Last Dose	Onset Day	Stop Day	COSTART Event(s)	Nature of Event/Maximum Intensity	Outcome
1163	42/F	RBX 4 mg	4.67	4	2	5	Dizziness	Episodic/Severe	Recovered
2175	46/F	RBX 4 mg	4.00	26	8	26	Headache	Constant/Severe	Recovered
4031	39/F	RBX 8 mg	-	25	-	-	Missing	Missing	Missing
1089	48/M	RBX 8 mg	8.57	29	8	-	Weight Loss	Chronic/Mild	Continues
2043	46/F	RBX 8 mg	7.43	8	2	11	Asthenia	Constant/Severe	Recovered
				8	2	11	Tinnitus	Constant/Moderate	Recovered
5022	41/M	RBX 8 mg	8.00	4	2	-	Depression	Constant/Severe	Continues
1098	49/M	RBX 8 mg	-	11	12	14	Urination Impaired	Constant/Moderate	Recovered
1099	38/M	RBX 8 mg	4.67	7	5	8	Headache	Episodic/Moderate	Recovered
				7	5	8	Tachycardia	Episodic/Mild	Recovered
				7	6	8	Nausea	Episodic/Moderate	Recovered
				7	6	8	Vomiting	Episodic/Mild	Recovered
				7	6	8	Urination Impaired	Constant/Mild	Recovered
2017	31/M	RBX 8 mg	7.33	16	12	-	Anxiety	Constant/Severe	Recovered Residual Effects
3002	34/F	RBX 8 mg	10.00	21	20	-	Tachycardia	Constant/Severe	Continues
3010	62/F	RBX 8 mg	8.00	26	21	-	Hypertension	Episodic/Moderate	Continues
				26	8	-	Tachycardia	Episodic/Moderate	Continues
1082	48/M	RBX 8 mg	8.00	25	14	27	Urinary Retention	Constant/Severe	Recovered
2058	45/F	RBX 8 mg	10.67	35	34	35	Anxiety	Constant/Severe*	Recovered
1115	50/F	RBX 8 mg	7.50	29	16	-	Dry Mouth	Constant/Moderate	Continues
3073	63/M	RBX 8 mg	12.00	3	1	4	Headache	Constant/Severe	Recovered
				3	1	4	Sweating	Episodic/Moderate	Recovered
3074	57/F	RBX 8 mg	8.00	15	15	-	Palpitation	Episodic/Severe	Continues
				15	15	-	Agitation	Episodic/Severe	Continues
				15	8	-	Insomnia	Episodic/Moderate	Continues

continued

Table 27. Patients Who Discontinued From the Study Due to Adverse Events

Patient No.	Age/ Sex	Treatment	Average Daily Dose (mg/d)	Day of Last Dose	Onset Day	Stop Day	COSTART Event(s)	Nature of Event/Maximum Intensity	Outcome
4061	52/M	RBX 8 mg	7.00	33	32	35	Abdominal Pain	Episodic	Recovered
5091	35/F	PBO	0.00	10	5	12	Anxiety	Constant/Mild	Recovered
2001	42/F	PBO	0.00	3	1	4	Vomiting	Constant/Severe	Recovered
				3	1	4	Dizziness	Constant/Severe	Recovered
2019	48/F	PBO	0.00	15	9	18	Constipation	Constant/Moderate	Recovered
4017	60/F	PBO	0.00	25	25	25	Urinary Retention	Constant/Moderate	Recovered
2065	35/M	PBO	0.00	13	3	16	Dry mouth	Episodic/Mild	Recovered
1031	49/F	PBO	0.00	13	2	16	Somnolence	Constant/Mild	Recovered
				6	2	7	Hypertension	Constant/Severe	Recovered
3006	52/F	PBO	0.00	29	28	28	Hostility	Constant/Severe	Recovered

* These events were not considered drug-related; all other events were considered drug-related.
Note: Two patients (#1004, #4032) in the RBX 2mg group, 1 patient (#5011) in the RBX 4-mg group, and 1 patient (#4031) in the RBX 8-mg group discontinued due to AEs, however, no AEs led to discontinuation according to the AE form.
RBX = reboxetine; PBO = placebo
Source: Section 14, Table 11.1

A total of 43 patients (9 in the RBX 2-mg group, 12 in the RBX 4-mg group, 15 in the RBX 8-mg group, and 7 in the PBO group) discontinued treatment due to AEs. Almost half (44.2% [19/43] of those discontinuing because of AEs did so within the first 2 weeks of the study**.** There was some increase in discontinuation due to nonserious AEs as the reboxetine dose increased. A total of 65 events led to discontinuation in the RBX-treatment groups; most (approximately 62% [40/65]) of these events were mild or moderate in severity with recovery noted for a majority of these events (approximately 69% [45/65]). Most of these events were nervous-system related (5 in the 2-mg group, 11 in the 4-mg group, 5 in the 8-mg group, and 4 in the PBO group), digestive (3 in the 2-mg group, 4 in the 4-mg group, 3 in the 8-mg group, and 3 in the PBO group), cardiovascular (3 each in the 2-mg and 4-mg groups, 5 in the 8-mg group, and 1 in the PBO group), body as a whole (2 in the 2-mg group, 4 each in the 4-mg and 8-mg groups), and urogenital (5 in the 4-mg group, 3 in the 8-mg group, and 1 in the PBO group). A total of 5 patients (3 in the RBX 4-mg group [patients #2036 and #2118, #5011], and 2 in the RBX 8-mg group [patients #1082 and #2058]) discontinued due to SAE. Three of 5 of these SAE were considered by the investigator as unrelated to study medication. Further details of these events can be found in Table 27 (above), in Table 12.1 (Section 14), or in SAE narratives (see Section 10.4.2.4).

10.4.2.4 Narratives

Below are narratives for the patients who experienced SAEs during the study by event (verbatim and by [COSTART term]). CRFs for these patients can be found in Appendix 14.

Reboxetine 8-mg group

Patient No: 1045 (Investigator: Blandiaux-18585)
Event: Depression Worse (Depression)

This 48 year-old male patient with major depression entered the study on 10 March 1998 with a total HAM-D score of 27. He took his first dose of study medication on 14 March 1998. On 15 March 1998, he was hospitalized due to increased depression and suicidal ideation. On 20 March, his HAM-D score was 39. There was no interruption of study medication. The event resolved on 24 March 1998 without residual effects and the HAM-D score on 26 March 1998 was 30. He completed the study per protocol on 23 April 1998. The investigator did not consider the event to be related to the study medication.

Patient No: 1089 (Investigator: Devoitille-9265)
Event: Aggressiveness (Hostility)

This 48 year-old male inpatient with major depression entered the study on 31 October 1997 and received study medication. On 29 November 1997, the investigator noted that the patient "became aggressive with bigger tension" and left the ward/hospital for 24 hours without medication or permission after a "relational problem" with another patient. This event was considered a serious reaction in the clinical judgment of the investigator and the study medication was discontinued. The event of aggressiveness was of moderate severity and resolved on the same day (29 November 1997) with residual effects. The patient did not

complete the study, as he was reported "lost to follow-up" on 29 November 1997. The investigator considered this event to be possibly related to the study drug or to lorazepam. Concomitant medications included naproxen, lorazepam, and paracetamol.

Patient No: 2058 (Investigator: Michel-18805)
Event: Anxiety (Anxiety)

This 45 year-old female patient with major depression entered the study on 18 September 1998 and was treated with study medication. She experienced an initial episode of anxiety on 16 October 1998, which resolved without problems on 20 October 1998. There was no interruption of study drug with this first episode. On 21 October 1998, the patient experienced a second episode of anxiety that required hospitalization that day. The investigator attributed the anxiety to personal problems. The patient was withdrawn from the study on 22 October 1998. This episode resolved on 22 October 1998 without residual effects. Neither the investigator nor the P&U monitor considered the AE to be related to study medication.

Patient No: 1082 (Investigator: DeClercq-18803)
Event: Urinary Retention (Urinary Retention)

This 48 year-old male patient with major depression entered the study on 17 December 1997 and was treated with study medication. No significant urinary history was noted at screening. The patient experienced an initial episode of urinary retention on 26 December 1997, which resolved on 30 December 1997 without interruption of study medication. On 30 December 1997, he experienced a second episode of urinary retention and on 10 January 1998, he was withdrawn from the study as the event was determined to be permanently or substantially disabling by the investigator. This second event resolved without residual effects on 12 January 1998. The investigator considered the event to be related to study medication.

Reboxetine 4-mg Group

Patient No: 1035 (Investigator: Tack-18468)
Event: Worsening of Depression-Hospitalization (Depression)

This 34 year-old female with major depression entered the study on 23 October 1997 and received study medication. Due to worsening of the depression, she was admitted to the hospital on 18 November 1997. Information on treatment during hospitalization is unknown. However, she remained on study medication and completed study per protocol on 4 December 1997. Neither the investigator nor the P&U monitor felt that this event was related to the study medication.

Patient No: 2036 (Investigator: Vallet-18251)
Event: Depression Worsening (Depression)

This 36 year-old female with major depression entered the study on 8 October 1998. On 27 October 1998, she experienced a worsening of depression that required hospitalization on 29 October 1998. The study medication was discontinued on 29 October 1998 and she began treatment with paroxetine 1 tablet/day (dose unknown). She was discharged on 29 November 1998 and experienced "persisting clinical improvement." She continued treatment of Seroxat (paroxetine) with resolution of worsening depression on 29 November 1998. Concomitant medication during the study included lorazepam. The relationship of this event to the study medication was assessed by the investigator as probable and by P&U monitor as unrelated.

Patient No: 5011 (Investigator: Alexandrovsky-19901)
Event: Severe Aggravation of Depression (Depression)

This 24 year-old male patient with major depression entered the study on 2 November 1998 and started study medication on 3 November 1998. On 19 November 1998, the patient experienced severe aggravation of depression that was considered life threatening by the investigator. He discontinued study medication on 21 November 1998 and was withdrawn from the study. He required hospitalization on 23 November 1998 due to a high risk of suicide. On 26 November 1998, he was noted to have a HAM-D item # 3 score = 3. Information on the treatment during hospitalization and follow-up is unknown. Neither the investigator nor the P&U monitor felt that this event was related to the study medication.

Patient No: 1166 (Investigator: DeClercq-18803)
Event # 1: Pharmacological Intoxication (Drug Level Increased)

This 38 year-old male with major depression entered the study on 16 September 1998 and received study medication. On 22 September 1998 (Day 7 of treatment), he took unknown amounts of lormetazepam, venlafaxine, alprazolam, and study medication. On 22 September 1998, he was hospitalized for pharmacological intoxication. Administration of study medication was interrupted on 24 September 1998. Information regarding treatment during the hospitalization is unknown. The patient recovered on the same day and was discharged from the hospital (date unknown) without residual effects. He resumed study medication on 27 September 1998 and completed treatment per protocol on

03 November 1998. Neither the investigator nor the P&U monitor felt the pharmacological intoxication was related to study medication.

Event #2 Anemia (Anemia)

At the baseline assessment, 11 September 1998, the patient's hemoglobin (Hb) was 14.5 g/dl (normal=12-17 g/dl). As noted in event #1, the patient was hospitalized on 22 September 1998 for pharmacological intoxication with lormetazepam, venlafaxine, alprazolam, and study medication. On 23 September 1998, he was found to be anemic with a Hb =9.3 g/dl. No information regarding hospital work-up or treatment of anemia is known. He interrupted study medication from 24 September 1998 till 27 September 1998, at which time he resumed study medication. On 21 October 1998 (study Day 28), Hb was 14.8g/dL and on 4 November 1998 (study Day 42), Hb was 14.3 g/dl. He did not receive medication to treat the anemia during the study. Concomitant medications included lorazepam, amlodipine, pyridoxine, thiamine, and ranitidine. The investigator considered the anemia to be possibly related to the study medication. The P&U monitor felt it was difficult to establish a causal relationship between study medication and anemia.

Patient No: 2118 (Investigator: Tignol-18259)
Event: Vaginal Hemorrhage (Vaginal Hemorrhage)

This 50 year-old female with major depression entered the study on 28 May 1998 and was treated with study medication. A history of uterine fibroma with repetitive gynecologic hemorrhage was noted. Laboratory assay values and blood pressure remained stable throughout the study. On 6 July 1998, the patient stopped study medication. She entered the hospital on 7 July 1998. This had been a scheduled admission prior to enrolling in the study, but the investigator failed to inform P&U about this planned surgical procedure. A uterine curettage was performed and the event resolved without sequelae. The patient was discharged on 9 July 1998. Neither the investigator nor the P&U monitor considered this event to be related to study medication.

Patient No: 1178 (Investigator: Tack-18468)

Event: Anal Hemorrhoids (Rectal Disorder)

This 43 year–old female with major depression entered the study on 14 August 1998 and was treated with study medication. She completed the study per protocol on 25 September 1998 with the exception of missing 1 capsule due to hospitalization. On 25 September 1998, hospitalization was required for surgical removal of anal hemorrhoids. There was no reported prior history of hemorrhoids. The patient was discharged on the same date and recovered without residual effects. Neither the investigator nor the P&U monitor considered this event to be related to study medication.

PBO Group

Patient No: 1172 (Investigator: Reynaert-146)
Event: Anxiety Crisis (Anxiety)

This 46 year-old male patient with major depression entered the study on 28 July 1998 and was started on placebo. On 8 August 1998, he experienced an anxiety crisis that required hospitalization but he was not withdrawn from the study. Information during hospitalization is unknown. This event resolved on 12 August 1998 without residual effects and he completed the study per protocol on 9 September 1998. The investigator did not consider this event to be related to study medication.

Patient No: 2061 (Investigator: Michel-18805)
Event #1: Anxious Crisis (Anxiety)

This 36 year-old female patient with major depression entered the study on 10 November 1998. On 13 November, she experienced an anxious crisis that required hospitalization on that day, but she continued on study medication (PBO). No information of treatment administered during her hospitalization is available. The event resolved on 17 November 1998 without residual effects. She completed the study per protocol on 22 December 1998. The investigator did not consider this event to be related to the study medication (PBO).

Event #2 Loneliness Feeling Plus Treatment Observance- (Depression)

This patient also experienced a loneliness episode on 20 November 1998 and she requested to be hospitalized that day. She continued on study medication. No information is available on treatment during her hospitalization. The event resolved on 1 December 1998 without residual effects. She completed the study per protocol on 22 December 1998. The investigator did not consider this event to be related to study medication (PBO).

Patient No.: 1084 (Investigator: DeClercq-18803)
Event: Hypertension (Hypertension)

This 48 year-old male with major depression entered the study on 12 February 1998 and was started on study medication (PBO). He had a history of hypertension; recorded sitting blood pressure at screening was 150/90 and remained elevated throughout the study. Screen EKG

was within normal limits. He received study medication (PBO) for 28 days. Hospitalization was required on 11 March 1998 for hypertension (B/P 160/100 at Day 21 visit), at which time study medication treatment was interrupted. Information on the patient's blood pressure and treatment during hospitalization is unavailable. The patient left the hospital on 13 March 1998, took study medication capsule (PBO) that evening but then did not take study medication on March 14 and 15. He resumed treatment schedule on March 16 (B/P at Day 28 visit was 145/110) and completed study on 31 March 1998. B/P was 140/110 at study termination. Concomitant medications included metoprolol succinate 200mg P.O. daily for treatment of hypertension, Deanxit and paracetamol. The investigator assessed the event to be possibly related to the study medication while the P&U monitor considered the event to be unrelated to study medication.

Patient No: 1150 (Investigator: Tack-18468)
Event: Concussion (Accidental Injury)/Alcohol intoxication (Alcohol Intolerance)

This 22 year-old male patient with major depression entered the study on 10 June 1998 and was treated with study medication (PBO). On 11 July 1998, he suffered a concussion from an accident due to alcohol intoxication and hospitalization was required. He recovered from alcohol intoxication on 12 July 1998, but effects of the concussion continued. Information on treatment during hospitalization is unknown. He missed one dose of study medication due to hospitalization, but then continued medication schedule and completed study per protocol on 22 July 1998. Neither the investigator nor the P&U monitor considered this event to be related to study medication.

10.4.3 Clinical Laboratory Evaluation

(Section 14, Tables 18.1, 18.2, 19.1, 19.2; Appendix 13, Tables 20.1, 20.2)

10.4.3.1 Hematology Assays

10.4.3.1.1 Mean Change From Baseline

Overall, no clinically important mean changes from baseline to Day 28 or Day 42 were observed for any of the hematology parameters. There were sporadic statistically significant differences among treatment groups for mean changes in erythrocytes, hematocrit, mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular volume (MCV) on Day 28. The magnitude of these changes was not clinically significant nor were the mean changes seen consistently over time. No dose-dependent relationship was observed for these changes (Section 14, Table 18.1).

The number of patients whose post-baseline hematology values exceeded normal ranges were comparable between treatment groups (Section 14, Table 19.1).

10.4.3.1.2 Values Outside the Predefined Limits

A listing of individual patients having a post-baseline hematology value exceeding the normal range is presented in Table 20.1 (Appendix 13). Overall, there did not appear to be any clinically significant changes related to RBX treatment.

10.4.3.2 Chemistry Assays

10.4.3.2.1 Mean Change From Baseline

The serum chemistry values for sodium, potassium chloride, creatinine, ALT and AST varied little from baseline to Day 28 or Day 42. There was no statistically significant difference in the overall p-values among treatment groups at Day 28 or Day 42 for sodium, potassium, creatinine AST or ALT. Overall p-values among treatment groups were significant at Day 28 (p = 0.0020) and Day 42 (p = 0.0055) for chloride. Mean decreases in chloride in the RBX-treated groups ranged from -0.5370 to -1.1833, while mean increases for the PBO-treated group ranged from 0.6719 to 0.8254. The magnitude of these changes was small and not clinically significant or dose-dependent. The values for the mean changes remained within the laboratory-specified normal range. Overall, no dose-dependent changes were noted in the RBX treatment groups for the chemistry assays (Section 14, Table 18.2). The number of patients whose post-baseline serum chemistry values exceeded normal ranges was comparable between treatment groups (Section 14, Table 19.2).

10.4.3.2.2 Values Outside Predefined Limits

A listing of individual patients having a post-baseline chemistry value exceeding the normal range is presented in Table 20.2 (Appendix 13). Overall, there did not appear to be any clinically significant changes related to RBX treatment**.**

10.4.4 Vital Signs

(Section 14, Tables 2.1, 15.1, 15.2, 15.3, 15.4, 16.1; Appendix 13, Table 17.1)

10.4.4.1 Mean Change From Baseline

No statistically significant differences from baseline were observed between the RBX and PBO groups in systolic or diastolic blood pressure, pulse rate, or body weight at baseline (Section 14, Table 2.1).

Blood pressure fluctuated little over the study period. No statistically significant mean changes in systolic blood pressure were seen. Although there were statistically significant changes among treatment groups (overall p-value=0.0282) in mean diastolic blood pressure on Day 14, these changes were small (pairwise p-value=0.0427 for the RBX 2-mg versus PBO group with a mean increase of 1.7 mmHg [RBX 2-mg] and pairwise p-value=0.0085 for the RBX 8-mg versus PBO group with a mean increase of 2.6 mmHg [RBX 8-mg]) and not clinically significant (Section 14, Tables 15.1, 15.2). No other statistically significant changes in mean diastolic blood pressure were seen among treatment groups. No dose-dependent changes in mean systolic or mean diastolic blood pressure were observed.

Statistically significant changes from baseline were noted in the pulse rate throughout the study among treatment groups and between each RBX group and PBO group. The median mean increase in the pulse rate for all RBX-treatment groups during the course of the study was 5.9 beats per minute. There was no dose-dependent relationship between RBX dose and

mean pulse rate increase. The pulse rate increase was seen on Day 7 and persisted with little change through Day 42 for each RBX treatment group (Section 14, Table 15.3).

No statistically significant changes were noted in body weight either among treatment groups or between each RBX group versus PBO group (Section 14, Table 15.4).

10.4.4.2 Values Outside of the Predefined Limits

The number of patients who had a post-baseline vital sign value exceeding the normal ranges was small (14 in the RBX 2-mg group, 9 in the RBX 4-mg group, 16 in the RBX 8-mg group, and 13 in the PBO group) and comparable between the groups (Section 14, Tables 16.1).

A listing of individual patients having a post-baseline vital sign value exceeding the normal range is presented in Table 17.1 (Appendix 13).

10.4.5 Electrocardiograms

(Section 14, Tables 21.1, 22.1, 23.1; Appendix 13, Tables 24.1, 25.1)

10.4.5.1 Treatment-Emergent ECG Abnormalities

The majority of patients reporting had normal ECGs at baseline (75.3% in the RBX 2-mg group, 73% in the RBX 4-mg group, 85.5% in the RBX 8-mg group, and 85.1% in the PBO group). Most of these patients maintained a normal ECG finding at end of study. A small number of patients (13.7% [10/73] in the RBX 2-mg group, 10.8% [8/74] in the RBX 4-mg group, 5.8% [4/69] in the RBX 8-mg group, and 1.4% [1/74] in the PBO group) had ECG that shifted from being normal at baseline to abnormal at the end of study. Most of these abnormal changes occurred in the RBX-treated patients, although a dose-dependent difference was not seen (Section 14, Table 22.1).

Table 25.1 (Appendix 13) is a listing of patients with post-baseline ECGs exceeding pre-defined limits. Eleven patients in the RBX 2-mg group, 10 patients in the RBX 4-mg group, 4 patients in the RBX 8-mg group, and 3 patients in the PBO group had post-baseline ECGs exceeding predefined limits. The most frequent treatment-emergent ECG abnormality was sinus tachycardia (6 patients in the RBX 2-mg group, 2 patients in the RBX 4-mg group and 1 patient in the RBX 8-mg group).

10.4.5.2 Mean Change From Baseline

No statistically significant differences were observed among treatment groups in the mean change from baseline in the PR, QRS, or QT intervals at the end of study visit. When the QT intervals were corrected for heart rate using either the modified Bazett's or Fridericia's correction formula, no statistically significant difference was observed among treatment groups for the corrected QT interval (QTc). In addition, no dose-related effect of RBX on QTc intervals was observed (Section 14, Table 21.1).

10.4.5.3 Values Outside of Predefined Limits

As shown in Table 28, which summarizes the frequency of patients with values outside of the predefined limits, RBX had no apparent effect on PR, QRS, QT, or QTc (Fridericia) intervals and was not associated with a greater frequency of bradycardia than placebo.

Table 28. Patients With at Least 1 Postbaseline Electrocardiogram (ECG) Value Exceeding the Predefined Limits

Parameter	Limit	RBX 2 mg		RBX 4 mg		RBX 8 mg		PBO	
		N*	n (%)†	N*	n (%)†	N*	n (%)†	N*	n (%)†
Bradycardia	≤50 beats/min	53	--	46	--	47	--	49	1 (2.0)
Tachycardia	≥120 beats/min	53	1 (1.9)	46	1 (2.2)	47	--	49	
PR Interval	≤110 msec	54	--	46	--	48	--	49	--
	≥210 msec	54	--	46	1 (2.2)	48	--	49	1 (2.0)
QRS Interval	≤30 msec	54	--	46	--	46	--	51	--
	≥110 msec	54	--	46	--	46	--	51	1 (2.0)
QT Interval	≥470 msec	55	--	46	--	48	--	51	--
QTc Interval (Bazett's)	≥450 msec (males)‡ ≥470 msec (females)	54	2 (3.7)	45	--	47	2 (4.3)	51	--
QTc Interval (Fridericia's)	≥450 msec (males)‡ ≥470 msec (females)	54	--	46	--	48	--	51	--

* 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.
‡ The definition of abnormal QTc interval varies according to the sex of the patient; however, these data were not separated by sex.

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

Source: Section 14, Table 23.1

Of the 4 patients in protocol 045 who had a normal baseline QTc value and at least 1 postbaseline QTc value exceeding predefined limits, none of the post-screen abnormal QTc intervals were deemed to be clinically significant (defined as an increase of ≥30 msec from the normally defined acceptable values of ≥450 msec for males and ≥470 msec for females). The patients in protocol 045 who had at least 1 postbaseline QTc value exceeding the predefined limits (≥450 msec for males or ≥470 msec for females) are summarized in Table 29.

Table 29. Patients With a Normal Baseline QTc Value and At Least One Postbaseline QTc Value Exceeding the Predefined Limits*

Patient No.	Gender (M/F)	Treatment	Study Day	QTc Interval (msec)†
5001	F	RBX 2 mg	Screen	428
			Day 42	482
2116	M	RBX 2 mg	Screen	407
			Day 42	466
2141	F	RBX 8 mg	Screen	446
			Day 42	470
1044	M	RBX 8 mg	Screen	401
			Day 42	458

* Predefined limits: ≥450 msec for males or ≥470 msec for females

† Modified Bazett's correction method.

Source: Appendix 13, Table 24.1

The patients in protocol 045 who had at least one postbaseline ECG that exceeded the predefined limits are listed in Appendix 13, Table 24.1.

10.4.6 Exposure in Utero

Despite the fact that patients who were pregnant were to be excluded from the study and that clear instructions were given to the patients to practice effective contraception, 1 RBX-treated patient (#4036) became pregnant during the study. The narrative is given below (CRF can be found in Appendix 15).

Patient No: 4036 (Investigator: Ermentini-18594)
Event: Exposure in Utero-1st trimester

This 41 year-old female with a history of major depression for 9 years, entered the study on 5 August 1998 and was administered study medication (RBX 4 mg/day). A serum pregnancy test was not done on screen or on treatment completion. She completed the study per protocol on 16 September 1998. She then chose to enter the follow-up period of the protocol and was dispensed study medication on 16 September 1998. On 24 September 1998, a serum pregnancy test was done and the results were positive. The study medication (RBX 4 mg/day) was immediately discontinued and the blind was broken to determine if the patient was on reboxetine or placebo treatment. The patient subsequently underwent an induced abortion on 13 October 1998. The gynecologist who performed the abortion noted that the histological analysis of the fetus was negative.

10.4.7 Safety Conclusions

Treatment-emergent AEs were reported at similar frequencies between treatment groups (67.8% in the RBX 2-mg group, 67.8% in the RBX 4-mg group, 76.4% in the RBX 8-mg group, and 59.8% in the PBO group). While the active treatment groups had slightly higher

rates of treatment-emergent AEs than the placebo group, no dose-dependent trend toward higher rates of these AEs with increasing reboxetine dose was observed. No deaths were reported in this study. The frequencies of SAEs were similar between the RBX-treated patients and patients in the PBO group. The SAEs were considered unrelated to reboxetine in 6 of the 10 (60%) reboxetine-treated patients who experienced an SAE. No dose-dependent trend toward a higher incidence of SAEs with increasing RBX dose was observed. A total of 65 events led to discontinuation in the RBX-treatment groups; most (approximately 62% [40/65]) of these events were mild or moderate in severity with recovery noted for a majority of these events (approximately 69% [45/65]). Most of these events were nervous-system related (5 in the 2-mg group, 11 in the 4-mg group, 5 in the 8-mg group, and 4 in the PBO group), digestive (3 in the 2-mg group, 4 in the 4-mg group, 3 in the 8-mg group, and 3 in the PBO group), cardiovascular (3 each in the 2-mg and 4-mg groups, 5 in the 8-mg group, and 1 in the PBO group]), body as a whole (2 in the 2-mg group, 4 each in the 4-mg and 8-mg groups), and urogenital (5 in the 4-mg group, 3 in the 8-mg group, and 1 in the PBO group). Five of 263 (1.9%) reboxetine-treated patients discontinued the study due to SAEs. Three of 5 of these patients had SAEs that were considered by the investigator as unrelated to study medication. No dose-dependent trend toward discontinuation from the study due of SAEs was observed. There was some increase in discontinuations due to nonserious AEs as the reboxetine dose increased.

The most common AEs were those that would be expected from an agent with noradrenergic activity. Among the AEs that were reported by at least 2% of patients in the RBX treatment groups, tachycardia, dry mouth, constipation, nausea, sweating, insomnia, and impaired urination were reported at least twice as frequently by patients in the RBX treatment groups compared to the PBO group. The incidence of AEs in general did not show a clear relationship to RBX dose. A trend toward increasing incidence of abdominal pain, palpitation, nausea, pharyngitis, rhinitis, and urination impairment with increasing RBX dose was observed (though for several of these, the numbers of AEs are small). A trend toward decreasing incidence of headache, dizziness, paresthesia, and sleep disorder with increasing RBX dose was observed (though for several of these, the numbers of AEs are small). For all other AEs, (ie, for the majority of the AEs) there was no trend between AE incidence and RBX dose. Most AEs were evenly distributed among the RBX treatment groups. The follow-up AE data for patients who continued treatment beyond the study defined treatment period (Day 42) are consistent with the data obtained during the study. However, due to the small sample size, conclusions in the follow-up group are limited.

No clinically significant changes among treatment groups or dose-dependent mean changes in systolic or mean diastolic blood pressure were seen. Statistically significant changes from baseline were noted in the pulse rate throughout the study among treatment groups and between each RBX group and PBO group. The median mean increase in the pulse rate for all RBX-treatment groups during the course of the study was 5.9 beats per minute. There was no dose-dependent relationship between RBX dose and mean pulse rate increase. The pulse rate increase was seen on Day 7 and persisted with little change through Day 42 for each RBX treatment group. Overall, no clinically important mean changes from baseline to Day 28 or

Day 42 were observed for any of the hematology or serum chemistry parameters. A small number of patients (13.7% in the RBX 2-mg group, 10.8% in the RBX 4-mg group, 5.8% in the RBX 8-mg group, and 1.4% in the PBO group) had ECG that shifted from being normal at baseline to abnormal at the end of study. Most of these changes occurred in the RBX-treated patients, although a dose-dependent difference was not seen. The most frequent treatment-emergent ECG abnormality was sinus tachycardia (6 patients in the RBX 2-mg group, 4 patients in the RBX 4-mg group and 1 patient in the RBX 8-mg group). Analysis of the ECG results indicates that RBX does not cause a clinically significant prolongation of the QTc interval. In addition, no dose-related effect of RBX on QTc intervals was observed.

11 DISCUSSION AND OVERALL CONCLUSIONS

This phase II, multicenter, multinational, double-blind, randomized, parallel group study with RBX was conducted in patients suffering from Major Depressive Disorder. The objective of this study was to assess the risk/benefit ratio of 3 fixed dose levels of RBX compared to placebo, with the aim of establishing among these doses, the lowest dose maximally effective in patients suffering from a Major Depressive Disorder.

The primary efficacy measure was the mean change from baseline on the 21-item HAM-D total score, comparing RBX (2-mg, 4-mg, or 8-mg dose) versus PBO. The secondary efficacy measures were CGI-Global Improvement Response Rate, the CGI-Severity of Illness scale, CGI-Efficacy Index, the mean change from baseline in the MADRS total score, 21 item HAM-D response/remission rates, and the PGI scale. Efficacy data were analyzed on an ITT population with both LOCF (primary) and OC (secondary) analyses.

At the end of treatment (Day 42), no significant difference was observed between any of the RBX treatment groups and the PBO group for the primary efficacy variable (HAM-D total score mean change from baseline). The HAM-D mean change from baseline was greater for the PBO group than for any active treatment group in both the LOCF and OC analyses. Similarly, at the end of treatment, no significant difference between any of the RBX groups and PBO was seen for the following secondary efficacy variables: CGI - Global Improvement Responder Status, CGI-Severity of Illness, CGI-Efficacy Index, MADRS mean change from baseline, HAM-D response/remission rates, or the PGI. Based on the HAM-D responder status (LOCF analysis), 38.4% of patients in the RBX 2-mg group, 36% of patients in the RBX 4-mg group, 43.2% of patients in the RBX 8-mg group, and 45.3% in the PBO group were classified as responders. Based on the HAM-D responder status (OC analysis), 49.2% of patients in the RBX 2-mg group, 54.5% of patients in the RBX -mg group, 54.7% of patients in the RBX 8-mg group, and 57.4% of patients in the PBO group were classified as responders. The PBO group's HAM-D response rate was higher than any active treatment group's response rate for both the LOCF and OC analysis.

The high placebo response in this study is the main reason that RBX failed to show a significant difference when compared to PBO. In fact, in this study, the improvement in the PBO group was greater than any active treatment group for the HAM-D, the primary efficacy measure. The high placebo response precluded a statistically significant comparison in favor

of RBX. High placebo response is a well-recognized problem in clinical trials of antidepressants. Placebo response rates are known to vary widely across patient groups; in groups of patients with major depressive disorder, the PBO response rate varies from 25%-60% [24]. The factors contributing to the high placebo response are not entirely understood. In this study, a post hoc exploratory analysis after breaking the blind could not identify factors responsible for the high placebo response. The placebo response was not related to disease severity, age, sex, prior depression history, treatment in a particular country, or consistency of investigator's baseline severity rating. When no overall difference between RBX and PBO can be demonstrated, a judgment regarding the relative merits of one dose's effectiveness over another is also not possible. In summary, this study failed to distinguish significant differences between RBX and PBO and failed to identify the minimal effective dose of RBX for the treatment of major depressive disorder.

The study demonstrated that reboxetine was a safe treatment for patients with major depressive disorder. There were no deaths during the study. In general, there was no dose-dependent relationship for incidence of treatment emergent AEs, SAEs, or discontinuation due to SAEs. The frequencies of SAEs were similar between the RBX-treated patients and patients in the PBO group. The AEs reported were characteristic of a medication with noradrenergic activity. For the majority of the individual AEs, there was no trend toward increasing AEs with increasing RBX dose. Analysis of the ECG results indicates that RBX does not cause a clinically significant prolongation of the QTc interval. In addition, no dose-related effect of RBX on QTc intervals was observed.

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13 REFERENCE LIST

1. Angst J. How recurrent and predictable is depressive illness? In: Montgomery S, Rouillon F, eds. Perspectives in Psychiatry, Volume 3: Long-term Treatment of Depression. Wiley: 1992:113.
2. Kamlet MS, Paul N, Greenhouse J, Kupfer D, Frank E, Wade M. Cost utility analysis of maintenance treatment for recurrent depression. In: Controlled Clinical Trials. Elsevier 1995;16:17-40.
3. Montgomery SA, Montgomery DB. Prophylactic treatment in recurrent unipolar depression. In: Montgomery S, Rouillon F, eds. Perspectives in Psychiatry, Volume 3: Long-term Treatment of Depression. Wiley:1992;53-79.
4. Wells KB, Golding J, Burnam MA. Psychiatric disorder and limitations in physical functioning in a general population. Am J Psychiatry 1988;145:712-7.
5. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. JAMA 1989;262:914-9.
6. Coryell WR, Noyes R, Clancy J. Excess mortality in panic disorder: a comparison with primary unipolar depression. Arch Gen Psychiatry 1982;39:701-3.
7. Kessler C, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric diagnoses in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.
8. Ambrosini A, Bonsignori A, Buonamici M, Ferrari M, Pegrassi L, Ricciardi S, et al. Study of the central nervous effects of FCE 20124, a potential antidepressive agent Farmitalia Carlo Erba Internal Report FCE 20124/207I, June 1982.
9. Riva M, Brunello N, Rovescalli AC, Galimberti R, Carfagna N, Carminati P, et al. Effect of reboxetine, a new antidepressant drug, on the central noradrenergic system: behavioural and biochemical studies. J Drug Dev 1989;4:243-53.
10. Herrman WM, Schneider J, Boden S, Wagner W, Rohmel J, Grunmach J. Safety and tolerance of reboxetine in healthy male volunteers - a single rising dose tolerance study. Pharmacia Internal Report FCE 20124/602i, June 1984.
11. Herrman WM, Schneider J, Irrgang U, Rosener B, William J, Rohmel J, et al. Reboxetine - quantitative pharmaco-EEG and pharmaco-psychological study. Pharmacia Internal Report FCE 20124/603i, January 1985.
12. Dubini A, Goldaniga GC, Montesanti L, Savoia L, Tamassia V, Vicario GP. Disposition and fate of ^{14}C-reboxetine administered orally to healthy volunteers. Pharmacia Internal Report FCE 20124/604i, March 1985.

13. Dubini A, Ban T. Open dose range finding study in patients hospitalized for major depressive disorders. Pharmacia Internal Report FCE 20124/701i, April 1989.

14. Dubini A, Ban T, Morey LC. Phase II controlled study of the activity and tolerability of reboxetine in comparison with placebo and desipramine in patients hospitalized for major depressive disorders. Farmitalia Carlo Erba Internal Report FCE 20124/702i, February 1991.

15. Ban TA, Dubini A, Giorgetti C, Petroccione A, Andreoli V, Caillard V, et al. Multicentre, multinational double-blind study of the activity and tolerability of reboxetine versus fluoxetine and placebo in patients suffering from major depressive episodes. Pharmacia Internal Report 9550080, December 1995.

16. Dubini A, Vanoni G, Petroccione A, Massana J, Möller HJ, Burrows GD, et al. Multicentre, multinational double-blind study of the activity and tolerability of reboxetine.

17. Ban TA, Dubini A, Giorgetti C, Petroccione A, Bercoff E, Chiu E, et al. Multicentre, multinational double-blind study of the activity and tolerability of reboxetine versus imipramine in elderly patients suffering from Depressive Disorders. Pharmacia Internal Report 9550089, January 1996.

18. Ban TA, Dubini A, Petroccione A, Castiglioni R, Gazner P, Mehilane L, et al. Multicentre, multinational double-blind study of the activity and tolerability of reboxetine vs placebo in the continuation therapy of major depressive episodes. Pharmacia Internal Report 9550077, December 1995.

19. Hamilton M. Developing a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;276-296.

20. Guy W. Clinical global impressions. In: ECDEU assessment manual for psychopharmacology. US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration. Rockville, Maryland, 1976.

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

22. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV). American Psychiatric Association, Washington, DC, USA.

23. Ban TA, Dubini A, Giorgetti C, Petroccione A, Andreoli V, Caillard V, et al. Multicentre, multinational double-blind study of the activity and tolerability of reboxetine versus fluoxetine and placebo in patients suffering from major depressive episodes. Pharmacia Internal Report 9550080, December 1995.

24. Quitkin FM. Placebos, Drug Effects, and Study Design: A Clinician's Guide. Am J Psychiatry 1999;156:829-836.