Studie 049

(97-CRBX049)

Studienbericht

Reboxetine Methanesulphonate CLINICAL DEVELOPMENT Issued 16 August 1999; Amended 09 November 1999 and 23 March 2001

Reboxetine (PNU-155950E) Versus Placebo in the Treatment of Major Depressive Disorders

Final Report of the Trial

Protocol Number 97-CRBX049

Final Report Originally Issued 16 August 1999;
Amended 09 November 1999 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	22 August 1997
Trial Completion Date	29 June 1998
Development Phase of Trial	III

This study has been performed in accordance with GCP requirements, including the archiving of essential documents.

1 SIGNATURE PAGE

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2 QUALITY ASSURANCE STATEMENT

The protocol required this study to be carried out according to the Tokyo revision of the Declaration of Helsinki and to be approved by the local Institutional Review Board (IRB). No protocol changes, other than those required for patient safety, were to be made once the study had started, without the specific written agreement between the investigators, the Ethics Committee, and the study monitor. In addition, the informed consent was to have been approved by the IRB or Ethics Committee and signed according to the regulations and requirements of each country.

3 SYNOPSIS

Name of Company: Pharmacia & Upjohn **Name of Finished Product:** VESTRA **Name of Active Ingredient:** Reboxetine mesylate	**Individual study table referring to part of the dossier**	(For national authority use only)
Title of study: Reboxetine (PNU-155950E) Versus Placebo in the Treatment of Major Depressive Disorders		
CTN: 97-CRBX049		**Document number:** a0027738
Investigator(s) and Study Centers: Multicenter study conducted at 9 sites in the US. John M. Downs, MD, Memphis, TN; Robert L. DuPont, MD, Rockville, MD; John P. Feighner, MD, San Diego, CA; Uriel Halbreich, MD, Buffalo, NY; Irving S. Kolin, MD, Winter Park, FL; Peter Londberg, MD, Seattle, WA; Sheldon Preskorn, MD, Wichita, KA; Jeffery S. Simon, MD, Brown Deer, WI; and Harold Udelman, MD, Phoenix, AZ.		
Publication (reference): None		
Studied period (years): 22 August 1997 - 29 June 1998		**Phase of development:** III
Objectives: To compare the safety and efficacy of reboxetine (RBX) with placebo (PBO) in the treatment of outpatients with Major Depressive Disorder.		
Methodology: This was a phase III, multicenter, double-blind, randomized, parallel-group, adjusted-dose study of RBX in outpatients aged 18 to 65 years who suffered from Major Depressive Disorder. Patients who were eligible based on the inclusion/exclusion criteria underwent an appropriate washout period and received a screening laboratory and electrocardiogram (ECG) assessment. After the washout period, patients who satisfied the study entrance criteria were randomized to receive treatment with RBX or PBO as outpatients for 42 days. On the baseline day, patients underwent a baseline assessment of standardized clinical psychopathological evaluations. Post-baseline assessments were done weekly.		
Number of patients planned: A total of 200 patients (100 in each group) were planned for this study. Each site was to enroll at least 20 patients. **Number of patients completed:** There were 212 patients randomized in the study of which 210 were included in the intent-to-treat population. A total of 152 patients completed the study—70 in the RBX group and 82 in the PBO group.		
Diagnosis and main criteria for inclusion: Patients had Major Depressive Disorder (DSM-IV) without Psychotic Features. Inclusion criteria were as follows: Patients of either sex, of any race, aged 18 to 65 years; a total score ≥22 on the 21-item HAM-D; and written informed consent		
Test product, dose and mode of administration, batch number: Reboxetine (RBX), 8-10 mg/day orally, administered as a scored tablet. Lot Number 27,985.		
Duration of treatment: 42 days		

Name of Company: Pharmacia & Upjohn **Name of Finished Product:** VESTRA **Name of Active Ingredient:** Reboxetine mesylate	**Individual study table referring to part of the dossier**	(For national authority use only)

Reference therapy, dose and mode of administration, batch number: Placebo (PBO), orally, administered twice daily (BID) as a scored tablet. Lot Number 27,984.

Criteria for Evaluation: Patients who received at least one dose of medication were included in the efficacy and safety analyses (intent-to-treat population). The Hamilton Rating Scale for Depression (HAM-D; 21 items), the HAM-D Item 1 score for depression, the HAM-D cluster analyses (ie, anxiety, cognitive, retardation and sleep disturbance), the Clinical Global Impression (CGI) scale, and the Montgomery-Asberg Depression Rating Scale (MADRS) were used to assess the efficacy of the study medications. The primary efficacy measure was the mean change from baseline on the HAM-D total score. The safety of the study medication was assessed by evaluation of newly-observed symptoms (treatment-emergent symptoms, TES), vital signs, laboratory tests, and electrocardiograms (ECG).

Statistical Methods Categorical variables were summarized using frequency counts. 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. 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 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 was the primary analysis and the OC analysis was 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 between treatment groups in the mean change from baseline at each post-baseline evaluation were analyzed using a paired t-test.

Efficacy Results For the HAM-D Total Score, LOCF analysis, the mean decrease from baseline did not achieve a level of significance when comparing RBX with PBO through 42 days of treatment. For the HAM-D Total Score, OC analysis, there was statistical significance in favor of RBX at Day 21 (p=0.0074), but thereafter only borderline significance from Day 28 (p=0.0543) through Day 42 (p=0.0509). There was no significance in HAM-D responder status for either OC or LOCF, though the p-values are closer to significance for the OC than LOCF analysis. The HAM-D Item 1 showed a slight improvement in depressed mood scores for patients receiving RBX. The HAM-D cluster analyses showed trends towards improved scores for RBX. In the MADRS Total Score, LOCF analysis, except for Day 35, there was statistical significance in favor of RBX from Day 21 (p=0.0471) through Day 42 (p=0.0190). For the MADRS Total Score, OC analysis, there was statistical significance in favor of RBX from Day 21 (p=0.0023) through Day 42 (p=0.0008). Though this was not the primary efficacy instrument, these results indicate that there is significant antidepressant efficacy of RBX versus PBO, as has been demonstrated in previous phase III RBX clinical trials.

Name of Company: Pharmacia & Upjohn **Name of Finished Product:** VESTRA **Name of Active Ingredient:** Reboxetine mesylate	**Individual study table referring to part of the dossier**	(For national authority use only)

Safety Results The total dropout rate (percent of patients who discontinued the trial) was 28.6% (60/210 patients). This is higher than the dropout rate for short-term PBO-controlled RBX studies in the existing RBX database, which was 18% to 20%. The majority of the discontinuations in this study were due to AEs, though there were no serious AEs. Twenty-six of 210 patients (12.4%) discontinued the study due to an AE. The percentage of patients who discontinued due to AEs was 21.7% (23/106) for RBX and 2.9% (3/104) for PBO. Many of the discontinuations occurred early in the study. Seventeen patients (28% of all discontinuations) discontinued in the first week; most of these (12/17; 70.6%) discontinued due to nonserious AEs. There were no serious AEs or deaths in this study. There were no clinically significant changes in clinical laboratory evaluations, vital signs or ECGs.

Summary - Conclusions In conclusion, this study did not achieve the primary goal of demonstrating a significant difference for RBX compared with PBO in reducing the mean total HAM-D scores at Day 42, the end of study. However, statistically significant differences from PBO were demonstrated on several secondary efficacy measures such as MADRS, beginning from Day 21 through Day 42. The high early dropout rate may have been a factor preventing more positive results.

Date of the report: Issued 16 August 1999; Amended 09 November 1999 and 23 March 2001

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations are defined and used in this report:

AE	Adverse event
ANOVA	Analysis of variance
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
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
MCV	Mean corpuscular volume
OC	Observed case
OTC	Over-the-counter
PBO	Placebo
PGI	Patient Global Impression
QAM	Once in the a.m.
QPM	Once in the p.m.
RBX	Reboxetine
SAS	Statistical Analysis System
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SSRI	Selective serotonin reuptake inhibitors
TES	Treatment-emergent symptom
TCA	Tricyclic antidepressant
US	United States
WBC	White blood cell
WHOART	World Health Organization Adverse Reaction Terminology

4 ETHICS

4.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The protocol and informed consent form were approved 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 U.S. Other than modifications for safety, no changes to the protocol were to be allowed once the study had started, without the specific written agreement of the investigators, the IEC or IRB, and the study monitor.

4.2 Ethical Conduct of the Study

The study was conducted in accordance with the Tokyo revision of the Declaration of Helsinki.

4.3 Patient Information and Consent

The investigator (or one of his/her associates) was to explain the nature, duration, and purpose of the study and the action of the drug to the patients in such a manner that they were aware of the potential risks, inconveniences, and adverse effects associated with their participation in the study. Informed consent forms, which were to have been approved by the investigator's IEC or IRB, were to be signed according to the regulations and requirements of the U.S.

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6 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 (Angst 1992). 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 (Angst 1992, Kamlet 1995, Montgomery 1992). 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 (Wells 1988, Wells 1989). A 15% mortality rate in association with suicide alone has been reported for patients whose depression is severe enough to require hospitalization (Coryell 1982).

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 (Kessler 1994). 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 (Kessler 1994).

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 GI adverse events (eg, diarrhea and nausea), as well as with some central nervous system (CNS) adverse events (eg, restlessness, agitation, insomnia, and somnolence). Thus, there is a need for new, effective antidepressant agents that are devoid of the adverse effects associated with the currently used antidepressant agents.

Reboxetine 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) (Ambrosini 1982). RBX has no relevant affinity for the serotonin or dopamine uptake sites or for the muscarinic or adrenergic receptors (Riva 1989). 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 (Herrman 1984), 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 (Herrman 1985). 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 (Dubini 1985). 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 (Dubini 1989).

This study was done in order to further characterize the safety and efficacy of RBX, to allow investigators in the US to have their first clinical experience with RBX and to serve as a back-up registration study (ie, an adequate and well-controlled study conducted in the US if the Food and Drug Administration were to require this for US registration).

7 OBJECTIVES

The objective of this study was to compare the antidepressant activity and safety of RBX with that of PBO in outpatients with Major Depressive Disorder.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This was a phase III, multicenter, double-blind, randomized, parallel-group, adjusted-dose study of RBX in outpatients aged 18 to 65 years who suffered from Major Depressive Disorder. Patients who were eligible based on the inclusion/exclusion criteria underwent a screening laboratory and ECG assessment and began an appropriate washout period. Optional PBO tablets (once in the morning) during the washout period were administered at the investigator's discretion. The washout period depended on the class of drugs with which the patient was currently being treated (4 days for TCAs, 14 days for MAOIs or SSRIs [except for fluoxetine] and 4 weeks for fluoxetine). Patients who were not currently being treated with a psychoactive drug could be randomized as soon as their laboratory test and ECG results were available. In addition, any patient, who in the opinion of the investigator, was deteriorating and required treatment could be randomized as soon as their laboratory test and ECG results were available even if they did not complete an optimal washout period. On the baseline day, following the washout period, patients underwent a baseline assessment of standardized clinical psychopathological evaluations. Information on patients screened for the study and found not to be eligible were collected in the appropriate form (screening form). Patients remaining eligible for the study were randomized into one of the two treatment groups. Post-baseline assessments were done weekly. After the washout period, patients who satisfied the study entrance criteria were randomized to receive treatment with RBX or PBO as outpatients for 42 days.

The Hamilton Rating Scale for Depression (HAM-D; 21 items, Hamilton 1967), the HAM-D Item 1 score for depression, the HAM-D cluster analyses (ie, anxiety, cognitive, retardation and sleep disturbance), the Clinical Global Impression (CGI) scale (Guy 1976), and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery 1979) were used to assess the efficacy of the study medications. The safety of the study medications was assessed by evaluation of newly-observed symptoms (treatment-emergent symptoms, TES), vital signs, laboratory tests, and ECGs.

The primary efficacy measure was the change from baseline on the Hamilton Rating Scale for Depression (HAM-D) total score. The secondary efficacy measures were: Clinical Global Impression (CGI) Severity of Illness mean change from baseline in the total score; CGI Global Improvement; CGI Global Improvement responder status (a responder is defined as having CGI Global Improvement <=2 (very much improved or much improved); the Montgomery-Asberg Depression Rating Scale (MADRS) mean change from baseline in total score; the HAM-D Item 1 Depressed Mood, mean change from baseline in the item score; the HAM-D cluster analyses (ie, anxiety, cognitive, retardation and sleep disturbance) mean change from baseline in the cluster score for; the mean of the Patient Global Impression (PGI) scale; Response Rate using HAM-D 21-item scale (a decrease of at least 50% in the 21-item HAM-D total score versus baseline will be considered a response); Remission Rate using HAM-D 21-item scale (remission is defined as a 21-item HAM-D total score of 10 or less); time to response using HAM-D 21-item scale; and time to remission using HAM-D 21-item scale.

Copies of the protocol and protocol amendments are in Appendix 1, sample case report forms are in Appendix 2, the randomization code is in Appendix 3, and the data displays are presented in Appendix 4.

8.2 Discussion of Study Design

The design of this study—double-blind, randomized, parallel-group—is generally recognized as one which provides an unbiased assessment of the efficacy and safety of an experimental drug.

8.3 Selection of Study Population

8.3.1 Inclusion Criteria

The patient inclusion criteria were as follows:

- Patients with Major Depressive Disorder (DSM-IV; Appendix A of the protocol) without Psychotic Features
- Patients of either sex, of any race, aged 18 to 65 years
- A total score ≥22 on the 21-item HAM-D
- Written informed consent

8.3.2 Exclusion Criteria

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

- Diagnosis of Major Depressive Episode with Psychotic Features

- Diagnosis of Dysthymic or Cyclothymic Disorder
- Diagnosis of Bipolar I or Bipolar II Disorder
- Resistance to antidepressant treatment (lack of response to at least two courses of previous antidepressants given at full doses for more than 1 month)
- Patients with an Axis IV history of psychosocial or environmental problems who, in the judgment of the investigator, are likely to respond to PBO
- History of major depressive disorders associated with endocrine disorders: hypo- and hyper-thyroidism tested by TSH and T4; hypo- and hyper-corticosteroidism, etc.
- Positive pregnancy test for women of childbearing potential
- 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 4 weeks preceding the study
- Meeting criteria for DSM-IV diagnosis of Substance Related Disorders, Schizophrenia or Other Psychotic Disorders
- 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 in the physical examination, laboratory tests and ECG at admission
- ECT in the previous 6 months
- High risk of suicide by Investigator judgment

8.3.3 Removal of Patients from Therapy or Assessment

Patients could withdraw from the study at any time and for any reason. A patient was withdrawn from treatment if, in the opinion of the investigator, it was medically necessary. Examples of this were:

- Unacceptable adverse events: this was defined as the occurrence of a Serious Adverse Event (SAE, see section 6.7.2.6 of the protocol)
- Lack of efficacy: this applied to patients who showed unacceptable deterioration after at least two weeks of treatment as measured by worsening of the CGI

- Switch to mania

In case of treatment discontinuation, the reasons for the withdrawal were to be clearly described and the patient should, whenever possible, irrespective of the reason for withdrawal, as soon as possible be examined. Relevant samples (lab tests, ECG and any diagnostic procedure which becomes necessary to define the event leading to withdrawal) should be obtained and all relevant assessments (HAM-D, MADRS, CGI, "end of study" form) should be completed, according to the schedule for final assessment. The CRFs should be completed as far as possible and collected by the Pharmacia & Upjohn Monitor.

8.4 Treatments

8.4.1 Treatments Administered

Patients were randomized to receive treatment with RBX or PBO. The study medications were provided as scored tablets which allowed for possible dose adjustments that could be made beginning at Week 3 in patients whom the investigator believed would benefit in terms of response (see Selection and Timing of Dose, Section 8.4.5.). Both study medications were to be taken BID. The RBX tablet contained 4 mg of RBX.

8.4.2 Identity of Investigational Product

The RBX and PBO supplies were manufactured and supplied by Pharmacia & Upjohn, Italy as identically-appearing tablets containing either 4 mg of RBX (one, 4-mg tablet) and excipients or excipients only (PBO). Information related to the study medications is summarized in Table 1.

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

Study Medication	Tablet Strength*	Supplier	Lot Number
RBX	4 mg	PNU, Italy	27,985
PBO	—	PNU, Italy	27,984

* Each tablet contained 4 mg of RBX plus excipients, or excipients only (PBO).

Six bottles of medication were supplied to each patient. Each bottle for each week contained the medication necessary for one week plus additional tablets for difficulties in scheduling visits and possible losses (total of 25 tablets), prepared according to the BID regimen with 1 tablet in the morning and 1 tablet for the evening dose for Weeks 1, 2, and 3 and 1½ tablets in the morning and 1 tablet in the evening for Weeks 4, 5, and 6. Patients were to return all unused medication at the end of the study or at the time of their termination if they discontinued the study early.

8.4.3 Method of Assigning Patients to Treatment Groups

A randomization list was prepared for patient allocation to one of the two treatments. Treatments were prepared on this basis by Pharmacia & Upjohn and labeled with the corresponding patient number.

Patient allocation to treatment was done at baseline by the investigator on the basis of the patient's temporal entry into the study. A randomization list by center was provided only after the data for the study had been analyzed.

8.4.4 Selection of Doses in the Study

The 8-10 mg/day doses of RBX for this study were chosen based on the results of previously conducted phase II and phase III studies which indicated these were effective doses with the most acceptable adverse event profile.

8.4.5 Selection and Timing of Dose for Each Patient

Patients were randomized to receive treatment with RBX or PBO. Medication was to be administered BID (from 8:00 AM to 9:00 AM and from 5:00 PM to 6:00 PM). The initial dose was one scored tablet (4 mg of RBX) twice daily that was to be taken by the patients from Days 1 to 21. At the Week 3 evaluation, the investigator could increase the morning dose to 1½ tablet for any patient he/she believed might benefit in terms of response and who might adequately tolerate the increased dose. The evening dose remained at one tablet daily for all patients. The RBX dose for those who increased was therefore RBX 6 mg QAM and 4 mg QPM (10 mg/day). The increased dose was to be taken daily during the final 3 weeks of the study. Patients whose morning dose was increased to 1½ tablets and who did not adequately tolerate the increased dose could return to the one tablet in the morning for the final 3 weeks.

8.4.6 Blinding

The investigator was given individual sealed envelopes or drug disclosure sheets containing the information on each patient's treatment. These could be opened only in case of emergency necessitating treatment identification. In the event of an emergency, the investigator was to immediately (within 24 hours) inform the study monitor and report full description of reasons for opening the code in the CRF (Adverse Event Form).

The sealed individual codes were then returned to Pharmacia & Upjohn (Kalamazoo, MI) at the end of the study.

8.4.7 Prior and Concomitant Therapy

No concomitant psychotropic medication other than hypnotics during the washout period were allowed during the study. The administration of other concomitant psychotropic drugs was considered to be a protocol deviation.

Other therapy considered necessary for the patient's welfare could be given at the discretion of the investigator. All such therapy had to be recorded in the Case Report Form (CRF). No other drug under investigation could be used concomitantly with the study drug. Patients were not allowed to participate concurrently in any other clinical study. Oral contraceptives could be used in order to satisfy the inclusion/exclusion criteria in female patients (see the item on potential child-bearing females). OTC medicines were allowed on a p.r.n. basis as a symptomatic treatment. All medications were recorded on the relevant form as well as the adverse event requiring treatment. All concomitant medication, including OTC drugs, were recorded in the Patient Diary.

8.4.8 Treatment Compliance

The experimental treatment was administered for 6 weeks. The compliance was strictly monitored. Treatment schedules to be filled in by the patient (ie, patient diary) were provided for daily recording of drug administration. These diaries were reviewed at each visit for each patient. Diaries remained source documents and were retained by the investigator.

8.5 Efficacy and Safety Variables

8.5.1 Flow Chart

Potential patients were screened to ensure study eligibility. Those who satisfied the study entrance criteria underwent a washout period that was based on the medication they received (see Section 10.1). Patients who satisfied the study entrance criteria at the end of the washout period (ie, at baseline) were randomized to receive treatment with RBX or PBO as outpatients for 6 weeks. The schedule of activities is summarized in Table 2.

Table 2. Schedule of Activities

Visit #	Screen	1	2	3	4	5	6	7*
Week		Baseline	1	2	3	4	5	6*
Day†	‡	Baseline	7	14	21	28	35	42*
Informed Consent	X							
Medical history; clinical and physical examination; history of mental disorder	X							
Randomization		X						
HAM-D, HAM-D Item 1, and HAM-D Cluster§	X	X	X	X	X	X	X	X
MADRS, CGI, PGI		X	X	X	X	X	X	X
End of Study form								X
Treatment-Emergent Symptoms		X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X
Hematology	X				X			X
Serum chemistry	X				X			X
Pregnancy test (female patients only)	X							
Urine drug screen	X							X
ECG	X				X			X

* For any patient who withdraws prior to Visit 7 (Week 6, Day 42), all tests and forms (ie, laboratory tests, ECG, vital signs, adverse events, HAM-D, MADRS, CGI, PGI) should be carried out/completed and the End of Study form completed
† Visits should be targeted to occur ± one day
‡ Screening visit must take place within 2 weeks prior to baseline
§Includes HAM-D anxiety, retardation, cognitive and sleep disturbance clusters

8.5.2 Efficacy Measures

8.5.2.1 Hamilton Rating Scale for Depression (HAM-D)

The severity of depression was quantified using the 21-item HAM-D (Hamilton 1967) 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 provides 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	0-3
21. Obsessional and Compulsive Symptoms	0-2

Hamilton 1967.

8.5.2.2 HAM-D Item 1 (Depressed Mood)

Item 1 on the HAM-D scale was a measure of depressed mood. This measure was obtained at Baseline and on Days 7, 14, 21, 28, 35, and 42.

8.5.2.3 HAM-D Cluster Analyses

Items 10, 11, 12, 13, 15 and 17 on the HAM-D scale were clustered to measure anxiety. Items 2, 3, 9, 19, 20 and 21 were clustered to measure cognition. Items 1, 7, 8 and 14 were clustered to measure retardation. Items 4, 5 and 6 were clustered to measure sleep disturbance.

8.5.2.4 Clinical Global Impression

The CGI (Guy 1976) consists of three subscales: Severity of Illness, Global Improvement, and Efficacy Index. In this study, all three subscales were used. The severity of the patient's illness was assessed at Baseline and on Days 7, 14, 21, 28, 35, and 42. Global improvement and the efficacy index were assessed on Days 7, 14, 21, 28, 35 and 42. 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 intolerance while a high score indicated that the patient's condition was unchanged or worse AND the intolerance 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
Compared with your total clinical experience with this particular population, how mentally ill is the patient at this time?	Compared to his condition at admission to the study, how much has he 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

Guy W. 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

8.5.2.5 Montgomery-Asberg Depression Rating Scale

The MADRS (Montgomery 1979) was completed by the investigator at Baseline and on Days 7, 14, 21, 28, 35, and 42. The MADRS consists of ten depression-related items, which were selected from the 67 items on the Comprehensive Rating Scale (Asberg 1978) because of their sensitivity to change. The ten items on the MADRS are as follows: 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. Each individual item was to be rated on a scale from 0 to 6; the scores for the individual items were then to be totaled to give the MADRS total score.

8.5.2.6 Patient's Global Impression

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

8.5.3 Safety Measures

8.5.3.1 Adverse Events

Adverse events were to be recorded at Baseline and on Days 7, 14, 21, 28, 35, and 42. For this study, an adverse event was any untoward medical occurrence that occurred during the protocol-specified adverse event reporting period (see Adverse Event Reporting Period, below) regardless of whether it was considered related to a medication.

In addition, any known untoward event that occurred subsequent to the adverse event reporting period that the investigator assessed as possibly related to the investigational medication was also considered to be an adverse event.

Adverse events included the following:

- All suspected adverse medication reactions
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. (If a medical condition was known to have caused the injury or accident [eg, a fall secondary to dizziness], the medical condition [dizziness] and the accident [fall] was to be reported as two separate adverse events. The outcome of the accident [eg, hip fracture secondary to the fall] was to be recorded under Comments.)
- Abnormalities in physiological testing or physical examination findings that required clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that required clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they were associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (eg, elevated liver enzymes in a patient with jaundice) were to be described under Comments on the report of the clinical event rather than listed as a separate adverse event.

8.5.3.2 Laboratory Tests

Hematology and serum chemistries were performed at the screening evaluation and on Days 21 and 42. A urine drug screen was performed at Screen and Day 42. The specific tests that were to be evaluated are summarized in Table 5.

Table 5. Laboratory Assays

Category	Assay
Hematology	Hemoglobin Hematocrit White blood cells (WBC) Neutrophils Lymphocytes Eosinophils Monocytes Basophils Red blood cells (RBC) Mean corpuscular volume (MCV) Platelets
Serum Chemistries	Serum glutamic-oxaloacetic transaminase (SGOT) Serum glutamic-pyruvic transaminase (SGPT) Glucose Alkaline phosphatase Creatinine Uric acid Bilirubin (total) Thyroid function (TSH and T4) - Screen only Pregnancy test (for all females) - Screen only
Urinalysis	Drug screen (Screen and Day 42 only)

8.5.3.3 Vital Signs

Systolic and diastolic blood pressure and radial pulse rate were measured (sitting position) at Screen, Baseline, and on Days 7, 14, 21, 28, 35, and 42.

8.5.3.4 Electrocardiograms

Standard 12-lead ECGs were obtained at Screen and on Days 21 and 42.

8.5.4 Appropriateness of Measurements

The efficacy measures that were used in this study (HAM-D, CGI, PGI, and MADRS) are of demonstrated reliability, validity, and sensitivity to drug effects and are widely recognized as useful scales for the assessment of antidepressant effects. The safety measures (adverse events, vital signs, laboratory tests, and ECGs) and the intervals at which they were assessed were appropriate to monitor the safety of the study medication.

8.5.5 Primary Efficacy Variable

The primary efficacy variable was the mean change from baseline on the HAM-D total score.

8.6 Data Quality Assurance

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

- Operating procedures for training on the assessment instruments (HAM-D, CGI, PGI, and MADRS) and for study monitoring and coordination were defined.
- 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.

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

8.7.1 Determination of Sample Size

The adequacy of the sample size was investigated by looking at the power of the parametric test on the change from baseline of the 21-item HAM-D total score. Power calculation was based on the results of a previously conducted RBX study 20124/014. Both studies have similar entry criteria and both are placebo controlled.

In study 20124/014, the difference between PBO and the RBX groups in the change from baseline of the 21-item HAM-D total score was 4.7 with a standard deviation of 9.5. One hundred patients per treatment group are necessary in order to test the null hypothesis of no difference in the change from baseline of the 21-item HAM-D total score between the active drug and PBO with a power of 93% and a two-sided alpha=0.05. With 100 patients per arm, 88% power is still achieved in the observed cases analyses if 20% of the patients drop out of the study.

8.7.2 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 was the primary analysis and the OC analysis was included as a secondary analysis.

8.7.3 Demographic and Baseline Characteristics

Continuous variables were summarized using treatment group means, standard deviations, and ranges. Categorical variables were summarized using frequency counts. Comparability 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.

8.7.4 Efficacy

8.7.4.1 For the continuous variables (such as HAMD total mean change from baseline and MADRS total mean change from baseline), testing for difference between two treatment groups was performed using a two-way analysis of variance (ANOVA) model that included treatment, investigator, and treatment-by-investigator interaction terms. The response variables were the mean change from baseline at each visit. Treatment-by-investigator interaction was tested to evaluate poolability of the 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 are not dependent on significance of the interaction term. Categorical data (such as response and remission) were analyzed by the Cochran-Mantel-Haenszel (CMH) test, stratified by investigator.

8.7.4.1.1 Means of individual components of the HAMD were displayed by treatment group and by visit to identify any components that may have had major influence on the HAMD total. This analysis was descriptive and did not include statistical hypothesis testing.

8.7.5 Safety

8.7.5.1 Adverse Events

The original terms that were used by the investigators to identify adverse events 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 adverse event was counted once according to the date of onset. If the onset was prior to the first dose of study drug and the event did not increase in severity after initiation of study drug, the adverse event was considered to be a pretreatment adverse event and was not counted in the adverse-event frequency tables. If the onset was prior to the first dose of study drug and the severity increased after baseline, the event was counted as an adverse event. This rule is consistent with the treatment-emergent symptom (TES) convention for counting adverse events.

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 adverse events that resulted in the termination of the study medication was also prepared.

8.7.5.2 Laboratory Tests

Summary statistics (mean, mean change from baseline, median change from baseline, and standard deviation) were calculated for each laboratory test. Differences between treatment groups in the mean change from baseline at each post-baseline evaluation were analyzed using a paired t-test.

The frequency of patients who had clinically significant values for laboratory tests was tabulated, and data for the individual patients were listed. The criteria used to identify patients with clinically significant laboratory values were the central laboratories normal ranges (see Appendix 5).

8.7.5.3 Vital Signs

Summary statistics (mean, mean change from baseline, median change from baseline, and standard deviation) were calculated for systolic and diastolic blood pressure, pulse rate, and weight. Differences between groups in the mean change from baseline at each post-baseline evaluation 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

8.7.5.4 Electrocardiograms

Summary statistics (mean, mean change from baseline, median change from baseline, and standard deviation) were calculated for QTc interval, heart rate, PR interval, QRS interval, and QT interval. Differences between groups in the mean change from baseline at each post-baseline evaluation were analyzed using a paired t-test.

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.

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

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

8.7.6 Rules for Estimation of Missing Data

8.7.6.1 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.

8.7.6.2 Safety Data

If the onset date for an adverse event was missing or incomplete, a "complete" date was estimated so that the event could be categorized into the appropriate study period of the study. If the onset date was completely missing, the date was estimated by the visit date. If the onset month was present, then the onset day was estimated as the first day of the month or the first day of the interval, whichever day was later.

8.7.7 Significance Levels

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.

8.7.8 Statistical Software

All data processing, summarization, and analyses utilized the Statistical Analysis System (SAS), Version 6.10 software package. The ANOVA results were based on Type III sums of squares computed by the General Linear Models (GLM) procedure.

8.8 Changes in the Conduct of the Trial or Planned Analysis

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.

Subset analyses for gender, severity were not done since no statistically significant differences were found in the primary efficacy measure. Also, time-to-response/remission were not done since no significant p-values were present.

9 RESULTS

Key data displays are included in the text. More detailed, supportive tables are included in Appendix 4; references to these tables are included in the text.

9.1 Patient Enrollment by Site

A total of 212 patients were enrolled by nine investigators in the trial. Of these, 107 received RBX and 105 received PBO. Patient enrollment by site for the randomized population is summarized in Table 6.

Table 6. Patient Enrollment by Site (*All Patients Randomized*)

	Treatment Groups		
Investigator	RBX n	PBO n	Overall
Feighner, J.	19	19	38
Kolin, I.*	6	6	12
Dupont, R.	20	20	40
Preskorn, S.	5	5	10
Simon, J.	12	10	22
Udelman, H.	9	9	18
Londborg, P.	10	10	20
Downs, J	10	10	20
Halbreich, U.	16	16	32
Total	**107**	**105**	**212**

Source: Appendix 4, Tables 1.1, 1.2
n=Number of patients entered by site.
Patient 168 (Kolin) and Patient 177 (Halbreich) were randomized but not included in the intent-to-treat population.
* Data for three patients (Patient Nos. 169, 172 and 277 [Kolin site]) were received in-house after the database for this study was closed. Therefore, these patients are not included in this table or any other patient counts and their data are not included in the report.

9.2 Disposition of Patients

The number of patients either completing or discontinuing the study and reasons for discontinuation are shown in Table 7.

Table 7. Summary of Patient Disposition

DISPOSITION	Treatment Group RBX N=107	Treatment Group PBO N=105
No. (%) of Patients Randomized	107 (100)	105 (100)
No. (%) of Patients Intent-to-Treat	106 (99.1)	104 (99.0)
No. (%) of Patients Who Completed the Trial	70 (65.4)	82 (78.1)
No. (%) of Patients Who Discontinued the Trial	37 (34.6)	23 (21.9)
Reason For Discontinuation		
Lack of Efficacy	4* (3.7)	6 (5.7)
Medical Events		
Nonserious	22* (20.6)	3 (2.9)
Serious	0 (0)	0 (0)
Death	0 (0)	0 (0)
Administrative		
Protocol Noncompliance	1 (0.9)	2 (1.9)
Patient Request	4 (3.7)	7 (6.7)
Lost to Follow-up	6 (5.6)	5 (4.8)

Source: Appendix 4, Tables 1.3, 1.4
N=Sample size
* One RBX-treated patient who had an AE that caused discontinuation was inadvertently reported as discontinuing the study due to lack of efficacy. Therefore, the actual n (%) for Nonserious Medical Events is 23 (21.5%) and the actual n (%) for Lack of Efficacy is 3 (2.8%).

Non-serious medical events were the main reason that RBX-treated patients discontinued the study. From the randomized population, 23 of 107 patients (21.5%) receiving RBX discontinued due to non-serious medical events compared to only 3 of 105 patients (2.8%) receiving PBO. The non-serious medical events leading to discontinuation are discussed in Section 9.7.3.3. All other reasons leading to discontinuation of treatment were generally comparable between the RBX and PBO groups.

9.2.1 Protocol Deviations

The following patients had protocol deviations. None of the patients were excluded from the efficacy evaluations.

Investigator	Patient	Treatment Group	Deviation
Kolin	279	RBX	Baseline HAM-D total of 21
Kolin	170	RBX	Patient tested positive for barbiturates at Screen, and Day 42.
Kolin	171	PBO	Patient tested positive for opiate at Screen and Day 42.
Dupont	159	RBX	Baseline HAM-D total of 21
Longborg	239	PBO	Baseline HAM-D total of 21
Feighner	106	PBO	Patient tested positive for amphetamine at Day 42.
Feighner	107	RBX	Patient tested positive for tetrahydrocannabinol at termination.
Feighner	218	RBX	Patient tested positive for opiate at Day 42.
Simon	148	PBO	Patient tested positive for tetrahydrocannabinol at Day 42.
Simon	222	RBX	Patient tested positive for cocaine and benzodiazepine at Day 42.
Udelman	256	PBO	Patient tested positive for benzodiazepine at Day 42.
Downs	186	PBO	Patient tested positive for benzodiazepine at Day 42.
Downs	293	RBX	Patient tested positive for tetrahydrocannabinol at Day 42.
Downs	321	PBO	Patient tested positive for amphetamine at Day 42.

9.3 Demographic and Other Baseline Characteristics

9.3.1.1 Demographic Characteristics

A summary of the demographic characteristics at Screen is presented in Table 8.

Table 8. Demographics at Screen (Intent-to-Treat)

Demographics	RBX N=106	PBO N=104	p-value
Sex			
Male	48 (45.3)	44 (42.3)	0.6639
Female	58 (54.7)	60 (57.7)	
Age (years)			
N	106	104	
Range	19-64	18-64	0.9063
Mean	39.9	39.7	
STD	11.6	11.1	
Weight (lb)			
N	106	104	
Range	102.0-280.0	110.0-298.0	0.6207
Mean	173.7	176.4	
STD	39.3	38.2	
Height (in)			
N	106	104	
Range	58.0-74.0	60.0-77.0	0.9926
Mean	67.0	67.0	
STD	3.49	4.16	
Race			
Caucasian	98 (92.5)	96 (92.3)	
Black	4 (3.8)	5 (4.8)	
Asian	1 (0.9)	1 (1.0)	0.9576
Other	3 (2.8)	2 (1.9)	

Source: Appendix 4, Tables 2.1, 2.2
N=Sample size; STD=Standard deviation

Overall, there were no statistically significant differences between groups in the demographic characteristics for this study (ie, sex, age, weight, height and race). Patients ranged in age from 18 to 64 years.

9.3.2 Psychiatric History

9.3.2.1 Previous History of Depression

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

Table 9. Previous History of Depression

	RBX N=106	PBO N=104	P-Value
Age (years) at Onset of Major Depression			
No. of Patients*	106	104	
Mean	27.9	27.0	
Range	4-64	5-64	0.5960
STD	13.0	13.3	
No. of Previous Episodes			
No. of Patients*	106	103	
Mean	4.3	5.7	
Range	0-99	0-99	0.4253
STD	10.5	15.1	
Approximate Duration of Last Episode (weeks)			
No. of Patients*	97	94	
Mean	56.8	66.9	
Range	0-676	0-1560	0.6290
STD	92.1	66.9	

Source: Appendix 4, Table 2.4

*For whom data were available; STD=Standard deviation

There were no statistically significant differences in the prior history of depression. The mean age at onset of major depression was in the late twenties for both groups. The mean number of previous episodes of depression was 4.3 in the RBX group and 5.7 in the PBO group. The mean duration of the last depressive episode was 56.8 weeks in the RBX group and 66.9 weeks in the PBO group.

9.3.2.2 Characteristics of the Present Depressive Episode

Table 10 summarizes data related to the present depressive episode.

Table 10. Characteristics of the Present Depressive Episode

Variables	RBX N=106	PBO N=104	P-Value
Approximate Duration of Present Episode (wk)			
No. of Patients*	106	104	
Mean	114.3	112.5	0.9583
Range	2-2288	2-1560	
STD	283.6	201.0	
Present Episode is Best Characterized as:			
Exacerbation of chronic condition	13 (12.3)	11 (10.6)	
Recurrence of similar previous conditions	77 (72.6)	65 (62.5)	0.1072
Significantly different from any previous conditions	1 (0.9)	0 (0)	
First occurrence, no previous psychiatric diagnosis	15 (14.2)	28 (26.9)	
Precipitating External Stress Was:			
Absent	41 (38.7)	39 (37.5)	
Probably present	32 (30.2)	29 (27.9)	0.8569
Definitely present	33 (31.1)	36 (34.6)	

Source: Appendix 4, Tables 2.4 and 2.5
( ) = percent
*For whom data were available; STD=Standard deviation

Overall, there were no statistically significant differences in the variables assessing the present depressive episode. The approximate duration of the present depressive episode ranged from 2 to 2288 weeks across the groups; the mean duration of the present episode was 114.3 weeks in the RBX group and 112.5 weeks in the PBO group. For the majority of patients in each group, the present episode was judged to represent a recurrence of a similar previous condition (72.6% in the RBX group and 62.5% in the PBO group). Most patients (≥61%) in each group had precipitating stress associated with their present episode.

9.3.2.3 Severity of Depression at Baseline

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

Table 11. Severity of Depression at Baseline

Variables	RBX N=106	PBO N=104	P-Value
Hamilton Rating Scale for Depression			
Mean Total Score	25.1	25.3	0.6866
Range	21-33	21-36	
STD	2.6	3.0	
Clinical Global Impression-Severity of Illness*			
Mean Score	4.3	4.3	0.7381
Range	3-6	4-6	
STD	0.6	0.5	
Montgomery-Asberg Depression Rating Scale			
Mean Total Score	29.2	29.2	0.9805
Range	19-40	14-39	
STD	4.2	4.6	

Source: Appendix 4, Table 2.3

STD=Standard deviation; *7-point scale on which 4 = moderately ill and 5 = markedly ill

There were no statistically significant differences between groups 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 total score.

9.3.3 Other Baseline Evaluations

There were no statistically significant differences between treatment groups in systolic and diastolic blood pressures, pulse rate, patient's educational background (eg, high school diploma, college degree, etc), occupations (eg, professional occupation, service occupation, etc.), living situation (eg, with family, alone, etc.) or current employment status (eg, full-time employment, part-time employment, etc.) (See Appendix 4, Tables 2.1, 2.2). Likewise, there were no statistically significant differences between the groups in the proportion of patients who had normal or abnormal physical examinations (Appendix 4, Table 2.6) or in patient medical histories (Appendix 4, Table 2.7).

9.4 Concomitant Medications

9.4.1 Prior to the Study

At the screening evaluation, 62.3% (66/106) of the patients in the RBX group and 67.3% (70/104) of the patients in the PBO group were taking at least one medication.

Concomitant study medications taken most frequently (≥5% for both groups) at pretreatment included acetaminophen (e.g. Tylenol), nonsteroidal anti-inflammatory agents (e.g. ibuprofen), antihistamines, salicylates (e.g. aspirin), oral contraceptives, and multivitamins. Prestudy medications are summarized in Appendix 4, Table 2.9.

9.4.2 During the Study Period

Non-investigational medications were taken concomitantly with the study medication by 80.2% (85/106) of the patients in the RBX group and by 81.7% (85/104) of the patients in the PBO group. Acetaminophen, antihistamines, antitussive combinations, decongestant antihistamines and analgesic combinations, nonsteroidal anti-inflammatory agents, nonnarcotic analgesic combinations, multivitamins, oral contraceptives, and salicylates were the most frequently taken agents (≥5%) in both groups. On-study, non-investigational medications are summarized in Appendix 4, Table 2.10.

9.5 Dosing Information

Patients in the RBX group were to receive 4 mg of RBX twice daily from Weeks 1 to 3. For Weeks 4 to 6, the investigator had the option to increase a patient's dose to 1½ tablets (6 mg) in the morning and 1 tablet (4 mg) in the evening. If a patient could not tolerate the scheduled increase in dose, the dose was to be reduced to the starting dose for the remainder of the trial. The mean dosing data at each post-baseline visit suggests that most patients complied with the protocol-specified dosing regimen. The mean daily dose, ie, the average dose that was taken over the specified treatment interval, is summarized for the RBX group in Table 12.

Table 12. Mean Daily Dose by Visit*

	RBX N=106	
Study Day	No. of Pts†	Mean Dose (mg/d)
7	102	7.486
14	87	7.679
21	79	7.906
28	76	9.108
35	71	9.263
42	71	9.643

Source: Appendix 4, Table 2.8

*Average dose over the previous treatment period

†Number of patients with dosing information at the specified visit

9.6 Efficacy Results

9.6.1 Data Sets Analyzed

The efficacy analyses were based on the intent-to-treat population, which includes patients who received at least one dose of study medication. Of the 212 patients who were randomized into the study, 210 patients—106 in the RBX group and 104 in the PBO group—satisfied this criterion and were, therefore, included in the intent-to-treat efficacy analyses (Appendix 4, Tables 1.1 and 1.2).

9.6.2 Primary Efficacy Variable

The primary efficacy variable was the mean change from baseline on the HAM-D total score.

9.6.2.1 Hamilton Rating Scale for Depression: Total Score

Two analyses were conducted for the primary efficacy measure, mean change from baseline in HAM-D total score. The "last observation carried forward" (LOCF) was the primary analysis and the "observed cases" (OC) was the secondary analysis.

For the LOCF analysis, the mean decrease from baseline in HAM-D total score did not achieve a level of significance through 42 days of treatment with RBX. From Day 21 on, the mean change from baseline to post-treatment visit HAM-D total scores was slightly better in the RBX group than the PBO which suggested a possible trend with RBX treatment.

For the OC analysis, the mean decrease from baseline in the HAM-D total score was better in the RBX group beginning at Day 14. This difference reached statistical significance (P=0.0074) at Day 21 and was marginally close to the protocol-defined level (p=0.05) at Days 28 (p=0.0543), 35 (p=0.0595) and 42 (p=0.0509).

Table 13 summarizes the mean change from baseline in the HAM-D total at each post-baseline evaluation for both the LOCF and OC analyses. Appendix 4, Tables 3.1A and 3.1B 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.

Appendix 4, Table 3.3 presents the mean of the HAM-D individual items by visit. Appendix 4, Tables 3.7A and 3.7B present the response status (defined as 50% or more decrease from baseline on HAM-D) at each post-baseline evaluation for HAM-D. This analysis showed no statistically significant differences in the numbers of patients in each group who were classified as responders. At the Day 42 visit, 39.6% of the patients in the RBX group and 33.7% of the patients in the PBO group had a 50% or greater decrease in HAM-D based on the LOCF analysis. Similarly, based on the OC analysis at Day 42, 50.7% of the RBX patients and 38.3% of the PBO patients were responders.

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

					Visit											
		Group or	Baseline		Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
Analysis	Statistic	Comparison	n	Mean	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	106	25.1	101	-3.3	101	-5.3	101	-7.1	101	-8.5	101	-9.1	101	-9.3
		PBO	104	25.3	100	-4.0	101	-5.7	101	-6.2	101	-7.7	101	-8.0	101	-8.3
	P-Value‡	RBX vs PBO	**NA**		**0.5699**		**0.5535**		**0.1009**		**0.3150**		**0.2035**		**0.1932**	
OC	Mean Change From Baseline	RBX	106	25.1	101	-3.3	87	-5.9	81	-8.2	76	-9.9	72	-10.6	71	-11.4
		PBO	104	25.3	100	-4.0	96	-5.8	92	-6.5	86	-8.3	83	-9.0	81	-9.5
	P-Value‡	RBX vs PBO	**NA**		**0.5699**		**0.3280**		**0.0074***		**0.0543**		**0.0595**		**0.0509**	

Source: Appendix 4, Tables 2.3, 3.1A, 3.1B and 3.2

Intent-to-treat population

† Mean change from baseline value

‡ P-value based on two-way ANOVA

* P-values ≤ 0.05 were flagged

9.6.3 Secondary Efficacy Variables

The secondary efficacy measures were: Clinical Global Impression (CGI) Severity of Illness mean change from baseline in the total score; CGI Global Improvement; CGI Global Improvement responder status (a responder is defined as having CGI Global Improvement <=2 (very much improved or much improved); the Montgomery-Asberg Depression Rating Scale (MADRS) mean change from baseline in total score; the HAM-D Item 1 Depressed Mood, mean change from baseline in the item score; the HAM-D cluster analyses (ie, anxiety, cognitive, retardation and sleep disturbance) mean change from baseline in the cluster score for; the mean of the Patient Global Impression (PGI) scale; Response Rate using HAM-D 21-item scale (a decrease of at least 50% in the 21-item HAM-D total score versus baseline will be considered a response); Remission Rate using HAM-D 21-item scale (remission is defined as a 21-item HAM-D total score of 10 or less); time to response using HAM-D 21-item scale; and time to remission using HAM-D 21-item scale.

9.6.3.1 HAM-D Item 1 (Depressed Mood)

There was a slight improvement in depressed mood scores for patients receiving RBX compared to PBO, based on the OC analysis. The mean change in scores at both the Day 21 and Day 28 visits was significantly lower (P=0.0193 and P=0.0408, respectively) in the RBX group. In the LOCF analysis, there was very little difference between groups in depressed mood scores.

9.6.3.2 HAM-D Anxiety Cluster

There was a slight improvement in anxiety scores for the patients receiving RBX compared to PBO, based on the OC analyses. The absolute mean change in scores at the Day 21 visit was significantly lower (P=0.0049) in the RBX group using the OC analysis. In the LOCF analysis, there was very little difference between groups in anxiety scores.

9.6.3.3 HAM-D Cognitive Cluster

There was a slight improvement in cognition scores for patients receiving RBX compared to PBO using the OC analysis. The absolute mean change in scores at the Day 21 visit was marginally significantly lower (P=0.0513) in the RBX group. In the LOCF analysis, there was very little difference between groups in cognition scores.

9.6.3.4 HAM-D Retardation Cluster

Scores for retardation decreased over time in both groups, but overall, the scores were lower in the RBX group. The absolute mean changes in scores for retardation were higher in the RBX group using both the LOCF and OC analyses. These changes were significant at Day 21 (P=0.0376) for the LOCF analysis and at Day 21, Day 28, Day 35 and Day 42 (P=0.0025, P=0.0062, P=0.0160, and P=0.0128 respectively) for the OC analysis.

9.6.3.5 HAM-D Sleep Disturbance Cluster

Scores for sleep disturbance decreased over time in both groups. The scores in the PBO group were lower than in the RBX group at Day 7; differences between groups were statistically significant (P=0.0068) using both the LOCF and OC analyses.

9.6.3.6 Clinical Global Impression Scales

As previously discussed, the CGI scale was comprised of the Clinical Global Improvement scale, Severity of Illness scale, and the Efficacy Index.

9.6.3.6.1 CGI-Global Improvement

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 Appendix 4, Tables 3.4A and 3.4B, for the LOCF and OC analyses, respectively. Overall, there was a trend towards better improvement in the CGI-Global Improvement scale in the RBX group compared to the PBO group.

Table 14 summarizes the CGI-Global Improvement response status (a measure of improvement) at each post-baseline visit for both the LOCF and OC analyses. Appendix 4, 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. For the OC analysis, the distribution of responders was statistically significant at Day 35 and 42.

Table 14. Clinical Global Impression (CGI)-Global Improvement Response Status[#]

			Visit											
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
Analysis	Statistic		n	%	n	%	n	%	n	%	n	%	n	%
LOCF	Responder	RBX	14	13.9	27	26.7	30	29.7	41	40.6	49	48.5	48	47.5
		PBO	10	10.1	20	20.0	26	26.0	31	31.0	38	38.0	36	36.0
	P-Value†	RBX vs PBO	**0.4180**		**0.2686**		**0.5662**		**0.1707**		**0.1513**		**0.1063**	
OC	Responder	RBX	14	13.9	27	31.0	29	35.8	37	48.7	42	58.3	42	59.2
		PBO	10	10.1	20	20.8	25	27.2	30	34.9	35	42.2	33	40.2
	P-Value†	RBX vs PBO	**0.4180**		**0.1090**		**0.2609**		**0.0951**		**0.0446***		**0.0120***	

Source: Appendix 4, Tables 3.6A and 3.6B

[#] CGI-Global Impression score of 1 (very much improved) or 2 (much improved)

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

[*] P-values ≤ 0.05 were flagged

9.6.3.6.2 CGI-Severity of Illness

There was very little difference in the CGI-Severity of Illness scores for the RBX and PBO groups for both the LOCF and OC analyses throughout the study. At Day 42, the mean decrease in the CGI-Severity of Illness scores was -1.2 in the RBX group and -0.9 in the PBO group for the LOCF analysis. At Day 42, the mean decrease in the CGI-Severity of Illness score was significantly greater (p=0.0381) in the RBX group (-1.5) than in the PBO group (-1.1) for the OC analysis.

Table 15 summarizes the mean change from baseline for the CGI-Severity of Illness score by visit. Appendix 4, Tables 3.10A and 3.10B provide additional information, including the p-values for the least square mean change, for the LOCF and OC analyses, respectively. Appendix 4, Table 3.11 presents a cross tabulation of the Baseline vs. Endpoint Scores.

Table 15. Mean Change From Baseline in Clinical Global Impression (CGI)-Severity of Illness Score[#]

					Visit											
			Baseline		Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
Analysis	Statistic	Group or Comparison	n	Mean	n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean Change From Baseline	RBX	106	4.3	101	-0.2	101	-0.4	101	-0.7	101	-0.9	101	-1.0	101	-1.2
		PBO	104	4.3	99	-0.3	100	-0.5	100	-0.6	100	-0.8	100	-0.9	100	-0.9
	P-Value‡	RBX vs PBO	NA		**0.3058**		**0.8063**		**0.6816**		**0.3309**		**0.2643**		**0.1247**	
OC	Mean Change From Baseline	RBX	106	4.3	101	-0.2	87	-0.5	81	-0.8	76	-1.1	72	-1.3	71	-1.5
		PBO	104	4.3	99	-0.3	96	-0.5	92	-0.7	86	-0.9	83	-1.0	82	-1.1
	P-Value‡	RBX vs PBO	NA		**0.3058**		**0.8301**		**0.1561**		**0.1441**		**0.1261**		**0.0381**[*]	

Source: Appendix 4, Tables 2.3, 3.10A, 3.10B, 3.4A and 3.4B

[#] 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 value

‡ P-values based on a two-way ANOVA

[*] P-values ≤ 0.05 were flagged

9.6.3.6.3 CGI-Efficacy Index

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.

There was no statistically significant difference between the RBX and PBO groups in the mean efficacy index values using the LOCF analysis (Appendix 4, Tables 3.9A). Significant differences between RBX and PBO, which were indicative of a positive efficacy index for RBX, were apparent at the Day 21, 28 and 42 visits using the OC analysis (Appendix 4, Table 3.9B).

Table 16 summarizes the mean efficacy index scores at each post-baseline evaluation for the LOCF and OC analyses. Appendix 4, Tables 3.9A and 3.9B, provide additional information related to this parameter.

Table 16. Clinical Global Impression Efficacy Index#

Analysis	Statistic	Group or Comparison	Visit											
			Day 7		Day 14		Day 21		Day 28		Day 35		Day 42	
			n	X†	n	X†	n	X†	n	X†	n	X†	n	X†
LOCF	Mean	RBX	101	11.3	101	10.2	101	9.4	101	8.8	101	8.5	101	7.9
		PBO	99	11.2	100	10.5	100	9.9	100	9.2	100	8.9	100	8.9
	P-Value‡	RBX vs PBO	**0.9455**		**0.3098**		**0.1498**		**0.1922**		**0.3657**		**0.0544**	
OC	Mean	RBX	101	11.3	87	9.7	81	8.7	76	7.8	72	7.3	71	6.3
		PBO	99	11.2	96	10.4	92	9.6	86	8.8	83	8.3	82	8.2
	P-Value‡	RBX vs PBO	**0.9455**		**0.1285**		**0.0110***		**0.0311***		**0.0706**		**0.0007***	

Source: Appendix 4, Tables 3.9A and 3.9B

A lower score is indicative of a more positive efficacy index

† Mean value

‡ P-values based on a two-way ANOVA

* P-values ≤ 0.05 were flagged

9.6.3.7 Montgomery-Asberg Depression Rating Scale

The difference between the RBX and PBO groups in the mean decrease from baseline in the MADRS total score was statistically significant on Days 21, 28 and 42 for the LOCF analysis and on Days 21, 28, 35, and 42 for the OC analysis. At Day 42, the mean decrease from baseline in the MADRS total score was 10.7 in the RBX group and 7.9 in the PBO group based on the LOCF analysis. The mean decrease from baseline in the MADRS total score for the OC analysis was somewhat greater in both groups, ie, 13.5 in the RBX group and 8.9 in the PBO group.

Table 17 summarizes the mean change from baseline in the MADRS total score at each post-baseline evaluation for both the LOCF and OC analyses. Appendix 4, 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.

9.6.3.8 Patient Global Impression (PGI) Scale Montgomery-Asberg Depression Rating Scale

For the LOCF analysis at Day 42, the mean PGI score in the reboxetine-treated group was 6.5 and the mean score in the PBO-treated group was 5.8. This difference was statistically significant (p=0.007) in favor of reboxetine.

For the OC analysis at Day 42, the mean PGI score in the reboxetine-treated group was 6.9 and the mean score in the PBO-treated group was 6.1 This difference was statistically significant (p=0.001) in favor of reboxetine.

The mean PGI scores at each postbaseline evaluation for the LOCF and OC analyses are summarized in Appendix 4, Tables 3.18A and 3.18B, respectively.

Table 17. Mean Change From Baseline in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score#

Analysis	Statistic	Group or Comparison	Baseline		Visit											
					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	Mean Change From Baseline	RBX	106	29.2	101	-2.7	101	-5.4	101	-7.8	101	-9.6	101	-10.0	101	-10.7
		PBO	104	29.2	100	-3.2	101	-4.9	101	-5.8	101	-7.4	101	-8.1	101	-7.9
	P-Value‡	RBX vs PBO			**0.5397**		**0.2580**		**0.0471***		**0.0387***		**0.1044**		**0.0190***	
OC	Mean Change From Baseline	RBX	106	29.2	101	-2.7	87	-6.3	81	-9.3	76	-11.5	72	-12.2	71	-13.5
		PBO	104	29.2	100	-3.2	96	-4.9	92	-6.1	86	-8.1	83	-9.0	82	-8.9
	P-Value‡	RBX vs PBO			**0.5397**		**0.0682**		**0.0023***		**0.0026***		**0.0108***		**0.0008***	

Source: Appendix 4, Tables 2.3, 3.5A and 3.5B

Intent-to-treat population

† Mean change from baseline value

‡ P-values based on a two-way ANOVA

* P-values ≤ 0.05 were flagged

9.6.4 HAM-D Remission Status

A total HAM-D score of 10 or less was considered to be an index for remission. There were no statistically significant differences in remission status of the RBX and PBO groups in either the LOCF or OC analyses. At Day 42, the percentage of patients achieving remission was 27.7% in the RBX group and 25.7% in the PBO group for the LOCF analysis. The percentage of patients achieving remission using the OC analysis was greater in the RBX group, ie, 36.6% in the RBX group and 28.4% in the PBO group (Appendix 4, Tables 3.12A, 3.12B) at Day 42.

9.7 Safety Evaluation

9.7.1 Extent of Exposure

There were 210 intent-to-treat patients—106 in the RBX group and 104 in the PBO group—who received at least one dose of medication and were included in the safety analyses. Data for three patients were received in-house after the database for this study was closed. Therefore, these data were not included in the analyses. Case report forms for these patients were reviewed and no treatment-emergent adverse events were reported.

9.7.2 Adverse Events

9.7.2.1 Brief Summary of Adverse Events

Overall, 175 of 210 patients (83.3%) had at least one AE. Treatment-related AEs were noted in 133 of 210 patients (63.3%). The RBX group had over twice as many patients with a treatment-related AE. Twenty-six of 210 patients (12.4%) discontinued the study due to an AE. The majority of these patients came from the RBX group (21.7% vs. 2.9% in the PBO group). None of the patients had a serious AE and there were no deaths during the study. Table 18 presents an overview of the AEs.

Table 18. Overview of AEs

	RBX N=106	PBO N=104
No. (%) of Pts with at Least One AE	98 (92.5)	77 (74.0)
No. (%) of Pts with at Least One Drug-Related AE	90 (84.9)	43 (41.3)
No. (%) of Pts with Serious AEs	0 (0)	0 (0)
No. (%) of Pts who Discontinued Due to AEs	23 (21.7)	3 (2.9)
No. (%) of Deaths	0 (0)	0 (0)

Source: Tables 4.1, 8.1, 11.1, 14.1

9.7.2.2 All Adverse Events

At least one TES was reported for 98 of 106 patients (92.5%) in the RBX group and in 77 of 104 patients (74.0%) in the PBO group. The frequency of TES is summarized by body system in Table 19.

Table 19. Summary of Treatment Emergent Symptoms (TES) by Body System*

Body System	RBX N=106	PBO N=104
No. (%) of Patients With At Least One TES	**98 (92.5)**	**77 (74.0)**
Digestive	78 (73.6)	34 (32.7)
Body	67 (63.2)	58 (55.8)
Nervous	61 (57.5)	27 (26.0)
Urogenital	35 (33.0)	8 (7.7)
Cardiovascular	27 (25.5)	4 (3.8)
Skin	21 (19.8)	8 (7.7)
Special Senses	15 (14.2)	4 (3.8)
Respiratory	8 (7.5)	12 (11.5)
Metabolic and Nutritional	4 (3.8)	2 (1.9)
Musculo-Skeletal	4 (3.8)	8 (7.7)
Hemic and Lymphatic	0 (0)	2 (1.9)

Source: Appendix 4, Table 4.1
N=Number of intent-to-treat patients
()= percentage of patients
* Arranged in decreasing order of frequency based on the RBX group
Each patient was counted once per body system.

More than twice as many patients in the RBX group had TES in the digestive, nervous, urogenital, cardiovascular, skin, and special senses body systems. AEs reported within body systems are discussed below.

Appendix 4, Table 4.1 summarizes all of the TES that were reported during the study by body system and treatment group. All patients who reported TES are listed in Appendix 4, Table 7.1. Appendix 4, Table 7.2 is a listing of all patients with TES by body system.

9.7.2.3 Adverse Events Reported in 1% or More of Reboxetine-Treated Patients

The TES that were reported by 1% or more of the RBX-treated patients are summarized in Table 20.

Table 20. Adverse Events in ≥1% of Patients in the Reboxetine Group*

	RBX N=106		PBO N=104	
Body System/COSTART Term	**n**	**%**	**n**	**%**
BODY				
Headache	40	37.7	34	32.7
Infection	14	13.2	21	20.2
Asthenia	9	8.5	5	4.8
Chills	8	7.5	0	0.0
Back pain	6	5.7	3	2.9
Abdominal pain	5	4.7	1	1.0
Pain	4	3.8	5	4.8
Flu Syndrome	4	3.8	1	1.0
Reaction Unevaluable	3	2.8	0	0.0
Allergic reaction	2	1.9	0	0.0
Chest pain	2	1.9	0	0.0
Fever	2	1.9	2	1.9
Neck pain	2	1.9	2	1.9
CARDIOVASCULAR				
Tachycardia	13	12.3	0	0.0
Vasodilation	8	7.5	2	1.9
Palpitations	6	5.7	0	0.0
Peripheral Vascular Disorder	4	3.8	0	0.0
Hypertension	2	1.9	0	0.0
Postural Hypotension	2	1.9	0	0.0
DIGESTIVE				
Dry Mouth	61	57.5	10	9.6
Constipation	28	26.4	3	2.9
Nausea	19	17.9	9	8.7
Dyspepsia	12	11.3	4	3.8
Anorexia	11	10.4	3	2.9
Vomiting	6	5.7	2	1.9
Diarrhea	2	1.9	11	10.6
Thirst	2	1.9	0	0.0
NERVOUS				
Insomnia	47	44.3	9	8.7
Dizziness	16	15.1	5	4.8
Anxiety	12	11.3	2	1.9
Nervousness	8	7.5	2	1.9
Paresthesia	5	4.7	3	2.9
Thinking Abnormal	3	2.8	0	0.0
Abnormal Dreams	2	1.9	3	2.9
Agitation	2	1.9	1	1.0
CNS Stimulation	2	1.9	0	0.0
Euphoria	2	1.9	1	1.0
Somnolence	2	1.9	3	2.9
Tremor	2	1.9	0	0.0
RESPIRATORY				
Cough Increased	3	2.8	0	0.0
Sinusitis	2	1.9	1	1.0
SKIN				
Sweating	16	15.1	2	1.9
Dry Skin	2	1.9	1	1.0
Rash	2	1.9	1	1.0

Table 20. Adverse Events in ≥1% of Patients in the Reboxetine Group*

Body System/COSTART Term	RBX N=106		PBO N=104	
	n	%	n	%
SPECIAL SENSES				
Taste Perversion	7	6.6	1	1.0
Abnormality of Accommodation	3	2.8	2	1.9
Conjunctivitis	2	1.9	0	0.0
UROGENITAL				
Urinary Retention	11	10.4	0	0.0
Urinary Frequency	7	6.6	1	1.0
Urination Impaired	5	4.7	0	0.0
Impotence	5	4.7	2	1.9
Abnormal Ejaculation	4	3.8	1	1.0
Sexual Function Abnormal	4	3.8	0	0.0
Dysuria	3	2.8	0	0.0
Dysmenorrhea	2	1.9	5	4.8
Penis Disorder	2	1.9	0	0.0
Prostatic Disorder	2	1.9	0	0.0
Urinary Tract Infection	2	1.9	0	0.0

continued

Source: Appendix 4, Table 4.1
* Arranged in decreasing order of frequency based on the RBX group
N=Number of patients reporting a TES
Each patient was counted once per body system

TES that were reported in at least 5% of the patients in the RBX group, and that were reported at a clinically relevant greater frequency (ie, at least twice as frequently) in the RBX group than in the PBO group included the following: chills, palpitations, tachycardia, vasodilation, anorexia, constipation, dry mouth, dyspepsia, nausea, vomiting, anxiety, dizziness, insomnia, nervousness, sweating, taste perversion, urinary frequency, and urinary retention. Among these events, dry mouth was the most frequently reported TES in the RBX group (57.5% versus 9.6% in the PBO group), followed by insomnia (44.3% vs. 8.7% in the PBO group), and constipation (26.4% vs. 2.9% in the PBO group). All three of these events, as well as sweating and tachycardia, have been associated with known pharmacologic effects of RBX.

Diarrhea and rhinitis were the only TES reported in at least 5% of the patients in the PBO group, and that was reported at a clinically relevant greater frequency (ie, at least twice as frequently) in the PBO group than in the RBX group. (see Appendix 4, Table 4.1)

9.7.2.4 Adverse Events by Maximum Severity

The majority of patients in each treatment group reported events that were mild to moderate in severity (67% in the RBX group and 62% in the PBO group). The maximum severity of TES was mild in 17.9% (19/106) of the patients in the RBX group and 23.1% (24/104) of the patients in the PBO group. The maximum severity of TES was moderate in 49.1% (52/106) of the patients in the RBX group and in 38.5% (40/104) of the patients in the PBO group. Severe TES were reported in 25.5% (27/106) of the patients in the RBX group, in 12.5% (13/104) of the patients in the PBO group.

The severe TES that were reported in more than one patient in the RBX group were asthenia (2 patients), headache (3 patients), peripheral vascular disorder (2 patients), constipation (5 patients), dry mouth (9 patients), nausea (3 patients), agitation (2 patients), anxiety (3 patients), insomnia (15 patients), nervousness (2 patients), sweating (3 patients), impotence (3 patients), and urinary retention (6 patients). The severe TES that were reported in more than one patient in the PBO group were asthenia (2 patients), headache (7 patients), dry mouth (2 patients) and insomnia (2 patients).

All TES are summarized by maximum severity (ie, mild, moderate or severe) in Appendix 4, Table 5.1.

9.7.2.5 TES by Age and Gender

Treatment-related symptoms were examined by age of the patient (ie, patients 65 years or younger vs. patients greater than 65 years) and gender. Since there were no patients in the study older than 65 years, no data are available for the age comparison (Appendix 4, Table 6.1).

For gender, there didn't appear to be any discernible effects that could be attributed to the patients' sex. In the RBX group, TES occurring at a frequency of 5% or higher in one sex over the other included: constipation, insomnia, anxiety, urinary retention, impotence, peripheral vascular disorder, urination impaired, abnormal ejaculation and dysuria for males; and infection, asthenia, back pain, palpitation, dry mouth, nausea, dyspepsia, anorexia, vomiting, nervousness, abnormal thoughts and increased cough for females. In the PBO group, TES occurring at a frequency of 5% or higher in one sex over the other included: asthenia, dry mouth, dyspepsia and rhinitis for males and headache, enlarged abdomen, insomnia, paresthesia, pharyngitis and dysmenorrhea for females (Appendix 4, Table 6.2).

9.7.2.6 Drug-Related Adverse Events

In the investigators' judgments, 84.9% (90/106) of the patients in the RBX group and 41.3% (43/104) of the patients in the PBO group experienced at least one drug-related TES (Appendix 4, Table 8.1). Of the drug-related TES that were reported in at least 5% of the patients in the RBX group, and that were reported at a clinically relevant greater frequency (ie, at least twice as frequently) in the RBX group than in the PBO group, dry mouth was the most frequently reported TES in the RBX group (55.7% versus 8.7% in the PBO group), followed by insomnia (41.5% vs. 5.8% in the PBO group), and constipation (25.5% vs. 2.9% in the PBO group). Sweating (14.2% vs. 1.9% in the PBO group) and tachycardia (11.3% vs. 0% in the PBO group) were also noted. All of these events have been associated with the known pharmacologic effects of RBX. Table 21 summaries the frequency of these drug-related TES for each group.

Table 21. Clinically-Relevant* Drug-Related† Adverse Events

Body System/COSTART Term	RBX N=106		PBO N=104	
	n	%	n	%
BODY				
Asthenia	7	6.6	2	1.9
Chills	8	7.5	0	0.0
CARDIOVASCULAR				
Palpitation	6	5.7	0	0.0
Tachycardia	12	11.3	0	0.0
Vasodilation	8	7.5	2	1.9
DIGESTIVE				
Anorexia	10	9.4	1	1.0
Constipation	27	25.5	3	2.9
Dry Mouth	59	55.7	9	8.7
Nausea	16	15.1	5	4.8
NERVOUS				
Anxiety	12	11.3	2	1.9
Dizziness	16	15.1	2	1.9
Insomnia	44	41.5	6	5.8
Nervousness	7	6.6	1	1.0
SKIN				
Sweating	15	14.2	2	1.9
SPECIAL SENSES				
Taste Perversion	6	5.7	1	1.0
UROGENITAL				
Urinary Frequency	6	5.7	1	1.0
Urinary Retention	11	10.4	0	0.0

Source: Appendix 4, Table 8.1

n=Number of patients reporting a TES considered drug-related

N=Number of intent-to-treat patients

* Reported in at least 5% of patients and ≥2 times more frequently in the RBX group than in the PBO group.

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

Each patient was counted once per body system

The TES that were judged by the investigators to be related to treatment with the study medications are summarized in Appendix 4, Table 8.1.

9.7.3 Deaths, Other Serious Adverse Events, and Discontinuations Due to Adverse Events

9.7.3.1 Deaths

There were no deaths in this study.

9.7.3.2 Other Serious Adverse Events

No serious adverse events were reported during the study.

9.7.3.3 Discontinuations Due to Adverse Events

From the ITT population, 23 of the 106 patients (21.7%) in the RBX group and three of the 104 patients (2.9%) in the PBO group discontinued treatment due to adverse events (Appendix 4, Table 9.1). The majority of patients had multiple events leading to their discontinuation. Of all events listed, insomnia was the most frequently reported event (11.3% in the RBX group and 0% in the PBO group) followed by dry mouth (6.6% in the RBX and 1.0% in the PBO group). None of the events that were reported were serious. All but four patients (3 RBX and 1 PBO) recovered from their event.

The TES that led to discontinuation of the study medication are summarized by patient in Appendix 4, Table 9.1 and by body system in Appendix 4, Table 11.2. Appendix 4, Table 11.1 presents a listing of the patients who discontinued due to TES.

The patients who discontinued treatment due to adverse events are summarized in Table 22.

Table 22. 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	Relationship to Study Drug	Outcome
110	47/F	RBX	7.43	26	22	26	Anorexia	EP/Mild	Yes	Recovered
			6.86	26	4	26	Nausea	EP/Moderate	Yes	Recovered
			11.00	26	26	26	Vomiting	EP/Mild	Yes	Recovered
214	63/F	RBX	--	7	8	17	Palpitation/Dyspnea	EP/Mild	Yes	Recovered
			--	7	8	17	Asthenia/ Dizziness	EP/Moderate	Yes	Recovered
			8.67	7	2	17	Insomnia/ Nervousness	EP/Mild	Yes	Recovered
			8.67	7	2	17	Headache/Nausea	EP/Moderate	Yes	Recovered
			8.67	7	6	11	Vomiting	EP/Mild	Yes	Recovered
279	29/F	RBX	10.00	8	2	10	Taste Perversion	Const/Mild	Yes	Recovered
			10.00	8	2	10	Asthenia/ Dizziness	Const/Moderate	Yes	Recovered
			10.00	8	1	10	Dry Mouth/ Nausea	Const/Mild	Yes	Recovered
			10.00	8	1	10	Sweating/Chills	Const/Moderate	Yes	Recovered
158	57/M	RBX	8.00	3	2	5	Vasodilation/Constipation/ Insomnia/Urinary Retention	EP/Severe	Yes	Recovered
			8.00	3	2	5	Dry Mouth/Anxiety	Const/Severe	Yes	Recovered
195	57/M	RBX	--	4	5	5	Headache	Const/Mild	Yes	Recovered
			8.00	4	2	10	Dry Mouth	Const/Mild	Yes	Recovered
			8.00	4	2	10	Dysuria/Urinary Retention	Const/Severe	Yes	Recovered
196	42/M	RBX	4.00	5	4	4	Abnormality of Accomodation	EP/Mild	Yes	Recovered
			4.00	5	2	7	Urinary Retention/Tachycardia	EP/Severe	Yes	Recovered
			4.00	5	5	6	Headache	Const/Moderate	Yes	Recovered
			4.00	5	2	7	Abdomen Enlarged/Dry Mouth/ Anxiety/Euphoria/Insomnia	Const/Severe	Yes	Recovered
198	52/M	RBX	8.00	22	3	--	Tachycardia	EP/Moderate	Yes	CONT
			8.00	22	7	--	Insomnia	EP/Moderate	Yes	CONT
			8.00	22	6	--	Dry Mouth	EP/Severe	Yes	CONT
			8.00	22	5	--	Impotence/Prostatic Disorder	EP/Severe	Yes	CONT
			8.00	22	2	--	Urinary Retention	EP/Severe	Yes	CONT
201	27/M	RBX	7.00	5	5	6	Headache	CONST/Moderate	Yes	Recovered
			7.00	5	2	5	Dizziness	EP/Moderate	Yes	Recovered
			7.00	5	2	5	Nausea/Paresthesia Reaction Unevaluable	EP/Severe	Yes	Recovered
204	36/M	RBX	--	2	2	7	Impotence/Urination Impaired	EP/Severe	Yes	Recovered
			--	2	2	7	Libido Decreased	CONST/Severe	Yes	Recovered

Source: Appendix 4, Table 11.1 EP=Episodic; CONST=Constant/Single Event; CHR=Chronic; CONT=Continues

Continued

Table 22. 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	Relationship to Study Drug	Outcome
271	31/M	RBX	6.00	7	6	6	Anorexia	EP/Severe	Yes	Recovered
			6.00	7	2	8	Constipation/Dry Mouth/ Nausea/Anxiety/Insomnia	EP/Severe	Yes	Recovered
			6.00	7	2	8	Headache	CONST/Severe	Yes	Recovered
273	47/M	RBX	10.00	28	28	33	Depression	EP/Moderate	Yes	Recovered
			10.00	28	28	33	Insomnia	EP/Severe	Yes	Recovered
129	50/F	RBX	10.29	35	3	--	Insomnia	CONST/Moderate	Yes	CONT
146	32/F	RBX	8.00	15	9	16	Insomnia	EP/Severe	Yes	Recovered
227	41/F	RBX	8.00	31	22	35	Rash	CONST/Moderate	Yes	Recovered
232	52/F	RBX	8.00	3	1	4	Insomnia	CHR/Severe	Yes	Recovered
259	46/F	RBX	6.67	7	2	21	Allergic Reaction	EP/Mild	Yes	Recovered
			6.67	7	7	11	Dizziness	EP/Moderate	Yes	Recovered
			6.67	7	4	11	Dyspnea	EP/Mild	Yes	Recovered
			6.67	7	6	11	Paresthesia	EP/Moderate	Yes	Recovered
			6.67	7	3	11	Chills	EP/Severe	Yes	Recovered
			6.67	7	2	11	Sweating	CHR/Severe	Yes	Recovered
237	49/M	RBX	6.67	18	2	22	Urination Impaired	CONST/Moderate	Yes	Recovered
240	44/M	RBX	6.00	5	2	8	Dry Mouth/Anxiety	EP/Moderate	Yes	Recovered
			6.00	5	2	8	Sweating/Taste Perversion	CONST/Mild	Yes	Recovered
			6.00	5	2	8	Urinary Frequency	CONST/Moderate	Yes	Recovered
			6.00	5	2	5	Insomnia	CONST/Mild	Yes	Recovered
190	26/F	RBX	25.00#	5	2	7	Headache/Insomnia	CONST/Moderate	Yes	Recovered
192	26/M	RBX	8.00	11	10	--	Impotence	CONST/Severe	Yes	CONT
290	41/M	RBX	7.43	23	18	31	Fever/Malaise	CONST/Mild	Yes	Recovered
			7.43	23	18	31	Pain/Penis Disorder	CONST/Severe	Yes	Recovered
295	60/F	RBX	6.00	3	2	4	Insomnia/Nervousness	CONST/Moderate	Yes	Recovered
265	27/F	RBX	--	--	2	3	Asthenia/Anxiety	CONST/Moderate	Yes	Recovered
163	34/F	PBO	0.00	10	2	11	Dry Mouth	CONST/Severe	Yes	Recovered
			0.00	10	2	11	Euphoria	EP/Severe	Yes	Recovered
136	25/M	PBO	0.00	21	16	--	Rash	CONST/Mild	Yes	CONT
294	36/F	PBO	0.00	15	12	12	Nervousness	EP/Moderate	Yes	Recovered

Source: Appendix 4, Table 11.1
EP=Episodic; CONST=Constant/Single Event; CHR=Chronic; CONT=Continues,
# Patient 190 did not return her medication after discontinuing the study at Week 1.

9.7.4 Clinical Laboratory Evaluation

9.7.4.1 Hematology

9.7.4.1.1 Mean Change From Baseline

There were no statistically significant or clinically important mean changes from baseline to Days 21 or 42 for any hematology parameter measured (basophils, eosinophils, erythrocytes, hematocrit, hemoglobin, leukocytes, lymphocytes, MCV, monocytes, neutrophils or platelet count) (Appendix 4, Table 18.1). The number of patients whose post-baseline hematology values exceeded normal ranges was generally comparable in each group (Appendix 4, Table 19.1).

9.7.4.1.2 Values Outside of Predefined Limits

A listing of individual patients having a post-baseline hematology value exceeding the normal range is presented in Appendix 4, Table 20.1. Overall, there did not appear to be any clinically significant changes that could be related to RBX treatment. The number of patients who had a hematology value exceeding the normal range by ±20% or more at the Day 21, Day 42, end of treatment or unscheduled visits was generally comparable between the RBX and PBO groups (basophils=2 RBX, 1 PBO; eosinophils=5 RBX, 5 PBO; lymphocytes=0 RBX, 1 PBO; monocytes=7 RBX, 6 PBO; and neutrophils=5 RBX, 1 PBO).

9.7.4.2 Chemistries

9.7.4.2.1 Mean Change From Baseline

There were statistically significant mean changes in serum chemistries for alkaline phosphatase (Day 21 p=0.0234, Day 42 p=0.0008) and uric acid (Day 21 p=0.0163, Day 42 p=0.0126). In the RBX group, the mean change in alkaline phosphatase was 5.3816 at Day 21 and 6.4545 at Day 42. In the PBO group the mean change in alkaline phosphatase decreased at both the Day 21 and 42 visits (-3.1279 and -6.7436, respectively). The mean change in uric acid decreased at both the Day 21 and 42 visit (-0.2342 and -0.1515, respectively) in the RBX group and increased at Day 21 and Day 42 (0.0326 and 0.1449, respectively) in the PBO group. None of these changes were considered to be clinically significant (Appendix 4, Table 18.2). The number of patients whose post-baseline serum chemistry values exceeded normal ranges was generally comparable in each group (Appendix 4, Table 19.2).

9.7.4.2.2 Values Outside of Predefined Limits

A listing of individual patients having a post-baseline serum chemistry value exceeding the normal range is presented in Appendix 4, Table 20.2. Overall, there did not appear to be any clinically significant changes that could be related to RBX treatment. The number of patients who had a chemistry value exceeding the normal range by ±20% or more at the Day 21, Day 42 , end of treatment or unscheduled visits was generally comparable between the RBX and PBO groups (ALT=10 RBX, 5 PBO; AST=5 RBX, 6 PBO; alkaline phosphatase=1 RBX, 1

PBO; bilirubin=0 RBX, 0 PBO; creatinine=3 RBX, 4 PBO; glucose=11 RBX, 4 PBO; and uric acid=0 RBX, 1 PBO).

9.7.4.3 Urine Drug Screen

There were eight patients in the reboxetine group and six patients in the placebo group who had a positive outcome on their urine drug screen (Appendix 4, Table 19.3). A positive outcome was present for alcohol (2 RBX), amphetamines (2 PBO), barbiturates (1 RBX), benzodiazepines (1 RBX, 2 PBO), cocaine (1 RBX), opiates (1 RBX, 1 PBO) and tetrahydrocannabinol (2 RBX, 1 PBO) use. While these were protocol violations, none of these patients were excluded from the safety analyses. A listing of patients with post-baseline urine drug screen values exceeding the normal ranges is presented in Appendix 4, Table 20.3.

9.7.5 Vital Signs

9.7.5.1 Mean Change From Baseline

No statistically significant differences were observed between the RBX and PBO groups in systolic or diastolic blood pressure, pulse rate, or body weight at baseline (Appendix 4, Table 2.1).

Blood pressures fluctuated little over the study period. Although there were statistically significant changes in mean systolic (Day 14, p=0.0034, Day 35 p=0.0257) and diastolic (Day 35 p=0.0186) blood pressure, these changes were small and not clinically significant (Appendix 4, Tables 15.1, 15.2).

There were statistically significant changes in mean pulse rate throughout the study (Appendix 4, Table 15.3), however, the actual number of patients who had a pulse rate outside of the pre-defined limits (≤50 and ≥120 bpm) was low (1 RBX and 2 PBO; Appendix 4, Table 17.1). These changes were not considered to be clinically significant.

Although there were statistically significant changes in body weight throughout the study (Appendix 4, Table 15.4), these changes were small (<2 pounds) and not clinically significant.

9.7.5.1.1 Values Outside of Predefined Limits

The number of patients who had a post-baseline vital sign value exceeding the normal ranges was small (6 RBX, 7 PBO) and comparable between the groups (Appendix 4, Table 16.1, 17.1).

A listing of individual patients having a post-baseline vital sign value exceeding the normal range is presented in Appendix 4, Table 17.1. Overall, fluctuations in vital sign data varied and there were no trends that appeared to be related to RBX treatment.

9.7.6 Electrocardiograms

There were statistically significant mean changes in the QT interval ($p<0.0001$), QTc Interval using Bazett's correction ($p=0.0131$) and heart rate ($p<0.0001$) (Appendix 4, Table 21.1). However, in all cases, the differences between groups were within the normal range for these parameters. There were no statistically significant mean changes for PR interval, QRS interval, or QTc interval using Fridericia's correction (Appendix 4, Table 21.1).

The majority of patients in each treatment group had normal ECG findings before treatment (baseline) and at the end of the study (Appendix 4, Table 24.1): 20.7% (19/92) of the RBX-treated patients and 13.7% (13/95) of the PBO-treated patients for whom ECG findings were available pre- and post-treatment had treatment-emergent ECG abnormalities, ie, normal findings at pretreatment and abnormal findings post-treatment. The treatment-emergent ECG abnormalities occurring in more than one patient were sinus tachycardia (six patients) and leftward axis (two patients) in the RBX group and sinus bradycardia (five patients) and sinus arrhythmia (two patients) in the PBO group.

Appendix 4, Table 22.1 displays the shifts in normal and abnormal findings (baseline vs. end-of-study). The majority of the patients in each group (73% RBX and 80% PBO) either maintained a normal ECG finding at their end-of-study ECG or had a shift from an abnormal ECG at baseline to normal ECG at the end-of-study.

Table 23.1 is a summary of all patients who had normal baseline ECGs and at least one post-baseline ECG exceeding the pre-defined limits. Only two patients in the RBX group and two patients in the PBO group had a post-baseline ECG finding outside of the pre-defined limit.

Table 24.1 is a listing of patients with post-baseline ECGs exceeding pre-defined limits. Table 25.1 is a listing of comments for patients with post-baseline abnormal ECGs.

10 DISCUSSION AND OVERALL CONCLUSIONS

This study was a double-blind, randomized, parallel-group US study of RBX versus PBO in the treatment of patients with major depression. This was a six week (42 day) treatment duration trial with 8-10 mg/day doses of RBX administered during the trial. A total of 212 patients were randomized between RBX (n=107) and PBO (n=105). Of these, a total of 210 patients were included in the ITT analysis randomized between RBX (n=106) and PBO (n=104). There were no significant pretreatment differences between these two groups in any of the demographic, historical, psychiatric, physical exam or laboratory parameters examined.

Efficacy data were analyzed on an Intent-to-Treat (ITT) basis with both Last Observation Carried Forward (LOCF) and Observed Cases (OC) analyses. The LOCF was the primary analysis and the OC was the secondary analysis. The primary efficacy measure was change from baseline on the 21-item HAM-D total score, comparing RBX versus PBO. Secondary efficacy measures were the HAM-D Item 1 score for depression, the HAM-D cluster analyses (ie, anxiety, cognitive, retardation and sleep disturbance), MADRS (Montgomery Asberg Depression Rating Scale), CGI (Clinical Global Impression), and HAM-D Cluster Scores.

The major points we noted in reviewing the data were as follows:

- For the HAM-D Total Score, LOCF analysis, the mean decrease from baseline did not achieve a level of significance when comparing RBX with PBO through 42 days of treatment. For the HAM-D Total Score, OC analysis, there was statistical significance in favor of RBX at Day 21 (p=0.0074), but thereafter only borderline significance from Day 28 (p=0.0543) through Day 42 (p=0.0509). There was no significance in HAM-D responder status for either OC or LOCF, though for the most part the p-values are closer to significance for the OC than LOCF analysis.
- In the MADRS Total Score, LOCF analysis, except for Day 35, there was statistical significance in favor of RBX from Day 21 (p=0.0471) through Day 42 (p=0.0190). For the MADRS Total Score, OC analysis, there was statistical significance in favor of RBX from Day 21 (p=0.0023) through Day 42 (p=0.0008). Though this was not the primary efficacy instrument, these results indicate that there is significant antidepressant efficacy of RBX versus PBO, as has been demonstrated in previous phase III RBX clinical trials.

The divergence of results for the HAM-D and MADRS scores, with MADRS showing significance in favor of RBX, while the HAM-D scores showed either nonsignificant or borderline significance was unexpected. In the previous phase II and III studies of RBX, these scores have always followed the same trend. While the MADRS has been noted to be more sensitive to change than the HAM-D, this divergence was not expected or previously seen in RBX development. Additional exploratory analyses of individual items or item clusters that measure similar parameters between the two scales (eg, suicidality, sleep parameters, retardation parameters and psychic anxiety/inner tension parameters) showed that these parameters were in fact well correlated. The divergent results must be explained by differences in factors other than those listed, though we were unable to precisely determine these factors. Perhaps this is further demonstration of the increased sensitivity of the MADRS compared to the HAM-D.

For the Responder Status in CGI Improvement, OC analysis, there was statistical significance at Day 35 (p=0.0446) and Day 42 (p=0.0120). There was no statistical difference between RBX and PBO for CGI Global Improvement scores through Day 42 for LOCF (p=0.3872) or for OC analyses (p=0.0627) though the p-values are closer to significance for the OC analysis than for LOCF analysis.

For the PGI, a patient-rated scale describing change in the patient's general condition compared to the study start, there was a statistically significant difference in favor of reboxetine compared to placebo at Day 42 (the study endpoint) for the mean PGI scores. This was true for both LOCF (p=0.007) and OC (p=0.001) analyses. Although the magnitude of the change was not large, the results indicated that there was a perceived slight to moderate improvement in the reboxetine-treated patients' general condition, which was significantly different than the perception in the placebo-treated patient group.

Several factors were considered to explain the lack of positive efficacy results in this study. There was no difference in the baseline characteristics of the RBX and PBO groups. In

particular, the RBX and PBO groups had similar mean baseline HAM-D scores (mean baseline HAM-D=25.1 for RBX; 25.3 for PBO). This study population appears to have baseline HAM-D scores comparable to those in other RBX studies. The results do not appear to be due to a high PBO-response rate in this study. The PBO response rate at Day 42 was 33.7% on LOCF analysis and 38.3% on OC analysis, which is in the range seen in other RBX studies showing positive RBX-PBO efficacy differences on HAM-D scores. The study was adequately powered, despite a higher dropout rate than planned for in the initial protocol. With a 30% dropout rate, the calculated power to detect a RBX-PBO HAM-D difference on LOCF analysis was 94% and 83% for OC analysis.

High early dropout rate may have been a factor preventing more positive results. The total dropout rate (percent of patients who discontinued the trial) was 28.6% (60/210 patients). This is higher than the dropout rate for short-term PBO-controlled RBX studies in the existing RBX database, which was 18% to 20%. The majority of the discontinuations in this study were due to AEs, though there were no serious AEs. Twenty-six of 210 patients (12.4%) from the ITT population discontinued the study due to an AE. The percentage of patients who discontinued due to AEs was 21.7% (23/106) for RBX and 2.9% (3/104) for PBO. Seventeen patients (28% of all discontinuations) discontinued in the first week. Most of these (12/17; 71%) discontinued in the first week due to nonserious AEs. We know from previous RBX studies that the severity of AEs tend to diminish with time, so if these patients had been able to continue, they may have eventually shown a response. The early dropout phenomenon may also explain why the OC values look better than the LOCF values in terms of efficacy. If a large enough number of patients discontinued in the first few weeks of treatment, they have not been on study long enough to show HAM-D improvement.

There were no serious AEs or deaths in this study. The TES described in this study have been noted in previous RBX clinical trials. Most of these relate to the known pharmacologic properties of RBX. Dry mouth and constipation have been the most frequent TES reported in the pre-existing database for short-term controlled studies (see ISS for RBX NDA Table 8.H-43). Insomnia has also been reported, though the 44.3% incidence in the RBX-treated group in this study is higher than the 12.0% incidence reported in the pre-existing database for short-term controlled studies (see ISS for RBX NDA Table 8.H-43). Insomnia was the most frequently reported AE associated with discontinuation from the study (11.3% in RBX group and 0% in PBO group). One possible explanation for this may be that in this study, concomitant psychoactive hypnotics such as short-acting benzodiazepines were not allowed, where they may have been allowed and blunted insomnia in other studies. Tachycardia and palpitations have been previously noted in phase II and III clinical studies of RBX. No unexpected AEs were encountered.

In conclusion, this study did not achieve the primary goal of demonstrating a significant difference compared with PBO in reducing the mean total HAM-D scores at Day 42, the end of study. However, statistically significant differences from PBO were demonstrated on several secondary efficacy measures such as MADRS, on Day 21, Day 28, and Day 42. In all cases, the OC analysis provided more favorable significance values than LOCF analysis. We believe this is related to a high percentage of early discontinuations seen in this study, where

patients discontinued before the antidepressant effect of the drug could be shown. There were no serious adverse events, deaths or unexpected adverse events noted during this study.

11 REFERENCES

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.

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.

Coryell WR, Noyes R, Clancy J. Excess mortality in panic disorder: a comparison with primary unipolar depression. Arch Gen Psychiatry 1982;39:701-3.

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

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.

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.

Hamilton M. Developing a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:276-296.

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.

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.

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.

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.

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.

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

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.

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.

Wells KB, Golding J, Burnam MA. Psychiatric disorder and limitations in physical functioning in a general population. Am J Psychiatry 1988;145:712-7.