# Studie 032

# (M2020/0032)

## Studienbericht

# REBOXETINE (PNU-155950E) VS FLUOXETINE IN A DOUBLE-BLIND STUDY FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDERS IN TAIWAN.

| | |
|---|---|
| Project Code: | PHA-950E-CNS-0005 |
| Final Report of the Study: | M/2020/0032 |
| Previous Reports of the Study: | None |
| Date of First Subject Enrolled: | 31 August 2000 |
| Date of Last Subject Enrolled: | 31 May 2001 |
| Date of Last Follow-up: | 20 July 2001 |
| Coordinating Investigator: | Ming-Been Lee, MD<br>Chairman, Department of Psychiatry;<br>Professor, National Taiwan University Hospital<br>7 Chung-Shan S. Rd.<br>Taipei 100, Taiwan, R.O.C. |
| Sponsor's Responsible Medical Officer: | Mark T. Brown, MD<br>Medical Development<br>Therapeutic Area CNS |
| Development Phase of Study: | 3 |

It is the policy of Pharmacia to conduct clinical studies (including study conduct and the archiving of essential documents) in compliance with company SOPs and Standard, which incorporate the requirements of the ICH Guideline for Good Clinical Practice.

This document contains confidential information belonging to Pharmacia. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor to use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, Pharmacia should be promptly notified.

**REBOXETINE (PNU-155950E) VS FLUOXETINE IN A DOUBLE-BLIND STUDY FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDERS IN TAIWAN**

## APPROVAL SIGNATURES

I have read the report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Mark T. Brown, MD, Clinical Program Director — Date
Medical Development, Therapeutic Area CNS
Pharmacia & Upjohn, Kalamazoo, MI, USA

Christopher C. Gallen, MD, PhD, Therapeutic Area Vice President — Date
Medical Development, Therapeutic Area CNS
Pharmacia & Upjohn, Kalamazoo, MI, USA

Scott E. Lancaster, MS, Statistician — Date
Clinical Biostatistics
Pharmacia & Upjohn, Kalamazoo, MI, USA

Julie A. Wagner, RN, BS, Clinical Research Specialist — Date
Medical Development, Therapeutic Area CNS
Pharmacia & Upjohn, Kalamazoo, MI, USA

Gary L. Neff, MS, Clinical Research Specialist — Date
Medical Development, Therapeutic Area CNS
Pharmacia & Upjohn, Kalamazoo, MI, USA

Clayton R. Rowland, PhD, Program Director — Date
Outcomes Research
Pharmacia & Upjohn, Kalamazoo, MI, USA

The approval signature of the coordinating investigator is in Appendix 1.13.

# SYNOPSIS

| | |
|---|---|
| **Name of Company:**<br>Pharmacia<br><br>**Name of Finished Product:**<br>(To be assigned)<br><br>**Name of Active Ingredient:**<br>Reboxetine mesylate | *(For National Authority Use only)* |

**Title of Study:** Reboxetine (PNU-155950E) vs Fluoxetine in a Double-Blind Study for the Treatment of Major Depressive Disorders in Taiwan

**Protocol Number:** M/2020/0032

**Investigators and Study Centers:** This multicenter study was conducted by the following 5 principal investigators at 5 study centers in Taiwan: Mei-Chih Tseng (National Taiwan University Hospital, Taipei), Shih-Ku Lin (Taipei City Psychiatric Center), Ying-Chiao Lee (Veterans General Hospital Taipei), Nien-Mu Chiu (Chang-Gung Memorial Hospital, Kaohsiung), and Ru-Band Lu (Tri Service General Hospital, Taipei).

**Publication Reference:** none

| **Studied Period:** | | **Phase of Development: 3** |
|---|---|---|
| Date of first subject enrolled: | 31 August 2000 | |
| Date of last subject enrolled: | 31 May 2001 | |
| Date of last follow-up: | 20 July 2001 | |

**Objectives:**

**Primary:** The primary objective of this study was to compare the antidepressant efficacy of reboxetine (administered at a dose of 8 to 10 mg/day for 8 weeks) with that of fluoxetine (administered at a dose of 20 to 40 mg/day for 8 weeks), as measured by the change from baseline in the 21-Item Hamilton Rating Scale for Depression (HAM-D) total score at the last assessment in patients suffering from major depressive disorder (MDD).

**Secondary:** The secondary efficacy objective of this study was to further compare the efficacy of reboxetine (administered at a dose of 8 to 10 mg/day for 8 weeks) with that of fluoxetine (administered at a dose of 20 to 40 mg/day for 8 weeks), as measured by the change from baseline in the Social Adaptation Self-evaluation Scale (SASS) total score and in the Clinical Global Impression (CGI) score at the last assessment in patients suffering from MDD.

The safety objective of this study was to compare the tolerability (based on adverse events, vital signs, safety laboratory tests, and electrocardiograms [ECGs]) of reboxetine (administered at a dose of 8 to 10 mg/day for 8 weeks) with that of fluoxetine (administered at a dose of 20 to 40 mg/day for 8 weeks) in patients suffering from MDD.

| | |
|---|---|
| **Name of Company:**<br>Pharmacia<br><br>**Name of Finished Product:**<br>(To be assigned)<br><br>**Name of Active Ingredient:**<br>Reboxetine mesylate | *(For National Authority Use only)* |

**Methodology:** This phase III, multicenter, randomized, double-blind, active-controlled, parallel-group study was conducted in 85 patients aged 18 to 65 years who suffered from MDD without psychotic features, as diagnosed using criteria defined by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV).

The patients were selected from a population of patients who were hospitalized or were receiving care at outpatient or day-hospital clinics. Patients who had a score of ≥22 on the 21-Item HAM-D at the screening and baseline visit and who met the other eligibility criteria were randomized to receive 8 weeks of treatment with reboxetine (8 mg/day, days 1-28; 8-10 mg/day, days 29-56), or fluoxetine (20 mg/day, days 1-28; 20-40 mg/day, days 29-56). The optional dose increase to 10 mg/day of reboxetine or 40 mg/day of fluoxetine was allowed after 4 weeks of therapy in those patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. Study visits were conducted weekly during the first 4 weeks of treatment and every 2 weeks during the last 4 weeks of treatment. Efficacy measures and certain safety measures (adverse events and vital signs) were assessed at each visit (days 0, 7, 14, 21, 28, 42, and 56); laboratory tests and ECGs were measured at screen, day 28, and day 56.

**Number of Subjects (Planned and Analyzed):** The planned enrollment in the study was 80 patients (40 patients in each treatment group). The actual enrollment was 85 patients (43 patients in the reboxetine group and 42 patients in the fluoxetine group). All of the randomized patients received at least 1 dose of study medication. Therefore, the intent-to-treat (ITT) population includes 43 reboxetine-treated patients and 42 fluoxetine-treated patients.

**Diagnosis and Main Criteria for Inclusion:** Patients of either sex, aged 18 to 65 years, who had a diagnosis of MDD without psychotic features (as defined by DSM-IV) and a total score of ≥22 on the 21-Item HAM-D were enrolled in the study. Patients were otherwise healthy and had no other significant psychiatric condition.

**Test Product, Dose and Mode of Administration, Batch Number:**
Reboxetine mesylate tablets (4-mg tablet or 1/2 of a 4-mg tablet) were inserted into gelatin capsules for use in this randomized study. During weeks 1 through 4, reboxetine was administered orally in twice-daily doses of 4 mg (lot number 00427.05), for a total daily dose of 8 mg of reboxetine. After 4 weeks of treatment, the reboxetine dose was increased to 10 mg/day by including a placebo capsule (lot number 00427.03) with the morning dose (to maintain the study blind) and a 2-mg capsule of reboxetine (lot number 00427.06) with the late afternoon dose in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose.

**Duration of Treatment:** 8 weeks

| **Name of Company:**<br>Pharmacia<br><br>**Name of Finished Product:**<br>(To be assigned)<br><br>**Name of Active Ingredient:**<br>Reboxetine mesylate | *(For National Authority Use only)* |
|---|---|

**Reference Therapy, Dose and Mode of Administration, Batch Number:**
The fluoxetine (Prozac™, Eli Lilly and Company, Indianapolis, IN) comparator was commercially available and was inserted into gelatin capsules by Pharmacia & Upjohn (Pharmacia).

During weeks 1 through 4, a 20-mg capsule of fluoxetine (lot number 00427.04) was administered orally, once daily, in the morning. After 4 weeks of treatment, the fluoxetine dose was increased to 40 mg/day by including a second 20-mg capsule (lot number 00427.04) with the morning dose in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. Placebo capsules (lot number 00427.03) were administered in the late afternoon to maintain the study blind.

During the placebo washout period, a placebo tablet (lot number H06A02) was administered orally, once daily.

**Endpoints and Criteria for Evaluation:**

**Efficacy:** The primary endpoint was the change from baseline in the HAM-D total score at the last assessment. The secondary efficacy endpoints included both continuous measures of efficacy, such as the mean change from baseline in the CGI Severity of Illness score and in the total score for the SASS, and categorical measures of efficacy, including the HAM-D response rate, the HAM-D remission rate, the CGI Global Improvement score, and the CGI Global Improvement response rate.

**Safety:** The secondary safety endpoints were adverse events, vital signs, safety laboratory tests, and ECGs. Adverse events and vital signs were assessed at each postbaseline visit. Safety laboratory tests and ECGs were obtained at screen, day 28, and day 56.

**Statistical Methods:**
The ITT population, which includes all patients who were randomized into the trial and who received at least one dose of study medication, was used for all of the analyses. Efficacy analyses were based on the population of ITT patients who had at least one postbaseline evaluation for the specified efficacy measure (eg, HAM-D, CGI). Two types of analyses were performed for all efficacy variables: "last observation carried forward" (LOCF) and "observed cases" (OC). The LOCF analyses used the last valid assessment as an estimate for all subsequent missing values. The OC analysis did not replace missing data. The LOCF analyses were the primary analyses, and the OC analyses were the secondary analyses. Comparisons were based on a 2-sided test at an alpha level of 0.05, unless otherwise specified.

Differences between the treatment groups in the mean change from baseline in the continuous efficacy endpoints were assessed at each visit using a 2-way ANOVA with investigator, treatment, and treatment-by-investigator interaction as factors. The 90% confidence interval (CI) for the difference between the treatment groups was presented for the primary efficacy endpoint.

For the categorical efficacy endpoints, differences between the treatment groups were assessed at each visit using the Cochran-Mantel-Haenszel test, stratified by investigator.

| **Name of Company:**<br>Pharmacia<br><br>**Name of Finished Product:**<br>(To be assigned)<br><br>**Name of Active Ingredient:**<br>Reboxetine mesylate | *(For National Authority Use only)* |
|---|---|

**SUMMARY OF RESULTS AND CONCLUSIONS:**

**Disposition of Subjects and Baseline Characteristics:**

The percentage of patients who completed the 8-week treatment period was similar among the treatment groups (65.1% [28/43] in the reboxetine group and 69.0% [29/42] in the fluoxetine group). In the reboxetine group, the most common reason for discontinuation of study medication was withdrawal of consent, which led to discontinuation of treatment in 16.3% (7/43) of reboxetine-treated patients and 4.8% (2/42) of fluoxetine-treated patients. In the fluoxetine group, the most common reason for discontinuation of study medication was adverse events, which led to discontinuation of treatment in 14.3% (6/42) of fluoxetine-treated patients and 11.6% (5/43) of reboxetine-treated patients.

The patients in the study ranged in age from 19 to 64 years. All of the patients were Asian, and the majority (>60%) of the patients were female. No statistically significant differences were noted among the treatment groups in the severity of depression at baseline, as judged by the mean total scores for the HAM-D, the CGI Severity of Illness, or the SASS.

**Efficacy Results:**

The results of this study demonstrate that the reboxetine and fluoxetine groups were comparable on the primary endpoint, the mean change from baseline in the HAM-D total score at day 56 in the LOCF analysis. Strong evidence of antidepressant activity was observed in both treatment groups, as demonstrated by mean change from baseline values in the HAM-D total score of -14.05 in the reboxetine group and -14.78 in the fluoxetine group (p=0.971). The difference between the treatment groups in the mean change values (0.72; lower limit of 90% CI, -2.19) was not considered to be either clinically significant (because the difference was <2) or statistically significant (because the lower limit of the 90% CI was <0).

As summarized in the table, the results on the primary endpoint were supported by results on the secondary measures of antidepressant efficacy. No statistically significant differences were observed between the treatment groups in the HAM-D response or remission rates, the CGI Global Improvement response rate, or the mean change from baseline in the CGI Severity of Illness score at day 56 in the LOCF analysis. Thus, the results of both the primary and secondary measures of antidepressant efficacy were consistent in demonstrating the comparable efficacy of reboxetine and fluoxetine for the treatment of patients with depression.

**Name of Company:**
Pharmacia

*(For National Authority Use only)*

**Name of Finished Product:**
(To be assigned)

**Name of Active Ingredient:**
Reboxetine mesylate

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

| Variable | Reboxetine N=43 | Fluoxetine N=42 | P Value |
|---|---|---|---|
| **Primary Endpoint** | | | |
| HAM-D total score, mean change from baseline | -14.05 | -14.78 | 0.971 |
| **Secondary Endpoints** | | | |
| **% Responders or Remitters** | | | |
| HAM-D Response | 55.3 | 57.5 | 0.697 |
| HAM-D Remission | 36.8 | 40.0 | 0.593 |
| CGI Global Improvement Response | 71.1 | 70.0 | 0.905 |
| **Mean Change From Baseline** | | | |
| CGI Severity of Illness | -2.0 | -2.1 | 0.530 |
| SASS total score | 7.3 | 3.6 | 0.038* |

* $p \leq 0.05$ (reboxetine superior to fluoxetine)
Abbreviations: CGI = Clinical Global Impression, HAM-D = Hamilton Rating Scale for Depression, SASS = Social Adaptation Self-evaluation Scale

The results of the final secondary endpoint, the SASS total score, demonstrated that reboxetine is superior to fluoxetine for the improvement of social function. The mean change from baseline in the SASS total score was significantly greater in the reboxetine group (mean change of 7.3) than in the fluoxetine group (mean change of 3.6) at day 56 in the LOCF analysis (p=0.038).

The results of the OC analyses (secondary analyses) of the primary and secondary efficacy endpoints were similar to the results of the LOCF analyses.

**Safety Results:**
Treatment-emergent signs and symptoms (TESS) were reported in 86.0% (37/43) of the reboxetine-treated patients and 78.6% (33/42) of the fluoxetine-treated patients. In the reboxetine group, the most frequently reported TESS (reported in at least 10% of patients) were dry mouth, nausea, constipation, hypoesthesia, dizziness, shivering, fatigue, palpitations, urinary retention, and postural hypotension. In the fluoxetine group, the most frequently reported TESS (reported in at least 10% of patients) were dry mouth, nausea, constipation, dizziness, headache, and fatigue.

Overall, the adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. Several adverse events, including hypoesthesia, shivering, palpitations, urinary retention, and postural hypotension, were reported at a higher frequency in this study than in the combined data from previous studies of reboxetine. However, the relevance of these differences is not clear, due to the small sample size of this study.

No deaths were reported during this study. Serious TESS were reported in an equal number of patients (3 patients) in both of the treatment groups.

| | |
|---|---|
| **Name of Company:**<br>Pharmacia<br><br>**Name of Finished Product:**<br>(To be assigned)<br><br>**Name of Active Ingredient:**<br>Reboxetine mesylate | *(For National Authority Use only)* |

The percentage of patients who discontinued treatment due to TESS was slightly lower in the reboxetine group (11.6%; 5/43) than in the fluoxetine group (14.3%; 6/42) group. No individual events led to discontinuation of treatment in more than 1 reboxetine-treated patient. Hypomania and suicide attempt each led to discontinuation of treatment in 2 fluoxetine-treated patients.

The majority of patients in each treatment group had postbaseline hematology and chemistry values that were within the predefined normal ranges. No evidence of a treatment-related effect was noted on any hematologic or chemistry assay.

No statistically significant changes from baseline values for sitting systolic or diastolic blood pressure were observed within either treatment group at any postbaseline evaluation.

Statistically significant changes from baseline values for pulse rate and ECG heart rate were observed in both treatment groups at each postbaseline evaluation. At the end of the study (day 56), the mean change from baseline pulse rate was +7.7 beats per minute in the reboxetine group and -6.4 beats per minute in the fluoxetine group, whereas the mean change from baseline ECG heart rate was +10.8 beats per minute in the reboxetine group and -6.1 beats per minute in the fluoxetine group. However, only 2 reboxetine-treated patients had postbaseline values for pulse rate that were above the predefined limit (≥120 beats/min), and no reboxetine-treated patients had postbaseline values for ECG heart rate that were above the predefined limit (≥120 beats/min).

**CONCLUSION:**
In conclusion, this phase III, multicenter, randomized, double-blind, active-controlled, parallel-group study demonstrated that the reboxetine and fluoxetine groups were comparable on the primary endpoint, the mean change from baseline in the HAM-D total score at day 56 in the ITT patient population. Overall, the adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. Several adverse events, including hypoesthesia, shivering, palpitations, urinary retention, and postural hypotension, were reported at a higher frequency in this study than in the combined data from previous studies of reboxetine. However, the relevance of these differences is not clear, due to the small sample size of this study. No new safety concerns associated with the use of reboxetine were identified.

**Date of the Report:** 19 November 2001

# TABLE OF CONTENTS

FIGURES





APPENDICES

# 1. ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ALT | alanine aminotransferase |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| CGI | Clinical Global Impression |
| CI | confidence interval |
| CRF | case report form |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition |
| ECG | electrocardiogram |
| HAM-D | Hamilton Rating Scale for Depression |
| IEC | Independent Ethics Committee |
| ITT | intent to treat |
| LOCF | last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MDD | major depressive disorder |
| OC | observed cases |
| SASS | Social Adaptation Self-evaluation Scale |
| SSRI | selective serotonin reuptake inhibitors |
| TCA | tricyclic antidepressants |
| TESS | treatment-emergent signs and symptoms |

# 2. ETHICS

## 2.1. Independent Ethics Committee

The protocol and all amendments for this study were reviewed by an Independent Ethics Committee (IEC) prior to the initiation of the study. Appendix 1.1 contains a copy of the protocol and its amendments, Appendix 1.2 contains copies of the unique pages of the case

report forms (CRF), Appendix 1.3 contains a copy of a sample informed consent statement, and Appendix 1.4 lists the IECs that were consulted.

### 2.2. Ethical Conduct of the Study

Monitoring procedures performed prior to, during, and upon completion of this study have verified that this study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Appendix 3.2 lists the protocol deviations.

### 2.3. Subject Information and Consent

Prior to inclusion in the study, each patient was given adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. All patients gave signed informed consent prior to inclusion in the study. Appendix 1.3 contains a copy of a sample informed consent form.

## 3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

A total of 5 principal investigators participated in this trial at 5 centers in Taiwan. Appendix 1.4 lists the investigators and their affiliations. Appendix 1.5 provides a curriculum vitae for each investigator. Appendix 1.13 contains the signature of the coordinating investigator.

Laboratory tests were performed at a central laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, CA). Electrocardiogram (ECG) results were analyzed by Cardiac Alert (London, England).

## 4. INTRODUCTION

Major depression is a common disorder, with a lifetime prevalence of 2% to 12% in men and 5% to 26% in women [1]. A diagnosis of depression depends on the presence of significant depressed mood and associated affects, but loss of interest, loss of energy, and impaired social function are also inherent components of major depression [2].

Depression can be treated effectively by a range of antidepressant agents [3]. Approximately 50% to 70% of patients in clinical trials will respond to antidepressants but will fail to go into remission [4], whereas 25% to 35% will experience full remission after treatment with an effective antidepressant agent [4, 5]. Recent meta-analytic reviews have suggested that the selective serotonin reuptake inhibitors (SSRIs) offer equal efficacy to some of the older antidepressant agents (eg, the tricyclic antidepressants [TCAs]), with the advantage of greater tolerability, as assessed by attrition due to adverse events [6, 7, 8]. Other reviewers have suggested that SSRIs may be of more limited utility in more severely depressed patients and in patients with melancholic symptoms. For example, non-SSRI antidepressants, such as venlafaxine and clomipramine, have been found to be significantly more effective than fluoxetine for the treatment of patients with severe depression [9]. However, the studies that

have found approximately equal outcomes on general measures of depression symptoms (eg, the Hamilton Rating Scale for Depression [HAM-D] total scores) do not provide any perspective on whether select agents offer superior treatment on a specific domain of depression symptoms.

Norepinephrine, one of the fundamental neurotransmitters of the brain, has been implicated in the neuronal systems that are important in vigilance, mood, and cognition. Modern neurochemical models of depression focus on the concept that norepinephrine is particularly important in the brain subsystems that underlie energy, interest, and motivation, whereas serotonergic systems have particular importance in modulating impulsivity. Both systems may overlap in modulating mood, sleep, anxiety, and appetite [10]. Current theories on depression have suggested that there are potential underlying genetic variations in the noradrenergic or serotoninergic systems. The suggestion has been made that roughly a quarter of depressions relate predominantly to noradrenergic problems, a quarter to serotoninergic problems, and that the remaining depressions relate to a mixture of these problems or other issues. This theory may explain why the SSRIs in general are associated with approximately one third full responses (normalization of HAM-D), one third partial responses (improvement but not normalization), and one third non-responses [4]. This conceptualization of depression implies the need for agents that are capable of specifically modifying brain norepinephrine systems. As such, this model is consistent with the original monoamine hypothesis of depression, which was first published by Schildkraut [11].

Reboxetine methanesulphonate (reboxetine mesylate, PNU-155950E, FCE 20124) is a highly selective norepinephrine reuptake inhibitor that has antidepressant activity. The affinity of reboxetine to bind to the norepinephrine reuptake transporter (1.1 nM) is similar to that of desipramine (1.2 nM) and higher than that of imipramine (24 nM), venlafaxine (1060 nM), fluoxetine (1015 nM), sertraline (420 nM), paroxetine (40 nM), or citalopram (4070 nM) [12, 13]. At clinically relevant doses, reboxetine does not block serotonin or dopamine reuptake, affect anticholinergic or antihistaminergic receptors, or affect cardiac conduction in the manner underlying the cardiotoxicity of the TCAs.

The currently available agents that affect the norepinephrine system have less receptor specificity than reboxetine and, more importantly, affect other pervasive neurotransmitter systems that produce histaminergic and anticholinergic symptoms, among others. The high level of norepinephrine-uptake selectivity and receptor specificity (ie, the relative lack of activity of reboxetine on other neurotransmitter systems) implies the potential utility of reboxetine as an antidepressant, particularly in depressions that are associated with underlying perturbations of the norepinephrine system and in patients who have symptoms that are associated with reduced energy, interest, and motivation.

The efficacy of reboxetine has been independently demonstrated in multiple short-term, randomized, double-blind, placebo-controlled studies (protocols 008 [14], 014 [15], 047 [16], and 091 [17]) and in a long-term, double-blind, placebo-controlled study (protocol 013 [18]).

The analyses of the trial endpoints from the placebo-controlled studies indicates that a clinically relevant benefit is obtained from a short course of treatment with reboxetine.

In addition to improvements in depressive symptoms, treatment-associated improvements in social behavior (measured using the Social Adaptation Self-Evaluation Scale [SASS] [19]) were noted in one study [15]. In this study, reboxetine was statistically and clinically superior to both placebo and fluoxetine in improving social functioning. The improvement was evident in both the patients who were and were not in remission from their depressive symptoms and indicated a better quality of remission for social adaptation in the reboxetine-treated patients.

The most frequently reported adverse events associated with the administration of reboxetine, as determined from combined safety data from controlled and uncontrolled studies in which 2140 patients have been treated with reboxetine, are dry mouth, constipation, nausea, insomnia, dizziness, headache, and sweating. However, these events were usually mild to moderate in severity, and only a small proportion of patients discontinued treatment with reboxetine for these reasons.

This study (protocol M/2020/0032) was conducted to test the hypothesis that reboxetine is effective for the treatment of depression in a Taiwanese population. In addition, this study was conducted to test the hypothesis that a noradrenergic-specific agent, such as reboxetine, is effective for improving the social functioning of patients with depression.

# 5. OBJECTIVES AND ENDPOINTS

## 5.1. Objectives

### 5.1.1. Primary Objective

The primary objective of this study was to compare the antidepressant efficacy of reboxetine (administered at a dose of 8 to 10 mg/day for 8 weeks) with that of fluoxetine (administered at a dose of 20 to 40 mg/day for 8 weeks), as measured by the change from baseline in the 21-Item HAM-D total score at the last assessment in patients suffering from major depressive disorder (MDD).

### 5.1.2. Secondary Objectives

The secondary efficacy objective of this study was to further compare the efficacy of reboxetine (administered at a dose of 8 to 10 mg/day for 8 weeks) with that of fluoxetine (administered at a dose of 20 to 40 mg/day for 8 weeks), as measured by the change from baseline in the SASS total score and in the Clinical Global Impression (CGI) score at the last assessment in patients suffering from MDD.

The safety objective of this study was to compare the tolerability (based on adverse events, vital signs, safety laboratory tests, and ECGs) of reboxetine, administered at a dose of 8 to

10 mg/day for 8 weeks, with that of fluoxetine, administered at a dose of 20 to 40 mg/day for 8 weeks, in patients suffering from MDD.

### 5.2. Endpoints

The primary endpoint was the change from baseline in the HAM-D total score at the last assessment.

The secondary efficacy endpoints included both continuous measures of efficacy, such as the mean change from baseline in the CGI Severity of Illness score and in the SASS total score, and categorical measures of efficacy, including the HAM-D response rate, the HAM-D remission rate, the CGI Global Improvement score, and the CGI Global Improvement response rate.

The secondary safety endpoints were adverse events, vital signs, safety laboratory tests, and ECGs. Adverse events and vital signs were assessed at each postbaseline visit. Safety laboratory tests and ECGs were obtained at screen, week 4, and week 8.

## 6. METHODS

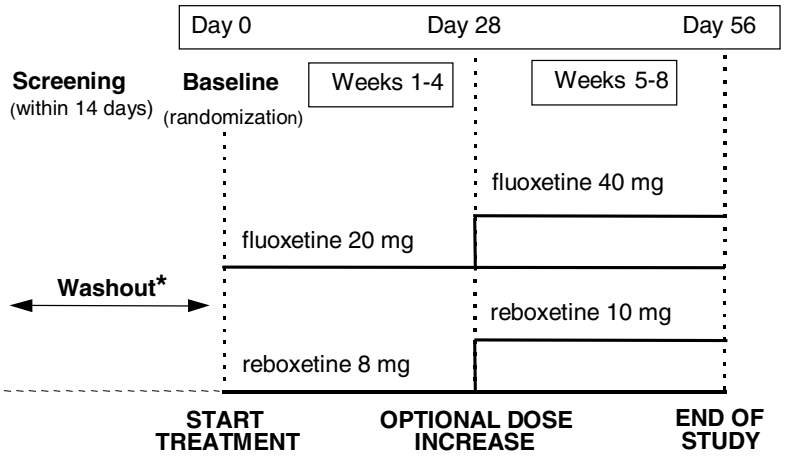
### 6.1. Overall Study Design and Plan

This phase III, multicenter, randomized, double-blind, active-controlled, parallel-group study was conducted in 85 patients aged 18 to 65 years who suffered from MDD without psychotic features, as diagnosed using criteria defined by the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) [2].

The patients were selected from a population of patients who were hospitalized or were receiving care at outpatient or day-hospital clinics. Patients who had a score of ≥22 on the 21-Item HAM-D at the screening visit and who met the other eligibility criteria were randomized to receive 8 weeks of treatment with reboxetine (8 mg/day, days 1-28; 8-10 mg/day, days 29-56) or fluoxetine (20 mg/day, days 1-28; 20-40 mg/day, days 29-56). The optional dose increase to 10 mg/day of reboxetine or 40 mg/day of fluoxetine was allowed after 4 weeks of therapy in those patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. Study visits were conducted weekly during the first 4 weeks of treatment and every 2 weeks during the last 4 weeks of treatment. Efficacy measures and certain safety measures (adverse events and vital signs) were assessed at each visit (days 0, 7, 14, 21, 28, 42, and 56); laboratory tests and ECGs were measured at screen, day 28, and day 56.

The study design is presented in Figure 1.

**Figure 1. Study Design and Timeline**




* The washout period varied according to the class of drugs with which the patient was being treated at the time of enrollment (eg, 4 days for tricyclic antidepressants, 14 days for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors other than fluoxetine, and 28 days for fluoxetine). Patients who were not being treated with antidepressant medication at the time of study enrollment could be randomized as soon as their laboratory test results were available and their eligibility was confirmed.

## 6.2. Discussion of Study Design

The double-blind, randomized, parallel-group design used in this study is generally recognized as one that provides an unbiased assessment of the efficacy and safety of an experimental drug. The washout period prior to administration of study medication varied according to the class of drugs with which the patient was being treated at the time of enrollment. The lengths of the washout periods were designed, based on the pharmacokinetics of each class of drugs, to allow sufficient time for elimination of the drug. This washout procedure has been used successfully in previous clinical studies with reboxetine.

## 6.3. Selection of Study Population

### 6.3.1. Inclusion Criteria

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

- Diagnosis of MDD without psychotic features, as defined by DSM-IV.
- Male or female, of any race, between the ages of 18 and 65 years (inclusive).
- Total score of ≥22 on the 21-Item HAM-D at screen and at baseline.
- General good health, as confirmed by routine clinical laboratory safety findings.

- Voluntary consent to participate in the study, documented in a written Patient Informed Consent Form that was signed prior to the start of any study procedures at the screening visit.

### 6.3.2. Exclusion Criteria

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

- DSM-IV diagnosis of the following concomitant psychiatric disorders: MDD with psychotic features, cyclothymic disorder, bipolar I or bipolar II disorders, substance-related disorders, schizophrenia, or other psychotic disorders.
- Resistance to antidepressive treatment, defined as a lack of response to at least 2 previous courses of antidepressant medications administered at full doses for more than 1 month or prior failure to respond to treatment with reboxetine or fluoxetine.
- History of MDD associated with endocrine disorders: hypo- or hyper-thyroidism tested by thyroid-stimulating hormone and thyroxine, adrenal insufficiency, or Cushing's syndrome.
- Positive pregnancy test for females of childbearing potential.
- Refusal by female patients of childbearing age to use an effective contraceptive method during the study.
- Breast-feeding by female patients.
- Participation in any clinical study with an investigational compound in the 1 month preceding the study.
- History or presence of gastrointestinal, liver, or kidney disease or other conditions known to interfere with the absorption, distribution, metabolism, and excretion of drugs.
- History of seizures or brain injury; current evidence of clinically important hematopoietic, respiratory, or cardiovascular diseases; current evidence of urinary retention or glaucoma.
- Clinically important illness in the 4 weeks preceding the study that might have interfered with the conduct of the trial.
- Clinically relevant abnormal findings in the physical examination, laboratory tests, or ECG at admission.
- Treatment with electroconvulsive therapy in the 6 months preceding the study.
- Major risk of suicide as assessed by the investigator, a score of ≥3 on Item 3 of the HAM-D at screen or baseline, or a history of suicide attempt during the current depressive episode.
- History of hypersensitivity to reboxetine or fluoxetine.
- Use of medications that are potent inhibitors of the drug-metabolizing enzymes cytochrome p450-3A4 or cytochrome p450-2D6. These medications include azole

antifungal agents, macrolide antibiotics (such as erythromycin), or fluvoxamine. Use of hormonal contraceptive medications was allowed during the study.

## 6.4. Treatments

### 6.4.1. Treatments Administered

During the washout period, 1 placebo tablet was administered orally, once daily (in the morning). The study medications that were administered during the treatment period (reboxetine, fluoxetine, and placebo) were provided as identically appearing capsules. Study medications were administered orally, twice daily.

During weeks 1 through 4 (days 1-28), reboxetine was administered in twice-daily doses of 4 mg, for a total daily dose of 8 mg of reboxetine. After 4 weeks of treatment, the reboxetine dose was increased to 10 mg/day in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. The increase to 10 mg/day was achieved by adding a placebo capsule to the morning dose (to maintain the study blind) and a 2-mg capsule to the evening dose.

During weeks 1 through 4 (days 1-28), fluoxetine was administered as a morning dose of 20 mg of fluoxetine and a evening placebo capsule (to maintain the study blind). After 4 weeks of treatment, the fluoxetine dose was increased to 40 mg/day in patients whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose. The increase to 40 mg/day was achieved by adding a 20-mg capsule to the morning dose and an additional placebo capsule to the evening dose (to maintain the study blind).

### 6.4.2. Identity of Investigational Product

Trial medication for the randomized treatment consisted of identically appearing capsules that contained reboxetine or fluoxetine. Placebo capsules (lactose-filled gelatin capsules) were provided to maintain the blinding of the study medications. The reboxetine and placebo supplies were manufactured and supplied by Pharmacia & Upjohn (Pharmacia). The fluoxetine (Prozac™, Eli Lilly and Company, Indianapolis, IN) comparator was commercially available and was inserted into gelatin capsules by Pharmacia. Information about the study medications is summarized in Table 1.

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

| Study Medication | Capsule Strength | Suppliers | Lot Numbers |
|---|---|---|---|
| Reboxetine | 4 mg (one 4-mg tablet) | Pharmacia | 00427.05 |
| Reboxetine | 2 mg (1/2 of one 4-mg tablet) | Pharmacia | 00427.06 |
| Fluoxetine | 20 mg (one 20-mg tablet) | Eli Lilly (repackaged by Pharmacia)* | 00427.04 |
| Placebo capsules† | | Pharmacia | 00427.03 |
| Placebo tablets (washout period) | | Pharmacia | H06A02 |

* Prozac capsules, supplied by Eli Lilly and Company were inserted into gelatin capsules by Pharmacia
† Placebo capsules were used to maintain the blinding of the study medication.

The study medications were provided in bottles that were labeled with the protocol number, the patient number, and a label indicating whether the dose was to be administered in the morning or evening. Each patient received 2 bottles of study medication for each week during weeks 1 through 4; 1 bottle (labeled AM) contained capsules for the morning dose, and 1 bottle (labeled PM) contained capsules for the evening dose. Two extra capsules (for a total of 9 capsules) were included in each bottle to allow for unexpected delays in the scheduling of appointments.

Patients who received the optional dose increase to 10 mg/day of reboxetine or 40 mg/day of fluoxetine received 2 additional bottles of study medication for each week during weeks 5 through 8; 1 bottle (labeled AM-2) contained capsules for the additional morning dose, and 1 bottle (labeled PM-2) contained capsules for the additional evening dose.

Medications were dispensed to patients at each visit during the treatment period (baseline, weeks 1-4, and week 6). At the same visit, the patients returned the bottles that had been dispensed at the previous visit. All unused medications and empty bottles were returned to Pharmacia.

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

### 6.4.3. Method of Assigning Subjects to a Treatment Group

Pharmacia prepared a randomization list for assignment of the patients to 1 of the 2 treatment groups. Study medication for each treatment group was prepared on this basis by Pharmacia and was labeled with the corresponding patient number. At the baseline visit, the investigator assigned each patient to a treatment group based on the patient's temporal entry into the study (ie, by assigning the lowest patient number available). A list of patient numbers and medication assignments was provided only after the data for the study had been analyzed.

Appendix 1.7 contains a copy of the randomization scheme and code.

### 6.4.4. Selection of Doses Used in the Study

The 8- to 10-mg/day doses of reboxetine that were administered in this study were chosen based on the results of previously conducted phase II and phase III studies in which these doses were shown to provide maximal response rates with the most acceptable adverse-event profile. The doses of fluoxetine that were administered in this study (20 mg/day, with an optional increase to 40 mg/day) are the recommended doses for the treatment of depression [20].

### 6.4.5. Selection and Timing of Dose for Each Subject

During the first 4 weeks of the study, patients in both of the treatment groups took one capsule in the morning and one capsule in the late afternoon at an approximately fixed time (eg, between 8 and 9 AM and between 5 and 6 PM), for a total daily dose of 8 mg of reboxetine or 20 mg of fluoxetine.

An optional dose increase (to 10 mg/day of reboxetine or 40 mg/day of fluoxetine) was permitted for weeks 5 through 8 if the investigator believed that the patient would benefit in terms of response and would adequately tolerate the increased dose (ie, in patients who had shown little or no improvement in the objective measures of depressive symptoms but who had no significant difficulty in tolerating the initial doses of study medication). A patient whose dose was escalated at the 4-week evaluation (day 28) continued with the higher dose until treatment was completed (day 56), unless the patient was unable to tolerate the increased dose, in which case she/he could resume the regimen that was used during weeks 1 through 4 of the study.

### 6.4.6. Blinding

Patients were randomized to a treatment in a double-blind fashion in order to minimize potential bias in the evaluation of clinical response and safety. The randomized medication consisted of identically appearing capsules containing reboxetine, fluoxetine, or placebo. The capsules were provided in bottles that were labeled with the protocol number, the patient number, and a label indicating whether the dose was to be administered in the morning or evening.

Investigators were given sealed drug-disclosure sheets that contained information about each patient's treatment. These sheets were opened only in case of emergency, when knowledge of the treatment was necessary for proper management of the patient. If the treatment code was opened, this was recorded on the serious adverse event report form, which was signed by the investigator. The investigator immediately (within 24 hours) informed the study monitor and reported a full description of the reason for opening the code on the Adverse Event Form of the CRF. When the treatment code was opened, the patient was withdrawn from the study.

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

### 6.4.7. Prior and Concomitant Treatment

No concomitant psychotropic medications other than temazepam, lorazepam, flurazepam, estazolam, and oxazepam, which could be administered as sleep inducers on an as-needed basis, were allowed during the study. The administration of other psychotropic drugs was considered to be a protocol violation. Use of St. John's Wort was not allowed during the study.

Other therapy that was considered to be necessary for the patient's welfare was permitted at the investigator's discretion. All such therapy was recorded on the Concomitant Medication CRF.

No other investigational drug was allowed to be taken concomitantly with the study medication, and patients were not allowed to participate concurrently in any other clinical study. Over-the-counter medications were allowed as needed for symptomatic treatment; these were recorded along with other medications on the Concomitant Medication CRF.

### 6.4.8. Treatment Compliance

The investigator maintained a record of the study medications that were received from the sponsor, those that were dispensed, and those that were returned. Discrepancies between dispensed and returned study medications were recorded.

Treatment compliance was monitored by the investigators and was recorded on the appropriate CRF (eg, Medication Record CRF, Concomitant Medication CRF) at each visit. Acceptable treatment compliance was defined as an overall drug intake of at least 80% of the prescribed amount.

### 6.4.9. Removal of Subjects From Treatment or Assessment

Patients were withdrawn from the study medication if the investigator judged it to be medically necessary or if it was the wish of the patient. The reasons for the withdrawal of a patient from study medication were noted. Regardless of the reason for withdrawal, the patient was examined as soon as possible. Relevant samples (eg, laboratory tests, ECGs, and any diagnostic procedures that were considered necessary to define the event that led to patient withdrawal) were obtained and relevant assessments were completed according to the schedule of final assessments. The CRFs were completed and forwarded to Pharmacia.

## 6.5. Efficacy and Safety Variables

### 6.5.1. Efficacy and Safety Measures Assessed

The primary efficacy endpoint was the change from baseline in the total score of the 21-Item HAM-D at the last assessment. The secondary efficacy endpoints included both continuous measures of efficacy, such as the mean change from baseline in the CGI Severity of Illness

score and in the SASS total score, and categorical measures of efficacy, including the HAM-D response rate, the HAM-D remission rate, the CGI Global Improvement score, and the CGI Global Improvement response rate.

Efficacy measures were assessed at each study visit (screen [HAM-D only] and days 0, 7, 14, 21, 28, 42, and 56).

The safety of the study medication was evaluated using the following safety measures:

- Standard medical history, obtained at screen.
- Standard clinical and physical examination, obtained at screen.
- Blood pressure and pulse, measured in the sitting position at each visit.
- Adverse events, recorded at baseline and at each subsequent visit.
- ECG, obtained at screen, day 28, and day 56 (end of treatment). The ECG results were analyzed by Cardiac Alert (London, England). Abnormal ECG patterns were assessed and the heart rate, PR, QRS, and QT intervals were measured.
- Laboratory assays: hematology and serum chemistries were performed at screen and on days 28 and 56, serum pregnancy tests (for females of childbearing potential) and a urine drug test were performed at screen and on day 56, and thyroid-function tests were performed at screen. Laboratory tests were performed at a central laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, CA).

The schedule of study activities is summarized in Table 2.

**Table 2. Schedule of Activities**

| Study Activity | Study Day* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Screen† | Baseline | 7 | 14 | 21 | 28 | 42 | 56‡ |
| Informed Consent | X | | | | | | | |
| Admission Checklist | X | | | | | | | |
| Demographics | X | | | | | | | |
| Diagnosis: DSM-IV | X | | | | | | | |
| Medical history | X | | | | | | | |
| Physical Exam | X | | | | | | | |
| Medication History | X | | | | | | | |
| Psychiatric History | X | | | | | | | |
| ECG | X | | | | | X | | X |
| Laboratory | X | § | | | | X | | X |
| Pregnancy test | X | | | | | | | X |
| Urine drug screen | X | | | | | | | X |
| Vital signs | X | X | X | X | X | X | X | X |
| 21-Item HAM-D | X | X | X | X | X | X | X | X |
| CGI | | X | X | X | X | X | X | X |
| SASS | | X | X | X | X | X | X | X |
| Treatment Completion | | | | | | | | X |
| Study Medication Record | | | X | X | X | X | X | X |
| Concomitant Medication | | X | X | X | X | X | X | X |
| Adverse Events | | X | X | X | X | X | X | X |
| Post Study Follow-Up | As needed for adverse events or serious adverse events after study completion | | | | | | | |

* Visits were targeted to occur within 1 day of the scheduled study day.
† The screening visit must have occurred within 2 weeks prior to baseline.
‡ Day-56 measurements were completed at early termination if the patient did not complete the study.
§ If significant abnormalities were noted on a laboratory test at screen, then the test was to be repeated at the baseline visit.

**Abbreviations:** CGI = Clinical Global Impression, ECG = electrocardiogram, HAM-D = Hamilton Rating Scale for Depression, SASS = Social Adaptation Self-evaluation Scale

## 6.5.2. Appropriateness of Measurements

The efficacy and safety measures that were used in this study represent standardized and well-accepted measures of antidepressant efficacy and safety in clinical studies (see Sections 6.5.3 and 6.5.4 below).

## 6.5.3. Efficacy Variables

### 6.5.3.1. Primary Efficacy Variable

The primary endpoint was the change from baseline in the total score of the 21-Item HAM-D at the last assessment.

The 21-Item HAM-D [21] is an observer-rated scale that is based on both a clinical interview and on observations of behavior made by an experienced clinician. This scale is well standardized and is intended to assess the state of the patient's condition at the time of the interview and over the preceding few days. The individual items on the HAM-D are graded according to severity on 0- to 2-point or 0- to 4-point scales. The HAM-D total score ranges from 0 to 62; scores of ≥25 are associated with severe depression, scores between 18 and 24 are associated with moderate depression, and scores between 8 and 17 are associated with mild depression. Scores of ≤10 are often used as the definition of disease remission. Response to study medication is defined as a decrease of ≥50% from baseline in the HAM-D total score at the postbaseline assessment.

### 6.5.3.2. Secondary Efficacy Variables

The secondary efficacy endpoints were as follows:

- HAM-D response rate, defined as the percentage of patients who had a decrease of ≥50% from baseline in the 21-Item HAM-D total score
- HAM-D remission rate, defined as the percentage of patients who had a total score of ≤10 on the 21-Item HAM-D
- CGI Severity of Illness, mean change from baseline
- CGI Global Improvement, percentage of patients by Global Improvement score
- CGI Global Improvement response rate, defined as the percentage of patients who had a CGI Global Improvement score of ≤2 (corresponding to "very much improved" or "much improved")
- SASS, mean change from baseline in the total score

The CGI [22] is a clinician-rated scale that consists of the following 3 parts: Severity of Illness, Global Improvement, and Efficacy Index. Only the Severity of Illness and Global Improvement portions of the scale were used in this study. A mean decrease from baseline on the CGI Severity of Illness score represents patient improvement. The questions from the Global Improvement index refer to changes since the beginning of the study, as evaluated at each postbaseline visit, and are not asked at baseline. Lower scores on the CGI Global Improvement index indicate patient improvement; a responder is defined as a patient who has a score of ≤2 (corresponding to "very much improved" or "much improved").

The SASS [19] is a 21-question self-evaluation questionnaire that explores the domains of work and leisure, relationships, and patient perception of his/her ability to manage the environment. The scale was validated using data from 4000 individuals in a general population survey and data from 549 depressed patients who were enrolled in clinical studies that compared reboxetine with placebo and/or fluoxetine [19]. Each item of SASS is scored on a scale of 0 to 3, with a higher score indicating better social functioning. A total score in the range of 35 to 52 points is considered to be normal (ie, this range was observed in 80% of

the general population) [19]. The SASS represents a useful tool for the evaluation of social functioning in depression because it is relatively simple to use and because it may help to differentiate the effects of different classes of antidepressants (eg, serotonergic agents regulating mood, noradrenergic agents sustaining drive) in a way that syndromic clinical rating scales are unable to do.

## 6.5.4. Safety Variables

### 6.5.4.1. Adverse Events

#### *6.5.4.1.1. Definition of Adverse Events*

For this study, an adverse event was defined as any untoward medical event that occurred during the protocol-specified adverse event reporting period (from baseline until the final clinic visit) regardless of whether it was considered to be related to study medication. In addition, any known untoward event that occurred subsequent to the adverse event reporting period and that the investigator assessed as possibly related to the investigational medication was also considered to be an adverse event.

Adverse events included all suspected adverse medication reactions; all reactions from medication abuse, withdrawal, sensitivity, or toxicity; apparently unrelated illnesses, including the worsening of a preexisting illness; any injury or accident; and any abnormality in physical examination or laboratory test results that required clinical intervention or further investigation (beyond ordering a repeat confirmatory test). If a medical condition was known to have caused the injury or accident (eg, a fall secondary to dizziness), then the medical condition (dizziness) and the accident (fall) were reported as 2 separate adverse events. The outcome of the accident (eg, hip fracture secondary to the fall) was recorded in the comments section of the CRF. Laboratory abnormalities that were associated with a clinical event (eg, elevated liver enzymes in a patient with jaundice) were described in the comments section of the CRF, rather than listed as a separate adverse event.

Diagnostic and therapeutic procedures, such as surgery, were not reported as adverse events. However, the medical condition for which the procedure was performed was reported if it met the definition of an adverse event (eg, an acute appendicitis that began during the adverse event reporting period would have been reported as an adverse event; the resulting appendectomy would have been noted in the comments section of the CRF).

Except for worsening of depressed mood (which would be reflected in a change in the HAM-D Item 1 score), an increase in the intensity of other symptoms of depression (eg, sleep difficulties, somatic symptoms, genital symptoms, weight change, anxiety, other psychiatric symptoms) was to be considered an adverse event if the intensity of the event increased during the treatment period.

#### *6.5.4.1.2. Eliciting Adverse Event Information*

Investigators reported all directly observed adverse events and all adverse events that were spontaneously reported by the patients. In addition, each patient was questioned about adverse events at each clinic visit following initiation of treatment, as follows: "Since your last clinic visit," (or "Since you began taking the investigational medication,") "have you had any health problems?"

#### *6.5.4.1.3. Adverse Events Reporting Period*

The adverse event reporting period began with the administration of the first dose of study medication (at the baseline [day 0] visit) and ended at the final clinic visit (day 56). An adverse event that occurred during the protocol-specified adverse event reporting period was reported, regardless of whether it was considered to be related to the study medication. A disorder that was present before the adverse event reporting period started and that was noted on the pretreatment medical history/physical examination form was not reported as an adverse event unless the condition worsened or episodes increased in frequency during the adverse event reporting period. Any known untoward event that occurred subsequent to the adverse event reporting period and that the investigator assessed as possibly related to the study medication was considered to be an adverse event.

#### *6.5.4.1.4. Assessment of Gravity and Intensity*

Each adverse event was classified by the investigator as serious or nonserious. A serious adverse event was one that was fatal or life-threatening (ie, resulted in immediate risk of death), required or prolonged hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly. Any other important adverse event that did not meet the preceding criteria was classified as serious if, based upon appropriate medical judgment, the event was considered to jeopardize the patient or if medical or surgical intervention was required to prevent the occurrence of one of the outcomes listed above. Serious adverse events also included any other adverse event that the investigator or company judged to be serious or that was defined as serious by the regulatory agency in the country in which the adverse event occurred.

Investigators characterized the intensity of adverse events as mild (did not interfere with patient's usual function), moderate (interfered to some extent with patient's usual function), or severe (interfered significantly with patient's usual function). The assessment of intensity was made independently of the assessment of gravity. It should be noted that severity is a measure of intensity, whereas seriousness is a measure of gravity. (A severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.)

#### *6.5.4.1.5. Assessment of Drug-Relatedness*

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

#### *6.5.4.1.6. Follow-up of Unresolved Events*

All adverse events were followed until they resolved or until the patient's participation in the study ended (ie, until a final report was completed for that patient). In addition, all serious adverse events and those nonserious events that were assessed by the investigator as possibly related to the study medication were followed after the patient's participation in the study was over, until the events resolved or until the investigator assessed them as "chronic" or "stable."

#### *6.5.4.1.7. Exposure In Utero*

If a patient became, or was found to be, pregnant while receiving or within 30 days of discontinuing study medication, then the investigator submitted an adverse event CRF that included the anticipated date of birth or pregnancy termination. The patient was followed by the investigator until the completion of the pregnancy. The following pregnancy outcomes were to be reported as serious adverse events: spontaneous abortion (including miscarriage and missed abortion), stillbirth, neonatal death within 1 month of birth, infant death that occurred after 1 month of birth and that the investigator assessed as possibly related to the in utero exposure, or congenital anomaly (including that in an aborted fetus). In the case of a live birth, the “normality” of the newborn was assessed at the time of birth (ie, there was no required minimum follow-up of a presumably normal infant). The “normality” of an aborted fetus was assessed by gross visual inspection unless pre-abortion laboratory findings were suggestive of a congenital anomaly.

### 6.5.4.2. Clinical Laboratory Evaluations

Hematology and serum chemistry assays were performed at screen and on days 28 and 56. Serum pregnancy tests (for females of childbearing potential) and a urine drug test were performed at screen and on day 56, and thyroid-function tests were performed at screen. The laboratory tests were performed at a central laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, CA).

The specific tests that were evaluated are summarized in Table 3.

**Table 3. Laboratory Assays**

| Category | Assay |
|---|---|
| Hematology | Hematocrit<br>Hemoglobin<br>Leukocytes<br>Differential<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils<br>Platelet count<br>Erythrocytes |
| Serum Chemistries | Electrolytes<br>Sodium<br>Potassium<br>Chloride<br>Carbon dioxide<br>Blood urea nitrogen<br>Creatinine<br>Glucose<br>Uric acid<br>Total bilirubin<br>Aspartate aminotransferase (AST)<br>Alanine aminotransferase (ALT)<br>Alkaline phosphatase<br>Thyroid stimulating hormone (TSH) and thyroxine (T4) – screen only<br>Pregnancy test (for all females of childbearing potential) – screen and day 56 |
| Urinalysis | Drug screen (screen and day 56) |

### 6.5.4.3. Vital Signs, Physical Findings, and Other Observations Related to Safety

Systolic and diastolic blood pressure and pulse were measured in the sitting position at each visit. Standard medical history and standard physical examinations were performed at screen.

ECGs were performed at screen and on days 28 and 56. The ECG results were analyzed by Cardiac Alert (London, England). Abnormal ECG patterns were assessed and the heart rate, PR, QRS, and QT intervals were measured.

## 6.6. Data Quality Assurance

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

- An investigator's meeting was held to familiarize the investigators with the protocol and with the assessment instruments.
- A reference manual was given to each investigator.

- Data were collected on standard CRFs that were provided to each investigator by the sponsor.
- Investigators and institutions guaranteed access to source documents for quality assurance audits by Pharmacia personnel and the appropriate regulatory agencies.
- Monitoring visits were made periodically during the study to ensure that all aspects of the protocol were followed.
- Source documents were reviewed to verify their agreement with the data on the patient CRFs.
- All safety laboratory measurements were conducted by SmithKline Beecham Clinical Laboratories (Van Nuys, CA), a central laboratory that is certified by the Clinical Laboratory Improvement Act and the College of American Pathologists.
- Laboratory data were entered at SmithKline Beecham and were transmitted electronically to Pharmacia for analysis.
- ECGs were evaluated by Cardiac Alert (London, England); the ECG data were then transmitted electronically to Pharmacia for analysis.
- Data (ie, HAM-D scores and adverse events) in the clinical database were reviewed to verify their agreement with the data on the patient CRFs.
- Pharmacia's Standard Operating Procedures were followed in the conduct and analysis of the study.

Pharmacia is responsible for independent quality assurance audits of the clinical study processes at company sites worldwide. Audits of selected clinical investigator sites are also conducted to assess and help assure compliance with Good Clinical Practice and applicable regulatory requirements. Independent audits of this clinical study were not performed.

## 6.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

### 6.7.1. Statistical and Analytical Plans

#### 6.7.1.1. Data Sets Analyzed

The intent-to-treat (ITT) population includes all patients who were randomized into the trial and who received at least one dose of study medication. All analyses were based on the ITT population. Efficacy analyses were based on the population of ITT patients who had at least one postbaseline evaluation for the specified efficacy measure (eg, HAM-D, CGI).

Information regarding visit number or study day was based on the visit numbers that were preprinted on the CRFs. For purposes of data analysis, the day of first dose of study medication was considered to be study day 1.

Two types of analyses were performed for all efficacy variables: "last observation carried forward" (LOCF) and "observed cases" (OC). The LOCF analyses used the last valid assessment as an estimate for all subsequent missing values. The OC analysis did not replace missing data. The LOCF analyses were the primary analyses, and the OC analyses were the secondary analyses. Comparisons were based on a 2-sided test at an alpha level of 0.05, unless otherwise specified.

### 6.7.1.2. Demographic and Baseline Characteristics

The demographic and baseline characteristics (eg, age, sex, race) of the patients in each treatment group were compiled. Categorical variables were summarized using frequency counts. The association between treatment groups and categorical variables was assessed using the chi-square test. Continuous variables were summarized using treatment group means, standard deviations, and ranges. The association between treatment groups and continuous variables was assessed using a 1-way analysis of variance (ANOVA) with treatment as a factor.

### 6.7.1.3. Efficacy Measures

#### *6.7.1.3.1. Continuous Endpoints*

Differences between the treatment groups in the mean change from baseline on the continuous efficacy endpoints were assessed at each visit using a 2-way ANOVA with investigator, treatment, and treatment-by-investigator interaction as factors. The treatment-by-investigator interaction was tested to evaluate the poolability of the data. If a statistically significant ($p \leq 0.10$) interaction effect was observed, then the results from individual investigators were presented to identify the source of the interaction.

On the primary efficacy endpoint (the HAM-D total score), a difference of 2 points on the change from baseline is generally considered to be a clinically relevant difference between treatment groups. Therefore, the protocol specified that both the difference between the treatment groups and the 90% confidence interval (CI) for the difference would be presented. If a clinically relevant difference between treatment groups was observed, then the statistical significance of the difference was evaluated based on the 90% CI. A clinically relevant difference was considered to be statistically significant if the 90% CI did not include 0 (ie, the lower limit of the 90% CI was >0). Thus, reboxetine was considered to be inferior to fluoxetine on the primary endpoint if the conditions for both a clinically relevant difference (difference of 2 points on the change from baseline) and a statistically significant difference (lower limit of 90% CI >0) were met.

Mean values for the individual items of the HAM-D were displayed by treatment group and by visit to identify any items that may have exerted a major influence on the total score; this analysis was descriptive and did not include statistical hypothesis testing.

#### *6.7.1.3.2. Categorical Endpoints*

For the categorical efficacy endpoints, differences between the treatment groups were assessed at each visit using the Cochran-Mantel-Haenszel test, stratified by investigator.

### 6.7.1.4. Safety Data

The original terms that were used by investigators to identify adverse events on the CRFs were translated according to the Medical Dictionary for Regulatory Activities (MedDRA) and were grouped according to the MedDRA system organ classes and preferred terms.

Each adverse event was counted once, according to the date of onset. If the adverse event began prior to the first dose of study medication and did not increase in severity after the first dose of study medication, then the adverse event was considered to be a pretreatment event and was not counted in the adverse event frequency tables. If the onset was prior to the first dose of study medication and the severity increased after baseline, then the event was considered to be an adverse event and was included in the adverse event frequency tables. This rule was consistent with the treatment-emergent signs and symptoms (TESS) convention for counting adverse events.

The incidence of TESS was summarized as follows: (1) by system organ class and preferred term; (2) by maximum severity; (3) by relationship to study medication; and (4) by gender. The relationship of an adverse event to study medication was based on the investigator's judgment. Summary tables were also presented for adverse events that resulted in termination of study medication, for serious adverse events, and for serious adverse events that resulted in termination of study medication. Corresponding patient data listings were prepared to support each of the above summaries.

For each vital sign, laboratory test, and ECG measure, the change from baseline at each postbaseline evaluation was analyzed using a paired *t* test. Differences between the treatment groups in the change from baseline at each postbaseline evaluation were analyzed using an ANOVA. The incidence of abnormal postbaseline vital signs, laboratory tests, and ECG results were summarized and corresponding patient data listings were prepared to support each of the summaries.

## 6.7.2. Determination of Sample Size

The sample size of 40 patients per treatment group was established after consultation with Taiwanese regulatory authorities.

The power calculation was based on the results of a previously conducted placebo- and fluoxetine-controlled study of reboxetine (protocol 014) in which the mean change from baseline in the HAM-D total score at week 8 was similar in the reboxetine (13.4 points) and fluoxetine (13.3 points) groups, with a standard deviation of approximately 9.0 points. A difference between 2 treatment groups of 2 points or less in the mean change from baseline in

the HAM-D total score is generally considered to be clinically insignificant. With a sample size of 40 patients per treatment group, the power to detect a difference of more than 2 points in the mean change from baseline in the HAM-D total score is 0.25 with a 1-sided alpha equal to 0.05 and a common standard deviation of 9.0.

Power calculations were made with nQuery Advisor Release 3.0, Statistical Solutions Ltd., Cork, Ireland.

## 6.8. Changes in the Conduct of the Study or Planned Analyses

### 6.8.1. Protocol Amendments

Changes to protocol M/2020/0032 were detailed in 2 amendments, which were implemented before any patients were enrolled in the study. The protocol and protocol amendments are provided in Appendix 1.1. The amendments, along with the reasons for each, are briefly summarized below.

#### 6.8.1.1. Amendment 1 (17 January 2000)

The protocol was amended to make the following changes or clarifications:

- The term "fixed-dose" was removed from the description of the study design, since dose-escalation was permitted in this study.
- The reference to a 40-mg fluoxetine capsule was removed from the description of the trial products, since only 20-mg fluoxetine capsules were used in this study.
- The description of the treatment schedule was changed to specify that all patients would receive placebo tablets during the washout period. (The original protocol indicated that the placebo washout tablets could be used at the investigator's request.)
- The description of the optional dose increase (to 10 mg/day of reboxetine or 40 mg/day of fluoxetine) was modified to clarify the description of the patients who would receive the dose-escalation. The original protocol stated that "These patients will generally be those who have had little or no improvement in their objective measures of depressive symptoms." With this amendment, the terms "little or no improvement" were defined as a change from baseline of ≤20% in the HAM-D total score or a score of ≥3 on the CGI Global Improvement scale. However, it should be noted that this definition was provided only as a guideline. The dose could be increased in any patient whom the investigator believed would benefit in terms of response and would adequately tolerate the increased dose.

#### 6.8.1.2. Amendment 2 (30 June 2000)

The protocol was amended to make the following changes or clarifications:

- The background information was updated to include data from 5 additional, short-term, placebo-controlled studies of reboxetine.
- The study design was modified to specify that the primary endpoint is the mean change from baseline in the 21-Item HAM-D total score, rather than the absolute change from baseline in the 21-Item HAM-D total score.
- The list of exclusion criteria was expanded to require that patients who had previously failed treatment with reboxetine or fluoxetine were to be excluded from the study.
- The planned analysis of ECG data was modified to specify that heart rate and PR, QRS, and QT intervals would be measured, but that the QTc interval would not be calculated.
- The statistical analysis plan was revised to clarify the power calculation and to eliminate the planned analysis of TESS by age (≤65 or >65 years), since only patients who are ≤65 years of age were enrolled in this study.

### 6.8.2. Changes in the Statistical Plan

#### 6.8.2.1. 90% Confidence Intervals

As discussed in Section 6.7.1.3.1, the difference between the treatment groups on the primary endpoint was evaluated in terms of the clinical relevance and the statistical significance of the difference. If a clinically relevant difference between the treatment groups was observed (defined as a difference of 2 points on the change from baseline in the HAM-D total score), then the statistical significance of the difference was evaluated based on the 90% CI.

The protocol specified that the 90% CI for the difference between treatment groups would be presented for all efficacy variables (not just the primary endpoint). However, for the secondary efficacy endpoints, generally accepted definitions of clinically relevant differences were not available. Therefore, the differences between the treatment groups and the 90% CI for the differences were not presented for the secondary efficacy endpoints.

#### 6.8.2.2. Exclusion of Efficacy Data

Although the rule was not specifically stated in the protocol, any efficacy measures that were completed at least 2 weeks after the patient's last dose of study medication (for patients who discontinued early from the study) were excluded from the efficacy analysis.

## 7. RESULTS

Key data tables are included in the text and are numbered sequentially (eg, Table 1, Table 2). More detailed, supportive tables are included in the end-of-text Tables and Figures section and are numbered separately with a "T" prefix (eg, Table T1, Table T2). References to these end-of-text tables are included in the text.

## 7.1. Study Subject Information

### 7.1.1. Disposition of Patients

A total of 85 patients were enrolled in the study and were randomized to receive treatment with reboxetine (43 patients) or fluoxetine (42 patients). All of the randomized patients received at least 1 dose of study medication. Therefore, the ITT population includes 43 reboxetine-treated patients and 42 fluoxetine-treated patients.

The percentage of patients who completed the 8-week treatment period was similar among the treatment groups (65.1% reboxetine and 69.0% fluoxetine). The reasons for study discontinuation are summarized in Table 4.

**Table 4. Patient Disposition**

| | Reboxetine | | Fluoxetine | |
|---|---|---|---|---|
| | n | %* | n | %* |
| **Number of patients** | | | | |
| Randomized | 43 | 100.0 | 42 | 100.0 |
| Intent to treat | 43 | 100.0 | 42 | 100.0 |
| Completed study | 28 | 65.1 | 29 | 69.0 |
| Discontinued study | 15 | 34.9 | 13 | 31.0 |
| **Reason for discontinuation** | | | | |
| Adverse event | 5 | 11.6 | 6 | 14.3 |
| Consent withdrawn | 7 | 16.3 | 2 | 4.8 |
| Lost to follow-up | 1 | 2.3 | 2 | 4.8 |
| Protocol-specific withdrawal criteria | 0 | 0 | 1 | 2.4 |
| Lack of efficacy | 2 | 4.7 | 1 | 2.4 |
| Progression of disease | 0 | 0 | 1 | 2.4 |

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

Source: Table T1

In the reboxetine group, the most common reason for discontinuation of study medication was withdrawal of consent, which led to discontinuation of treatment in 16.3% (7/43) of reboxetine-treated patients and 4.8% (2/42) of fluoxetine-treated patients. Of the 7 reboxetine-treated patients who withdrew consent, 5 patients (patient nos. 211, 227, 256, 258, and 274) were enrolled at Dr. Lu's site and 2 patients were enrolled at other sites (patient no. 230 at Dr. Lin's site and patient no. 265 at Dr. Lee's site). According to comments on the treatment-termination CRF, patient no. 211 refused to return for the next study visit (no reason given), patient no. 227 refused to return because she disagreed with the diagnosis of MDD, patient no. 258 refused to return because she thought that she was getting better, patient no. 230 did not take the study medications as scheduled, patient no. 274 discontinued from the study because she wanted to visit another doctor for the treatment of insomnia (although insomnia was not reported as an adverse event for this patient), and patient no. 256 discontinued from the study because she was concerned about dry mouth (dry mouth was reported as an adverse event). No comments were provided on the treatment-termination CRF for patient no. 265.

In the fluoxetine group, the most common reason for discontinuation of study medication was adverse events, which led to discontinuation of treatment in 14.3% (6/42) of fluoxetine-treated patients and 11.6% (5/43) of reboxetine-treated patients. (Discontinuations due to adverse events are discussed in Section 7.4.2.3.)

Table T2 summarizes patient enrollment by investigator. The patients who prematurely discontinued from the study are listed in Appendix 3.1.

## 7.1.2. Protocol Deviations

### 7.1.2.1. Deviations From Inclusion/Exclusion Criteria or Disallowed Concomitant Medications

The occurrences of the following protocol deviations were summarized in each treatment group: (1) HAM-D total score of <22 at screen or baseline, (2) HAM-D Item 3 score of ≥3 at screen or baseline, (3) positive serum pregnancy test at screen, (4) use of disallowed psychotropic medications, and (5) positive urine drug test at screen (Table 5).

**Table 5. Protocol Deviations**

| | Reboxetine N=43 | | Fluoxetine N=42 | |
|---|---|---|---|---|
| | n | % | n | % |
| HAM-D total score <22 at screen or baseline | 1* | 2.3 | 0 | 0 |
| HAM-D Item 3 score ≥3 at screen or baseline | 3 | 7.0 | 9 | 21.4 |
| Positive serum pregnancy test at screen | 1 | 2.3 | 0 | 0 |
| Use of disallowed psychotropic medications† | 20 | 46.5 | 21 | 50.0 |
| Positive urine drug screen (other than benzodiazepines)‡ | 0 | 0 | 3 | 7.1 |

* This patient (patient no. 238) had HAM-D total scores of 31 at the screening visit and 21 at the baseline visit.
† Based on information recorded on the concomitant medication case report form
‡ The urine drug screen tested for the presence of the following: amphetamines, barbiturates, benzodiazepines, marijuana metabolites, cocaine metabolites, methadone, methaqualone, opiates, phencyclidine, and propoxyphene. However, because the use of certain benzodiazepines was allowed during the study (and the urine drug screen does not distinguish between allowed and disallowed benzodiazepines), positive results for benzodiazepines are not counted in this table.
Source: Appendices 3.2 and 3.8.6

Although the protocol specified that female patients who had a positive serum pregnancy test at screen were to be excluded from the study, 1 patient (patient no. 298 in the reboxetine group) had a positive test at screen and at baseline. This patient had been pregnant and had undergone a dilatation and curettage procedure approximately 1 month before the screening visit. Before the patient was enrolled in the study, an ultrasound examination was performed, which confirmed that the pregnancy had been terminated. Therefore, the elevated HCG value was attributed to the previously terminated pregnancy, and the patient was enrolled in the study. At the end of the study (week 8), the pregnancy test result was negative for this patient.

Although, the protocol specified that patients who had a HAM-D Item-3 score of ≥3 at the screen or baseline visit were to be excluded from the study, 3 reboxetine-treated patients (patient nos. 272, 277, 288) and 9 fluoxetine-treated patients (patient nos. 219, 225, 226, 229, 257, 271, 279, 287, 289) who had HAM-D Item-3 scores of ≥3 at the screen or baseline visits were enrolled in the study. All 12 patients were enrolled at a single study site (Dr. Lu). Comments on the CRF indicated that the investigator considered suicidal ideation to be characteristic of major depression and not a reason to exclude the patient from the study. None of the 12 patients who had HAM-D Item 3 scores of ≥3 at the screen or baseline visits and were enrolled in the study attempted suicide during the study.

The protocol specified that no concomitant psychotropic medications other than temazepam, lorazepam, flurazepam, estazolam, and oxazepam, which could be administered as sleep inducers on an as-needed basis, were allowed during the study. However, concomitant use of disallowed psychotropic medications were reported in 46.5% (20/43) of reboxetine-treated patients and 50.0% (21/42) of fluoxetine-treated patients (based on information recorded on the concomitant medication CRF). Of the 20 reboxetine-treated patients and 21 fluoxetine-treated patients who used disallowed concomitant medications, approximately half of the patients (8 reboxetine-treated patients and 13 fluoxetine-treated patients) were enrolled at the same study site (Dr. Lu). The concomitant psychotropic medications that were used were primarily short-acting benzodiazepines other than the benzodiazepines that were specifically allowed by the protocol (Table T10.2). In approximately half of the cases, the disallowed concomitant medications were used for the same purpose (sedative/hypnotic) as were the allowed benzodiazepines. No evidence of the concomitant use of antidepressant medications (other than the study medications) was observed during the study.

Other than benzodiazepines (which were discussed above based on information recorded on the concomitant medication CRF), the only drugs that were detected on the urine drug screen were marijuana metabolites, which were detected in 1 fluoxetine-treated patient (patient no. 271 at screen and day 28), and opiates, which were detected in 2 fluoxetine-treated patients (patient no. 269 at screen and patient no. 208 at day 56).

Patients who met the criteria for protocol deviations are listed with their adverse event profiles in Appendix 3.2. Concomitant medications that were taken during the study are listed in Table T10.2, and positive urine drug screen results are listed in Appendix 3.8.6.

### 7.1.2.2. Deviations From Planned Trial Conduct

The protocol specified that the efficacy scales, including the HAM-D, CGI, and SASS, were to be administered during the in-clinic study visits. However, at 3 of the 5 study sites, the efficacy scales were administered via telephone interviews when patients were unable to return to the clinic for a scheduled study visit. As summarized in Table 6, telephone interviews were conducted for 13 patients and accounted for a total of 18 study visits.

**Table 6. Study Visits at Which Efficacy Scales Were Administered Via Telephone Interviews**

| Investigator | Patient No. | Treatment Group | Study Visit (Day)* |
|---|---|---|---|
| Chiu | 295 | FLX | 14 and 42 |
| Lee | 247 | RBX | 42 |
| | 264 | FLX | 42 |
| Lu | 210 | FLX | 21 |
| | 211 | RBX | 7 and 56 |
| | 212 | FLX | 7 |
| | 215 | FLX | 14 and 21 |
| | 216 | RBX | 7 |
| | 222 | RBX | 28 |
| | 224 | RBX | 21 |
| | 275 | FLX | 56 |
| | 276 | RBX | 42 and 56 |
| | 277 | RBX | 42 and 56 |

* Study visit at which the efficacy scales were administered via telephone interviews.
Abbreviations: FLX = fluoxetine, RBX = reboxetine

To determine whether the use of telephone interviews affected the efficacy results, 2 separate analyses of the data from the HAM-D, CGI, and SASS scales were conducted. The first analysis included data for all visits (those conducted in the clinic or via telephone interviews), whereas the second analysis excluded the data that were collected during telephone interviews. The results of both analyses are included in the Tables section of this report.

## 7.1.3. Data Sets Analyzed

The ITT population includes all patients who were randomized into the trial and who received at least 1 dose of study medication. All of the 85 randomized patients received at least 1 dose of study medication. Therefore, the ITT population includes 43 reboxetine-treated patients and 42 fluoxetine-treated patients (Table T1).

All analyses were based on the ITT population. Efficacy analyses were based on the population of ITT patients who had at least one postbaseline evaluation for the specified efficacy measure (eg, HAM-D, CGI).

## 7.1.4. Demographic and Other Baseline Characteristics

### 7.1.4.1. Demographic Characteristics

No statistically significant differences were noted among the treatment groups in the age, sex, or race of patients at screen. The patients in the study ranged in age from 19 to 64 years. All of the patients were Asian, and the majority (>60%) of the patients were female. Selected demographic characteristics are compared by treatment group in Table 7.

**Table 7. Patient Demographics at Screen**

| Variable | | Reboxetine N=43 | Fluoxetine N=42 | P Value* |
|---|---|---|---|---|
| Age, years | Mean ± SD | 40.65 ± 14.57 | 35.98 ± 12.70 | 0.119 |
| | Range | 19.0 - 64.2 | 19.6 - 62.0 | |
| Sex: n (%) | Male | 16 (37.2%) | 16 (38.1%) | 0.933 |
| | Female | 27 (62.8%) | 26 (61.9%) | |
| Race: n(%) | Asian or Pacific Islander | 43 (100%) | 42 (100%) | -- |

* P values for continuous variables are based on a 1-way ANOVA with treatment as the main effect; p values for categorical variables are based on a chi-square test.

Source: Table T3

No statistically significant differences were noted between the treatment groups in the other continuous (eg, height or weight) or categorical (eg, patient's educational background, occupation, living situation, or current employment status) demographic characteristics that were assessed at screen. Likewise, no statistically significant differences were noted between the treatment groups in the mean systolic or diastolic blood pressure or pulse rate values at baseline (Table T3).

No statistically significant differences were noted between the treatment groups in the proportion of patients who had normal or abnormal physical examinations (Table T6). Although statistical testing was not performed, the findings for medical histories were generally similar between the 2 treatment groups (Table T7).

Appendix 3.4 contains a listing of demographic data by subject.

### 7.1.4.2. Psychiatric History

#### *7.1.4.2.1. Previous History of Depression*

No statistically significant differences were noted between the treatment groups in the mean age of patients at the onset of their first depressive episode, in the mean number of previous depressive episodes, or in the mean duration of the previous episode. Likewise, no statistically significant differences were noted between the treatment groups in the number of patients who were previously hospitalized for depression or in the mean age of patients at the time of their first hospitalization. Although a statistically significant difference was noted between the treatment groups in the mean number of previous hospitalizations for depression, this difference is considered to be of little relevance because of the small number of patients on which it is based (4 patients in the reboxetine group and 1 patient in the fluoxetine group) (Table 8).

**Table 8. Previous History of Depression**

| Variable | Reboxetine N=43 | Fluoxetine N=42 | P Value† |
|---|---|---|---|
| **Age (years) at onset of major depression** | | | |
| n | 42 | 42 | 0.077 |
| Mean ± SD | 37.7 ± 15.0 | 32.4 ± 12.2 | |
| Range | 17 - 63 | 15 - 56 | |
| **Number of previous episodes** | | | |
| n | 38 | 41 | 0.549 |
| Mean ± SD | 0.9 ± 1.8 | 1.2 ± 2.6 | |
| Range | 0 - 10 | 0 - 15 | |
| **Approximate duration of last episode (weeks)** | | | |
| n | 17 | 22 | 0.663 |
| Mean ± SD | 29.2 ± 47.5 | 23.8 ± 28.6 | |
| Range | 0.0 - 182.0 | 1.0 - 104.0 | |
| **Previous hospitalization for depression** | | | |
| No. (%) of patients who were ever hospitalized | 4 (9.3%) | 1 (2.4%) | 0.175 |
| **No. of hospitalizations** | | | 0.010* |
| n | 4 | 1 | |
| Mean ± SD | 1.8 ± 1.0 | 8.0 ± NA | |
| Range | 1 - 3 | 8 - 8 | |
| **Age at first hospitalization** | | | 0.846 |
| n | 3 | 1 | |
| Mean ± SD | 42.0 ± 19.7 | 47.0 ± NA | |
| Range | 21 - 60 | 47 - 47 | |

* p≤0.05

† P values for continuous variables are based on a 1-way ANOVA with treatment as the main effect; p values for categorical variables are based on a chi-square test.

Source: Table T4

### *7.1.4.2.2. Previous Use of Psychotropic Medication Other Than Antidepressants*

No statistically significant differences were noted among treatment groups in the previous use of psychotropic medications other than antidepressants. The most commonly used psychotropic medications other than antidepressants were benzodiazepines, which were previously used by 46.5% (20/43) of reboxetine-treated patients and 47.6% (20/42) of fluoxetine-treated patients (Table 9).

**Table 9. Previous Use of Psychotropic Medication Other Than Antidepressants**

| Variable | Reboxetine N=43 | | Fluoxetine N=42 | | P Value* |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Any psychotropic medication other than antidepressants | 19 | 44.2 | 22 | 52.4 | 0.385 |
| Benzodiazepines | 20 | 46.5 | 20 | 47.6 | 0.573 |
| Anti-psychotics | 0 | 0 | 1 | 2.4 | |
| Other | 2 | 4.7 | 3 | 7.1 | |

* P values are based on a chi-square test.

Source: Table T4

### *7.1.4.2.3. Characteristics of the Present Depressive Episode*

No statistically significant differences were noted among the treatment groups at screen in the other characteristics of the present depressive episode (Table 10). The majority (>60%) of patients in each treatment group were receiving no treatment immediately prior to screen. The mean duration of the present depressive episode was 24 weeks in the reboxetine group and 23 weeks in the fluoxetine group. The present episode was diagnosed as a recurrent episode in approximately half of the patients in each treatment group (48.8% in the reboxetine group and 54.8% in the fluoxetine group).

**Table 10. Characteristics of the Present Depressive Episode**

| Variable | Reboxetine N=43 | Fluoxetine N=42 | P Value* |
|---|---|---|---|
| **No. (%)† of patients by treatment status immediately prior to screen** | | | |
| No treatment | 27 (62.8) | 26 (61.9) | 0.720 |
| Outpatient treatment only | 14 (32.6) | 14 (33.3) | |
| Partial hospitalization (day treatment) | 0 | 1 (2.4) | |
| Inpatient treatment | 2 (4.7) | 1 (2.4) | |
| **Approximate duration of present episode** | | | |
| Mean ±SD (weeks) | 23.86 (33.97) | 22.87 (34.45) | 0.8936 |
| Range (weeks) | 0.7 - 104.0 | 0.4 - 208.0 | |
| **No. (%)† of patients whose present episode was diagnosed as:** | | | |
| Single episode | 22 (51.2) | 19 (45.2) | 0.5847 |
| Recurrent episode | 21 (48.8) | 23 (54.8) | |
| **No. (%)† of patients whose present episode was best characterized as:** | | | |
| Exacerbation of chronic condition | 9 (20.9) | 2 (4.8) | 0.0908 |
| Recurrence of similar previous conditions | 15 (34.9) | 21 (50.0) | |
| Significantly different from any previous conditions | 0 | 1 (2.4) | |
| First occurrence, no previous psychiatric diagnosis | 19 (44.2) | 18 (42.9) | |

* P values for continuous variables are based on a 1-way ANOVA with treatment as the main effect; p values for categorical variables are based on a chi-square test.

Source: Tables T4, T5

### *7.1.4.2.4. Severity of Depression at Baseline*

No statistically significant differences were noted among the treatment groups in the severity of depression at baseline, as judged by the mean total scores for the HAM-D, the CGI Severity of Illness, or the SASS (Table 11). A statistically significant difference was noted among the treatment groups in the mean HAM-D Item 1 score at baseline, which was lower in the reboxetine group (2.5) than in the fluoxetine group (2.8).

**Table 11. Severity of Depression at Baseline**

| Variable | Reboxetine N=43 | Fluoxetine N=42 | P Value† |
|---|---|---|---|
| **HAM-D total score** | | | |
| No. of patients | 43 | 42 | |
| Mean ± SD | 27.2 ± 5.4 | 28.3 ± 5.3 | 0.3440 |
| Range | 21 - 43 | 22 - 41 | |
| **HAM-D Item 1 score** | | | |
| No. of patients | 43 | 42 | |
| Mean ± SD | 2.5 ± 0.7 | 2.8 ± 0.8 | 0.0423* |
| Range | 1 - 4 | 1 - 4 | |
| **CGI Severity of Illness score** | | | |
| No. of patients | 43 | 42 | |
| Mean ± SD | 4.7 ± 0.9 | 4.9 ± 1.1 | 0.3016 |
| Range | 3 - 7 | 2 - 7 | |
| **SASS total score** | | | |
| No. of patients | 42 | 42 | |
| Mean ± SD | 26.8 ± 8.1 | 27.4 ± 7.9 | 0.7144 |
| Range | 7 - 45 | 15 - 44 | |

* $p \leq 0.05$

† P values are based on a 1-way ANOVA with treatment as the main effect

Abbreviations: CGI = Clinical Global Impression, HAM-D = Hamilton Rating Scale for Depression, SASS = Social Adaptation Self-evaluation Scale

Source: Table T8

## 7.1.5. Concomitant Medications and Other Therapies

### 7.1.5.1. Prior to the Study

At the screening evaluation, similar percentages of patients in each treatment group were taking at least one medication: 90.7% (39/43) of patients in the reboxetine group and 92.9% (39/42) of patients in the fluoxetine group. The medications that were taken most frequently (≥5% in any treatment group) were as follows: alprazolam, clonazepam, diclofenac sodium, estazolam, flurazepam, lorazepam, magnesium oxide, paracetamol, and zolpidem. Medications that were taken prior to the study are summarized in Table T9.1.

### 7.1.5.2. During the Treatment Period

Non-investigational medications were taken concomitantly with the study medication by similar percentages of patients in each treatment group: 93.0% (40/43) of patients in the reboxetine group and 97.6% (41/42) of patients in the fluoxetine group (Table T10.1). The medications that were taken most frequently (≥5% in any treatment group) were as follows: alprazolam, bisacodyl, bromazepam, calcium carbonate, clonazepam, diclofenac sodium, dimeticone, estazolam, flurazepam, flurazepam hydrochloride, lorazepam, hydrotalcite, magnesium hydroxide, magnesium oxide, oxazolam, paracetamol, zolpiclone, and zolpidem. Medications that were taken during the study are summarized in Table T10.1.

The concomitant use of psychotropic medications other than temazepam, lorazepam, flurazepam, estazolam, and oxazepam was not allowed during the study. The use of disallowed concomitant medications during the study is presented in Section 7.1.2, Protocol Deviations.

## 7.2. Dosage Information

### 7.2.1. Extent of Exposure

The mean daily doses of study medication are presented by visit in Table 12. These mean-dosing data suggest that most patients complied with the dosing regimens that were specified in the protocol for the reboxetine group (8 mg/day, weeks 1-4; 8-10 mg/day, weeks 5-8) and for the fluoxetine group (20 mg/day, weeks 1-4; 20-40 mg/day, weeks 5-8). Approximately 16% of the reboxetine-treated patients and 32% of the fluoxetine-treated patients who remained in the study were escalated during weeks 4 to 6 of the study (Appendix 3.5).

**Table 12. Mean Daily Dose by Visit**

| Study Week | Reboxetine | | Fluoxetine | |
|---|---|---|---|---|
| | No. of Patients | Mean Dose* (mg/day) | No. of Patients | Mean Dose* (mg/day) |
| 1 | 43 | 7.48 | 42 | 18.24 |
| 2 | 39 | 7.28 | 36 | 19.00 |
| 3 | 35 | 7.80 | 36 | 18.37 |
| 4 | 34 | 7.75 | 34 | 19.27 |
| 6 | 32 | 8.14 | 31 | 24.83 |
| 8 | 29 | 8.08 | 30 | 26.76 |

* Mean daily dose was based on the average dose for all patients who took the study medication between the preceding visit and the specified visit.

Source: Table T11

The majority of the patients in both treatment groups showed acceptable treatment compliance, defined as an overall drug intake of at least 80% of the prescribed amount. In the reboxetine group, unacceptable compliance was noted in 3 patients (patient nos. 211, 220, and 297), whose mean daily doses were <6 mg for at least 2 consecutive weeks. Likewise, in the fluoxetine group, unacceptable compliance was noted in 4 patients (patient nos. 203, 215, 232, and 259), whose mean daily doses were <16 mg for at least 2 consecutive weeks. Two additional fluoxetine-treated patients (patient nos. 223 and 289) who discontinued from the study after 1 week had mean daily doses of <16 mg during the 1 week when they were enrolled in the study.

Appendix 3.5 contains a listing of the mean daily dose for each patient.

## 7.3. Efficacy Results

### 7.3.1. Data Sets Analyzed

Efficacy analyses were based on the population of ITT patients who had at least one postbaseline evaluation for the specified efficacy measure (eg, HAM-D, CGI). As discussed in Section 7.1.2.2, 2 separate analyses of the data from the HAM-D, CGI, and SASS scales were conducted: the first analysis included data for all visits (those conducted in the clinic or via telephone interviews) and the second analysis excluded the data that were collected during telephone interviews. The discussion of efficacy results in the following sections focuses on the results of the first analysis and briefly summarizes the results of the second analysis. The full results of both analyses are included in the Tables section.

### 7.3.2. Primary Efficacy Variable

#### 7.3.2.1. Analysis of Data From All Visits

The mean change from baseline in the HAM-D total score was similar in the reboxetine and fluoxetine groups at each postbaseline evaluation in the LOCF analysis. For example, the mean change from baseline in the HAM-D total score was -8.18 in the reboxetine group and -7.35 in the fluoxetine group at day 14, -10.79 in the reboxetine group and -11.50 in the fluoxetine group at day 28, and -14.05 in the reboxetine group and -14.78 in the fluoxetine group at day 56. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Table 13).

At the end of the study (day 56), the difference between the treatment groups in the mean change from baseline in the LOCF analysis was 0.72 (lower limit of 90% CI, -2.19). This difference was not considered to be clinically significant because the difference was less than 2 points. Likewise, the difference was not considered to be statistically significant because the lower limit of the 90% CI was <0 (Table 13). These results indicate that the reboxetine and fluoxetine groups were comparable on the primary endpoint, the mean change from baseline in the HAM-D total score at day 56 in the LOCF analysis.

Consistent with the results of the LOCF analyses, no clinically or statistically significant differences were observed between the treatment groups in the OC analysis of the mean change from baseline in the HAM-D total score at each postbaseline evaluation (Table 13). At the end of the study (day 56), the mean change from baseline in the HAM-D total score was -16.57 in the reboxetine group and -17.10 in the fluoxetine group, based on the OC analysis.

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

| | | | Study Visit | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Baseline | | Day 7 | | Day 14 | | Day 21 | | Day 28 | | Day 42 | | Day 56 | |
| | | | n | Mean | N | X* | n | X* | n | X* | n | X* | n | X* | n | X* |
| LOCF | Mean Change | RBX | 43 | 27.23 | 38 | -5.53 | 38 | -8.18 | 38 | -9.34 | 38 | -10.79 | 38 | -13.34 | 38 | -14.05 |
| | | FLX | 42 | 28.33 | 39 | -6.54 | 40 | -7.35 | 40 | -8.93 | 40 | -11.50 | 40 | -13.60 | 40 | -14.78 |
| | Statistic | Difference† | -- | | 1.01 | | -0.83 | | -0.42 | | 0.71 | | 0.26 | | 0.72 | |
| | | LL 90% CI | -- | | -0.65 | | -3.06 | | -3.06 | | -1.78 | | -2.52 | | -2.19 | |
| | | P-Value‡ | -- | | 0.7117 | | 0.3709 | | 0.5631 | | 0.8373 | | 0.6875 | | 0.9711 | |
| Observed Cases | Mean Change | RBX | 43 | 27.23 | 38 | -5.53 | 37 | -8.05 | 35 | -9.63 | 34 | -11.59 | 29 | -16.00 | 28 | -16.57 |
| | | FLX | 42 | 28.33 | 39 | -6.54 | 36 | -7.81 | 34 | -10.44 | 32 | -13.47 | 31 | -16.13 | 29 | -17.10 |
| | Statistic | Difference† | -- | | 1.01 | | -0.25 | | 0.81 | | 1.88 | | 0.13 | | 0.53 | |
| | | LL 90% CI | -- | | -0.65 | | -2.58 | | -1.97 | | -0.60 | | -2.70 | | -2.43 | |
| | | P-Value‡ | -- | | 0.7117 | | 0.5938 | | 0.9367 | | 0.4132 | | 0.6411 | | 0.8785 | |

* Mean change from baseline value.
† Mean change in the reboxetine group minus the mean change in the fluoxetine group.
‡ P values are based on a ANOVA Type III sum of squares, adjusting for investigator.
Abbreviations: ANOVA = analysis of variance, CI = confidence interval, FLX= fluoxetine, HAM-D = Hamilton Rating Scale for Depression, LL = lower limit, LOCF = last observation carried forward, RBX = reboxetine
Source: Tables T12.1, T12.2, T12.3, T12.4

#### 7.3.2.2. Exclusion of Data From Telephone Interviews

When the analysis of the mean change from baseline in the HAM-D total score was repeated to exclude the data that were collected via telephone interviews, the results remained consistent with the results of the original analysis.

Excluding the data from the telephone interviews, the mean change from baseline in the HAM-D total score was similar in the reboxetine and fluoxetine groups at each postbaseline evaluation in the LOCF analysis. For example, the mean change from baseline in the HAM-D total score was -8.18 in the reboxetine group and -7.20 in the fluoxetine group at day 14, -10.71 in the reboxetine group and -11.50 in the fluoxetine group at day 28, and -13.63 in the reboxetine group and -14.78 in the fluoxetine group at day 56 (excluding data from telephone interviews). None of the differences between the reboxetine and fluoxetine groups were statistically significant (Tables T12.5, T12.6, T12.7, T12.8).

At the end of the study (day 56), the difference between the treatment groups in the mean change from baseline in the LOCF analysis (excluding data from telephone interviews) was 1.14 (lower limit of 90% CI, -1.76). As in the original analysis, the difference between the treatment groups was not considered to be either clinically significant (because the difference was <2) or statistically significant (because the lower limit of the 90% CI was <0).

### 7.3.3. Secondary Efficacy Variables

#### 7.3.3.1. HAM-D Response Rate

##### *7.3.3.1.1. Analysis of Data From All Visits*

The HAM-D response rate was similar in the reboxetine and fluoxetine groups at the postbaseline evaluations in the LOCF analysis. For example, the HAM-D response rate was 26.3% in the reboxetine group and 17.5% in the fluoxetine group at day 14, 34.2% in the reboxetine group and 45.0% in the fluoxetine group at day 28, and 55.3% in the reboxetine group and 57.5% in the fluoxetine group at day 56. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Table 14).

Consistent with the results of the LOCF analyses, the HAM-D response rate was similar in the reboxetine and fluoxetine groups in the OC analysis. None of the differences between the reboxetine and fluoxetine groups were statistically significant. At the end of the study (day 56), the HAM-D response rate was 67.9% in the reboxetine group and 65.5% in the fluoxetine group, based on the OC analysis (Table 14).

**Table 14. HAM-D Response* Rate**

| Type of Analysis | Treatment Group or Statistic | Study Visit | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 7 | | Day 14 | | Day 21 | | Day 28 | | Day 42 | | Day 56 | |
| | | n | % | n | % | n | % | n | % | n | % | n | % |
| LOCF | RBX | 3 | 7.9 | 10 | 26.3 | 13 | 34.2 | 13 | 34.2 | 17 | 44.7 | 21 | 55.3 |
| | FLX | 3 | 7.7 | 7 | 17.5 | 12 | 30.0 | 18 | 45.0 | 21 | 52.5 | 23 | 57.5 |
| | P-Value† | 0.9821 | | 0.3893 | | 0.7615 | | 0.3233 | | 0.4009 | | 0.6972 | |
| Observed Cases | RBX | 3 | 7.9 | 9 | 24.3 | 12 | 34.3 | 12 | 35.3 | 16 | 55.2 | 19 | 67.9 |
| | FLX | 3 | 7.7 | 7 | 19.4 | 12 | 35.3 | 17 | 53.1 | 19 | 61.3 | 19 | 65.5 |
| | P-Value† | 0.9821 | | 0.6840 | | 0.8242 | | 0.1403 | | 0.5465 | | 0.9840 | |

* Response was defined as a decrease of ≥50% in the 21-Item HAM-D total score versus baseline.

† P values are based on a Cochran-Mantel-Haenszel test, adjusting for investigator

Abbreviations: FLX= fluoxetine, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, RBX = reboxetine

Source: Tables T13.1, T13.2

#### *7.3.3.1.2. Exclusion of Data From Telephone Interviews*

When the analysis of the HAM-D response rate was repeated to exclude the data that were collected via telephone interviews, the results remained consistent with the results of the original analysis. Excluding the data from the telephone interviews, the HAM-D response rate was 26.3% in the reboxetine group and 17.5% in the fluoxetine group at day 14, 34.2% in the reboxetine group and 45.0% in the fluoxetine group at day 28; and 55.3% in the reboxetine group and 57.5% in the fluoxetine group at day 56 in the LOCF analysis. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Tables T13.3, T13.4).

### 7.3.3.2. HAM-D Remission Rate

#### *7.3.3.2.1. Analysis of Data From All Visits*

The HAM-D remission rate was similar in the reboxetine and fluoxetine groups at the postbaseline evaluations in the LOCF analysis. The HAM-D remission rate was 5.3% in the reboxetine group and 10.0% in the fluoxetine group at day 14, 15.8% in the reboxetine group and 27.5% in the fluoxetine group at day 28, and 36.8% in the reboxetine group and 40.0% in the fluoxetine group at day 56. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Table 15).

Consistent with the results of the LOCF analyses, the HAM-D remission rate was similar in the reboxetine and fluoxetine groups in the OC analysis. None of the differences between the reboxetine and fluoxetine groups were statistically significant. At the end of the study (day 56), the HAM-D remission rate was 50.0% in the reboxetine group and 48.3% in the fluoxetine group, based on the OC analysis (Table 15).

**Table 15. HAM-D Remission* Rate**

| Type of Analysis | Treatment Group or Statistic | Study Visit | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 7 | | Day 14 | | Day 21 | | Day 28 | | Day 42 | | Day 56 | |
| | | n | % | n | % | n | % | n | % | n | % | n | % |
| LOCF | RBX | 1 | 2.6 | 2 | 5.3 | 4 | 10.5 | 6 | 15.8 | 13 | 34.2 | 14 | 36.8 |
| | FLX | 1 | 2.6 | 4 | 10.0 | 8 | 20.0 | 11 | 27.5 | 15 | 37.5 | 16 | 40.0 |
| | P-Value† | 0.9433 | | 0.3952 | | 0.1409 | | 0.1164 | | 0.5691 | | 0.5929 | |
| Observed Cases | RBX | 1 | 2.6 | 2 | 5.4 | 4 | 11.4 | 6 | 17.6 | 13 | 44.8 | 14 | 50.0 |
| | FLX | 1 | 2.6 | 4 | 11.1 | 8 | 23.5 | 10 | 31.3 | 14 | 45.2 | 14 | 48.3 |
| | P-Value† | 0.9433 | | 0.3856 | | 0.0789 | | 0.0985 | | 0.8097 | | 0.9827 | |

* Remission was defined as a total score of ≤10 on the 21-Item HAM-D.
† P values are based on a Cochran-Mantel-Haenszel test, adjusting for investigator
Abbreviations: FLX= fluoxetine, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, RBX = reboxetine
Source: Tables T14.1, T14.2

#### *7.3.3.2.2. Exclusion of Data From Telephone Interviews*

When the analysis of the HAM-D remission rate was repeated to exclude the data that were collected via telephone interviews, the results remained consistent with the results of the original analysis. Excluding the data from the telephone interviews, the HAM-D remission rate was 5.3% in the reboxetine group and 10.0% in the fluoxetine group at day 14, 15.8% in the reboxetine group and 27.5% in the fluoxetine group at day 28; and 34.2% in the reboxetine group and 40.0% in the fluoxetine group at day 56 in the LOCF analysis. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Tables T14.3, T14.4).

### 7.3.3.3. CGI Severity of Illness

#### *7.3.3.3.1. Analysis of Data From All Visits*

The mean change from baseline in the CGI Severity of Illness score was similar in the reboxetine and fluoxetine groups at the postbaseline evaluations in the LOCF analysis. For example, the mean change from baseline in the CGI Severity of Illness score was -1.0 in the reboxetine group and -0.8 in the fluoxetine group at day 14, -1.4 in the reboxetine group and -1.5 in the fluoxetine group at day 28, and -2.0 in the reboxetine group and -2.1 in the fluoxetine group at day 56. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Table 16).

Consistent with the results of the LOCF analyses, the mean change from baseline in the CGI Severity of Illness score was similar in the reboxetine and fluoxetine groups in the OC analysis. None of the differences between the reboxetine and fluoxetine groups were statistically significant. At the end of the study (day 56), the mean change from baseline in the CGI Severity of Illness score was -2.3 in both the reboxetine and fluoxetine groups, based on the OC analysis (Table 16).

**Table 16. Mean Change From Baseline in the CGI Severity of Illness Score**

| Type of Analysis | Treatment Group or Statistic | Study Visit | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | | Day 7 | | Day 14 | | Day 21 | | Day 28 | | Day 42 | | Day 56 | |
| | | n | Mean | n | X* | n | X* | n | X* | n | X* | n | X* | n | X* |
| LOCF | RBX | 43 | 4.7 | 38 | -0.3 | 38 | -1.0 | 38 | -1.1 | 38 | -1.4 | 38 | -1.7 | 38 | -2.0 |
| | FLX | 42 | 4.9 | 39 | -0.6 | 40 | -0.8 | 40 | -1.2 | 40 | -1.5 | 40 | -1.7 | 40 | -2.1 |
| | P-Value† | -- | | 0.6023 | | 0.1509 | | 0.6864 | | 0.6814 | | 0.3338 | | 0.5303 | |
| Observed Cases | RBX | 43 | 4.7 | 38 | -0.3 | 37 | -1.0 | 35 | -1.1 | 34 | -1.5 | 29 | -2.0 | 28 | -2.3 |
| | FLX | 42 | 4.9 | 39 | -0.6 | 36 | -0.9 | 34 | -1.4 | 32 | -1.7 | 31 | -2.0 | 29 | -2.3 |
| | P-Value† | -- | | 0.6023 | | 0.2158 | | 0.9488 | | 0.9894 | | 0.3191 | | 0.3900 | |

* Mean change from baseline value.
† P values are based on a ANOVA Type III sum of squares, adjusting for investigator.
Abbreviations: ANOVA = analysis of variance, CGI = Clinical Global Impression, FLX= fluoxetine, LOCF = last observation carried forward, RBX = reboxetine
Source: Tables T18.1, T18.2, T18.3, T18.4

#### *7.3.3.3.2. Exclusion of Data From Telephone Interviews*

When the analysis of the mean change from baseline in the CGI Severity of Illness score was repeated to exclude the data that were collected via telephone interviews, the results remained consistent with the results of the original analysis. Excluding the data from the telephone interviews, the mean change from baseline in the CGI Severity of Illness score was -1.0 in the reboxetine group and -0.8 in the fluoxetine group at day 14, -1.4 in the reboxetine group and -1.5 in the fluoxetine group at day 28, and -1.9 in the reboxetine group and -2.1 in the fluoxetine group at day 56 in the LOCF analysis. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Tables T18.5, T18.6, T18.7, and T18.8).

### 7.3.3.4. CGI Global Improvement Response Rate

#### *7.3.3.4.1. Analysis of Data From All Visits*

The CGI Global Improvement response rate was similar in the reboxetine and fluoxetine groups at the postbaseline evaluations in the LOCF analysis. For example, the CGI Global Improvement response rate was 34.2% in the reboxetine group and 35.0% in the fluoxetine group at day 14, 52.6% in the reboxetine group and 62.5% in the fluoxetine group at day 28, and 71.1% in the reboxetine group and 70.0% in the fluoxetine group at day 56. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Table 17).

Consistent with the results of the LOCF analyses, the CGI Global Improvement response rate was similar in the reboxetine and fluoxetine groups in the OC analysis. None of the differences between the reboxetine and fluoxetine groups were statistically significant. At the end of the study (day 56), the CGI Global Improvement response rate was 85.7% in the reboxetine group and 79.3% in the fluoxetine group, based on the OC analysis (Table 17).

**Table 17. CGI Global Improvement Response* Rate**

| Type of Analysis | Treatment Group or Statistic | Study Visit | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 7 | | Day 14 | | Day 21 | | Day 28 | | Day 42 | | Day 56 | |
| | | n | % | n | % | n | % | n | % | n | % | n | % |
| LOCF | RBX | 4 | 10.5 | 13 | 34.2 | 17 | 44.7 | 20 | 52.6 | 24 | 63.2 | 27 | 71.1 |
| | FLX | 10 | 25.6 | 14 | 35.0 | 18 | 45.0 | 25 | 62.5 | 28 | 70.0 | 28 | 70.0 |
| | P-Value† | 0.1072 | | 0.9278 | | 0.9319 | | 0.4027 | | 0.4593 | | 0.9050 | |
| Observed Cases | RBX | 4 | 10.5 | 12 | 32.4 | 16 | 45.7 | 19 | 55.9 | 22 | 75.9 | 24 | 85.7 |
| | FLX | 10 | 25.6 | 13 | 36.1 | 17 | 50.0 | 23 | 71.9 | 25 | 80.6 | 23 | 79.3 |
| | P-Value† | 0.1072 | | 0.8056 | | 0.5476 | | 0.1928 | | 0.6355 | | 0.6175 | |

* Response was defined as a score of ≤2 (corresponding to "very much improved" or "much improved") on the CGI Global Improvement scale.

† P values are based on a Cochran-Mantel-Haenszel test, adjusting for investigator

Abbreviations: CGI = Clinical Global Impression, FLX= fluoxetine, LOCF = last observation carried forward, RBX = reboxetine

Source: Tables T17.1, T17.2

The distribution of patients by category of CGI Global Improvement score at each visit is presented in Tables T16.1 (LOCF analysis) and T16.2 (OC analysis).

#### *7.3.3.4.2. Exclusion of Data From Telephone Interviews*

When the analysis of the CGI Global Improvement response rate was repeated to exclude the data that were collected via telephone interviews, the results remained consistent with the results of the original analysis. Excluding the data from the telephone interviews, the CGI Global Improvement response rate was 34.2% in the reboxetine group and 35.0% in the fluoxetine group at day 14, 52.6% in the reboxetine group and 62.5% in the fluoxetine group at day 28; and 71.1% in the reboxetine group and 70.0% in the fluoxetine group at day 56 in the LOCF analysis. None of the differences between the reboxetine and fluoxetine groups were statistically significant (Tables T17.3, T17.4).

The distribution of patients by category of CGI Global Improvement score at each visit (excluding data from telephone interviews) is presented in Tables T16.3 (LOCF analysis) and T16.4 (OC analysis).

### 7.3.3.5. Social Adaptation Self-evaluation Scale

#### *7.3.3.5.1. Analysis of Data From All Visits*

Statistically significant differences, in favor of reboxetine over fluoxetine, were observed in the mean change from baseline in the SASS total score at days 14, 21, and 56 in the LOCF analysis (Table 18). At the end of the study (day 56), the mean change from baseline in the SASS total score was 7.3 in the reboxetine group and 3.6 in the fluoxetine group (p=0.038), based on the LOCF analysis.

Consistent with the results of the LOCF analyses, statistically significant differences, in favor of reboxetine over fluoxetine, were observed in the OC analysis of the mean change from baseline in the SASS total score at days 14, 21, and 56 (Table 18). At the end of the study (day 56), the mean change from baseline in the SASS total score was 9.1 in the reboxetine group and 4.1 in the fluoxetine group (p=0.035), based on the OC analysis.

**Table 18. Mean Change From Baseline in the SASS Total Score**

| Type of Analysis | Treatment Group or Statistic | Study Visit | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | | Day 7 | | Day 14 | | Day 21 | | Day 28 | | Day 42 | | Day 56 | |
| | | n | Mean | n | X† | n | X† | n | X† | n | X† | n | X† | n | X† |
| LOCF | RBX | 42 | 26.8 | 38 | 1.8 | 38 | 3.0 | 38 | 4.0 | 38 | 4.6 | 38 | 6.1 | 38 | 7.3 |
| | FLX | 42 | 27.4 | 39 | 0.9 | 40 | 0.9 | 40 | 1.0 | 40 | 2.5 | 40 | 3.6 | 40 | 3.6 |
| | P-Value‡ | -- | | 0.0558 | | 0.0373* | | 0.0282* | | 0.1757 | | 0.0776 | | 0.0381* | |
| Observed Cases | RBX | 42 | 26.8 | 38 | 1.8 | 37 | 3.1 | 34 | 4.4 | 34 | 5.0 | 29 | 8.0 | 28 | 9.1 |
| | FLX | 42 | 27.4 | 39 | 0.9 | 36 | 0.4 | 34 | 1.0 | 32 | 2.5 | 31 | 3.8 | 29 | 4.1 |
| | P-Value‡ | -- | | 0.0558 | | 0.0325* | | 0.0404* | | 0.1867 | | 0.0731 | | 0.0350* | |

* $p \leq 0.05$
† Mean change from baseline value.
‡ P values are based on a ANOVA Type III sum of squares, adjusting for investigator.
Abbreviations: ANOVA = analysis of variance, FLX= fluoxetine, LOCF = last observation carried forward, RBX = reboxetine, SASS = Social Adaptation Self-evaluation Scale
Source: Tables T20.1, T20.2, T20.3, T20.4

#### *7.3.3.5.2. Exclusion of Data From Telephone Interviews*

When the analysis of the mean change from baseline in the SASS total score was repeated to exclude the data that were collected via telephone interviews, the results remained consistent with the results of the original analysis. Statistically significant differences, in favor of reboxetine over fluoxetine, were observed in the mean change from baseline in the SASS total score at days 14, 21, 42, and 56 in both the LOCF and OC analyses (Tables T20.5, T20.6, T20.7, T20.8). At the end of the study (day 56), the mean change from baseline in the SASS total score (excluding data from telephone interviews) was 7.2 in the reboxetine group and 3.6 in the fluoxetine group (p=0.043) in the LOCF analysis.

### 7.3.4. Efficacy Conclusions

The results of this study demonstrate that the reboxetine and fluoxetine groups were comparable on the primary endpoint, the mean change from baseline in the HAM-D total score at day 56 in the LOCF analysis. Strong evidence of antidepressant activity was observed in both treatment groups, as demonstrated by mean change from baseline values in the HAM-D total score of -14.05 in the reboxetine group and -14.78 in the fluoxetine group (p=0.971). The difference between the treatment groups in the mean change values (0.72; lower limit of 90% CI, -2.19) was not considered to be either clinically significant (because the difference was <2) or statistically significant (because the lower limit of the 90% CI was <0).

As summarized in Table 19, the results on the primary endpoint were supported by results on the secondary measures of antidepressant efficacy. No statistically significant differences were observed between the treatment groups in the HAM-D response or remission rates, the CGI Global Improvement response rate, or the mean change from baseline in the CGI Severity of Illness score at day 56 in the LOCF analysis. Thus, the results of both the primary and secondary measures of antidepressant efficacy were consistent in demonstrating the comparable efficacy of reboxetine and fluoxetine for the treatment of patients with depression.

**Table 19. Summary of Antidepressant Efficacy Measures at Day 56 (LOCF Analysis)**

| Variable | Reboxetine N=43 | Fluoxetine N=42 | P Value |
|---|---|---|---|
| **Primary Endpoint** | | | |
| HAM-D total score, mean change from baseline | -14.05 | -14.78 | 0.971 |
| **Secondary Endpoints** | | | |
| **% Responders or Remitters** | | | |
| HAM-D Response | 55.3 | 57.5 | 0.697 |
| HAM-D Remission | 36.8 | 40.0 | 0.593 |
| CGI Global Improvement Response | 71.1 | 70.0 | 0.905 |
| **Mean Change From Baseline** | | | |
| CGI Severity of Illness | -2.0 | -2.1 | 0.530 |
| SASS total score | 7.3 | 3.6 | 0.038* |

* $p \leq 0.05$ (reboxetine superior to fluoxetine)
Abbreviations: CGI = Clinical Global Impression, HAM-D = Hamilton Rating Scale for Depression, SASS = Social Adaptation Self-evaluation Scale
Source: Tables T12.1, 12.2, 13.1, 14.1, 17.1, 18.1, 18.2, 20.1, 20.2

The results of the final secondary endpoint, the SASS total score, demonstrated that reboxetine is superior to fluoxetine for the improvement of social function. The mean change from baseline in the SASS total score was significantly greater in the reboxetine group (mean change of 7.3) than in the fluoxetine group (mean change of 3.6) at day 56 in the LOCF analysis (p=0.038).

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

## 7.4. Safety Results

### 7.4.1. Treatment-Emergent Adverse Events

#### 7.4.1.1. Brief Summary

The percentages of patients who reported at least 1 TESS or at least 1 drug-related TESS were slightly higher in the reboxetine group (86.0% TESS and 79.1% drug-related TESS) than in the fluoxetine group (78.6% TESS and 66.7% drug-related TESS) (Table 20). However, the percentage of patients who discontinued due to TESS was slightly lower in the reboxetine group (5/43, 11.6%) than in the fluoxetine group (6/42, 14.3%). Serious TESS were reported in an equal number of patients (3 patients) in each treatment group.

Table 20 presents an overview of the percentage of patients in each treatment group who had at least one TESS (overall, drug-related, or serious) or who discontinued due to a TESS.

**Table 20. Overall Summary of Treatment-Emergent Signs and Symptoms (TESS)**

| | Reboxetine N=43 | | Fluoxetine N=42 | |
|---|---|---|---|---|
| | n | % | n | % |
| Patients with at least one TESS | 37 | 86.0 | 33 | 78.6 |
| Drug-related* | 34 | 79.1 | 28 | 66.7 |
| Serious | 3 | 7.0 | 3 | 7.1 |
| Patients who discontinued due to TESS | 5 | 11.6 | 6 | 14.3 |

* TESS were considered to be drug-related if, in the opinion of the investigator, there was a reasonable possibility that the event was caused by the investigational medication.

Source: Tables T21, T24, T25.1, T26.1

### 7.4.1.2. All Treatment-Emergent Signs and Symptoms

#### *7.4.1.2.1. Treatment-Emergent Signs and Symptoms by System Organ Class*

The frequency of TESS is summarized by system organ class in Table 21. In both of the treatment groups, the most frequently reported TESS were events that were related to the gastrointestinal and nervous systems.

**Table 21. Frequency of Treatment-Emergent Signs and Symptoms (TESS) by System Organ Class**

| MedDRA System Organ Class* | Reboxetine N=43 | | Fluoxetine N=42 | |
|---|---|---|---|---|
| | n | % | n | % |
| Patients with at least one TESS | 37 | 86.0 | 33 | 78.6 |
| Gastrointestinal disorders | 28 | 65.1 | 23 | 54.8 |
| Nervous system disorders | 20 | 46.5 | 20 | 47.6 |
| General disorders and administration site conditions | 15 | 34.9 | 10 | 23.8 |
| Cardiac disorders | 12 | 27.9 | 2 | 4.8 |
| Renal and urinary disorders | 10 | 23.3 | 6 | 14.3 |
| Vascular disorders | 6 | 14.0 | 3 | 7.1 |
| Skin & subcutaneous tissue disorders | 4 | 9.3 | 3 | 7.1 |
| Ear and labyrinth disorders | 3 | 7.0 | -- | -- |
| Psychiatric disorders | 3 | 7.0 | 6 | 14.3 |
| Reproductive system and breast disorders | 3 | 7.0 | 3 | 7.1 |
| Respiratory, thoracic, and mediastinal disorders | 3 | 7.0 | -- | -- |
| Investigations | 2 | 4.7 | -- | -- |
| Blood and lymphatic system disorders | 1 | 2.3 | -- | -- |
| Eye disorders | 1 | 2.3 | 3 | 7.1 |
| Hepato-biliary disorders | 1 | 2.3 | -- | -- |
| Infections and infestations | 1 | 2.3 | 1 | 2.4 |
| Metabolism and nutrition disorders | 1 | 2.3 | 2 | 4.8 |
| Musculoskeletal, connective tissue, and bone disorders | 1 | 2.3 | 3 | 7.1 |

* Arranged in decreasing order of frequency based on the reboxetine group.
-- No patients reported this event.
Source: Table T21

Table T21 summarizes the TESS by system organ class and treatment group. The patients who reported TESS are listed in Appendix 3.7.1 (by patient) and Appendix 3.7.2 (by system organ class and preferred term).

### *7.4.1.2.2. Treatment-Emergent Signs and Symptoms by Preferred Term*

The TESS that were reported in at least 5% of the patients in any treatment group are summarized in Table 22.

**Table 22. TESS Reported in ≥5% of Patients in Either Treatment Group**

| MedDRA System Organ Class/ Preferred Term* | Reboxetine N=43 | | Fluoxetine N=42 | |
|---|---|---|---|---|
| | n | % | n | % |
| GASTROINTESTINAL DISORDERS | | | | |
| Dry mouth | 20 | 46.5 | 14 | 33.3 |
| Nausea | 8 | 18.6 | 7 | 16.7 |
| Constipation | 7 | 16.3 | 6 | 14.3 |
| Abdominal distension | 1 | 2.3 | 3 | 7.1 |
| NERVOUS SYSTEM DISORDERS | | | | |
| Hypoesthesia | 9 | 20.9 | 1 | 2.4 |
| Dizziness (excluding vertigo) | 5 | 11.6 | 6 | 14.3 |
| Paraesthesia NEC | 4 | 9.3 | 2 | 4.8 |
| Tremor NEC | 3 | 7.0 | 4 | 9.5 |
| Insomnia NEC | 3 | 7.0 | 3 | 7.1 |
| Taste disturbance | 3 | 7.0 | 1 | 2.4 |
| Headache NOS | -- | -- | 5 | 11.9 |
| Somnolence | -- | -- | 3 | 7.1 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | | |
| Shivering | 7 | 16.3 | 4 | 9.5 |
| Fatigue | 5 | 11.6 | 5 | 11.9 |
| Feeling hot | 3 | 7.0 | -- | -- |
| Chest pain NEC | 1 | 2.3 | 3 | 7.1 |
| Feeling cold | 1 | 2.3 | 3 | 7.1 |
| CARDIAC DISORDERS | | | | |
| Palpitations | 7 | 16.3 | 2 | 4.8 |
| Tachycardia NOS | 4 | 9.3 | -- | -- |
| RENAL AND URINARY DISORDERS | | | | |
| Urinary retention | 8 | 18.6 | 4 | 9.5 |
| VASCULAR DISORDERS | | | | |
| Postural hypotension | 6 | 14.0 | 2 | 4.8 |
| SKIN & SUBCUTANEOUS TISSUE DISORDERS | | | | |
| Sweating increased | 3 | 7.0 | -- | -- |
| EAR AND LABYRINTH DISORDERS | | | | |
| Vertigo NEC | 3 | 7.0 | -- | -- |

* Arranged in decreasing order of frequency based on the reboxetine group.
-- No patients reported this event.
Abbreviations: NEC = not elsewhere classified, NOS = not otherwise specified, TESS = treatment-emergent signs and symptoms
Source: Table T21

In the reboxetine group, the most frequently reported TESS (reported in at least 10% of patients) were dry mouth, nausea, constipation, hypoesthesia, dizziness, shivering, fatigue, palpitations, urinary retention, and postural hypotension.

In the fluoxetine group, the most frequently reported TESS (reported in at least 10% of patients) were dry mouth, nausea, constipation, dizziness, headache, and fatigue.

### *7.4.1.2.3. Treatment-Emergent Signs and Symptoms by Maximum Intensity*

The majority of TESS reported by patients in each treatment group were mild to moderate in intensity. Severe TESS were reported in 25.6% (11/43) of the patients in the reboxetine group and in 14.3% (6/42) of the patients in the fluoxetine group (Appendix 3.7.1). The TESS that were reported in at least 5% of the patients in any treatment group are summarized by maximum intensity in Table 23.

**Table 23. TESS Reported in ≥5% of Patients in Either Treatment Group by Maximum Intensity**

| MedDRA System Organ Class/ Preferred Term* | Reboxetine N=43 n (%) | | | Fluoxetine N=42 n (%) | | |
|---|---|---|---|---|---|---|
| | Mild | Mod | Severe | Mild | Mod | Severe |
| GASTROINTESTINAL DISORDERS | | | | | | |
| Dry mouth | 4 (9.3%) | 14 (32.6%) | 2 (4.7%) | 3 (7.1%) | 10 (23.8%) | 1 (2.4%) |
| Nausea | 5 (11.6%) | 2 (4.7%) | 1 (2.3%) | 6 (14.3%) | 1 (2.4%) | -- |
| Constipation | 3 (7.0%) | 3 (7.0%) | 1 (2.3%) | 4 (9.5%) | 2 (4.8%) | -- |
| Abdominal distension | 1 (2.3%) | -- | -- | 1 (2.4%) | 1 (2.4%) | 1 (2.4%) |
| NERVOUS SYSTEM DISORDERS | | | | | | |
| Hypoesthesia | 5 (11.6%) | 4 (9.3%) | -- | 1 (2.4%) | -- | -- |
| Dizziness (excluding vertigo) | 2 (4.7%) | 3 (7.0%) | -- | 4 (9.5%) | 2 (4.8%) | -- |
| Paraesthesia NEC | 1 (2.3%) | 3 (7.0%) | -- | 1 (2.4%) | 1 (2.4%) | -- |
| Tremor NEC | 2 (4.7%) | 1 (2.3%) | -- | 4 (9.5%) | -- | -- |
| Insomnia NEC | -- | 3 (7.0%) | -- | 3 (7.1%) | -- | |
| Taste disturbance | 2 (4.7%) | 1 (2.3%) | -- | -- | -- | 1 (2.4%) |
| Headache NOS | -- | -- | -- | 3 (7.1%) | 2 (4.8%) | -- |
| Somnolence | -- | -- | -- | 3 (7.1%) | -- | -- |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | | | | |
| Shivering | -- | 7 (16.3%) | -- | 1 (2.4%) | 3 (7.1%) | -- |
| Fatigue | 2 (4.7%) | 3 (7.0%) | -- | 5 (11.9%) | -- | -- |
| Feeling hot | 2 (4.7%) | 1 (2.3%) | -- | -- | -- | -- |
| Chest pain NEC | 1 (2.3%) | -- | -- | 2 (4.8%) | 1 (2.4%) | -- |
| Feeling cold | 1 (2.3%) | -- | -- | 3 (7.1%) | -- | -- |
| CARDIAC DISORDERS | | | | | | |
| Palpitations | 5 (11.6%) | 2 (4.7%) | -- | 2 (4.8%) | -- | -- |
| Tachycardia NOS | 4 (9.3%) | -- | -- | -- | -- | -- |
| RENAL AND URINARY DISORDERS | | | | | | |
| Urinary retention | 1 (2.3%) | 7 (16.3%) | -- | 3 (7.1%) | 1 (2.4%) | -- |
| VASCULAR DISORDERS | | | | | | |
| Postural hypotension | 2 (4.7%) | 4 (9.3%) | -- | 1 (2.4%) | 1 (2.4%) | -- |
| SKIN & SUBCUTANEOUS TISSUE DISORDERS | | | | | | |
| Sweating increased | 2 (4.7%) | 1 (2.3%) | -- | -- | -- | -- |
| EAR AND LABYRINTH DISORDERS | | | | | | |
| Vertigo NEC | 2 (4.7%) | 1 (2.3%) | -- | -- | -- | -- |

* Arranged in decreasing order of frequency based on the reboxetine group.
-- No patients reported this event.
Abbreviations: NEC = not elsewhere classified, NOS = not otherwise specified, TESS = treatment-emergent signs and symptoms
Source: Table T22

All TESS are summarized by maximum intensity in Table T22.

### *7.4.1.2.4. Treatment-Emergent Signs and Symptoms by Gender*

The TESS that were reported in ≥2 male or female patients in either treatment group are summarized by gender in Table 24.

**Table 24. TESS Reported in ≥2 Male or Female Patients in Either Treatment Group by Gender**

| MedDRA System Organ Class/ Preferred Term* | Reboxetine n (%) | | Fluoxetine n (%) | |
|---|---|---|---|---|
| | Male N=16 | Female N=27 | Male N=16 | Female N=26 |
| Patients with at least one TESS | 13 (81.3%) | 24 (88.9%) | 11 (68.8%) | 22 (84.6%) |
| GASTROINTESTINAL DISORDERS | | | | |
| Dry mouth | 8 (50.0%) | 12 (44.4%) | 6 (37.5%) | 8 (30.8%) |
| Nausea | 4 (25.0%) | 4 (14.8%) | 2 (12.5%) | 5 (19.2%) |
| Constipation | 2 (12.5%) | 5 (18.5%) | -- | 6 (23.1%) |
| Sore throat NOS | -- | 2 (7.4%) | -- | -- |
| Abdominal distension | 1 (6.3%) | -- | -- | 3 (11.5%) |
| NERVOUS SYSTEM DISORDERS | | | | |
| Hypoesthesia | 5 (31.3%) | 4 (14.8%) | -- | 1 (3.8%) |
| Dizziness (exc vertigo) | 1 (6.3%) | 4 (14.8%) | 1 (6.3%) | 5 (19.2%) |
| Paraesthesia NEC | 2 (12.5%) | 2 (7.4%) | 1 (6.3%) | 1 (3.8%) |
| Tremor NEC | 1 (6.3%) | 2 (7.4%) | 2 (12.5%) | 2 (7.7%) |
| Insomnia NEC | 2 (12.5%) | 1 (3.7%) | 1 (6.3%) | 2 (7.7%) |
| Taste disturbance | 2 (12.5%) | 1 (3.7%) | -- | 1 (3.8%) |
| Headache NOS | -- | -- | -- | 5 (19.2%) |
| Somnolence | -- | -- | 1 (6.3%) | 2 (7.7%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | | |
| Shivering | 3 (18.8%) | 4 (14.8%) | 2 (12.5%) | 2 (7.7%) |
| Fatigue | 1 (6.3%) | 4 (14.8%) | 1 (6.3%) | 4 (15.4%) |
| Feeling hot | -- | 3 (11.1%) | -- | -- |
| Chest pain NEC | 1 (6.3%) | -- | 1 (6.3%) | 2 (7.7%) |
| Feeling cold | 1 (6.3%) | -- | 3 (18.8%) | -- |
| CARDIAC DISORDERS | | | | |
| Palpitations | 4 (25.0%) | 3 (11.1%) | -- | 2 (7.7%) |
| Tachycardia NOS | 2 (12.5%) | 2 (7.4%) | -- | -- |
| RENAL AND URINARY DISORDERS | | | | |
| Urinary retention | 4 (25.0%) | 4 (14.8%) | 3 (18.8%) | 1 (3.8%) |
| VASCULAR DISORDERS | | | | |
| Postural hypotension | 4 (25.0%) | 2 (7.4%) | 1 (6.3%) | 1 (3.8%) |
| SKIN & SUBCUTANEOUS TISSUE DISORDERS | | | | |
| Sweating increased | 2 (12.5%) | 1 (3.7%) | -- | -- |
| EAR AND LABYRINTH DISORDERS | | | | |
| Vertigo NEC | 1 (6.3%) | 2 (7.4%) | -- | -- |
| EYE DISORDERS | | | | |
| Vision blurred | -- | 1 (3.7%) | -- | 2 (7.7%) |

**Table 24. TESS Reported in ≥2 Male or Female Patients in Either Treatment Group by Gender**

| MedDRA System Organ Class/ Preferred Term* | Reboxetine n (%) | | Fluoxetine n (%) | |
|---|---|---|---|---|
| | Male N=16 | Female N=27 | Male N=16 | Female N=26 |
| Patients with at least one TESS | 13 (81.3%) | 24 (88.9%) | 11 (68.8%) | 22 (84.6%) |
| PSYCHIATRIC DISORDERS | | | | |
| Hypomania | 1 (6.3%) | -- | 2 (12.5%) | -- |
| METABOLISM AND NUTRITION DISORDERS | | | | |
| Appetite decreased NOS | -- | 1 (3.7%) | -- | 2 (7.7%) |
| MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS | | | | |
| Back pain | -- | 1 (3.7%) | -- | 2 (7.7%) |

* Arranged in decreasing order of frequency based on the reboxetine group.
-- No patients reported this event.
Abbreviations: NEC = not elsewhere classified, NOS = not otherwise specified, TESS = treatment-emergent signs and symptoms
Source: Table T23

Of the TESS that were reported in ≥2 male or female reboxetine-treated patients, sore throat, dizziness, fatigue, and feeling hot were reported at least 2 times more frequently (on a percentage basis) in the reboxetine-treated female patients than in the reboxetine-treated male patients, whereas hypoesthesia, insomnia, taste disturbance, palpitations, postural hypotension, and increased sweating were reported at least 2 times more frequently in the reboxetine-treated male patients than in the reboxetine-treated female patients.

Of the TESS that were reported in ≥2 male or female fluoxetine-treated patients, constipation, abdominal distension, dizziness, headache, fatigue, palpitations, blurred vision, decreased appetite, and back pain were reported at least 2 times more frequently (on a percentage basis) in the fluoxetine-treated female patients than in the fluoxetine-treated male patients, whereas feeling cold, urinary retention, and hypomania were reported at least 2 times more frequently in the fluoxetine-treated male patients than in the fluoxetine-treated female patients.

All TESS are summarized by gender in Table T23.

### 7.4.1.3. Drug-Related Treatment-Emergent Signs and Symptoms

TESS that were judged by the investigators to have been caused by the study medication were reported in 79.1% (34/43) of reboxetine-treated patients and 66.7% (28/42) of fluoxetine-treated patients. The drug-related TESS that were reported in at least 5% of patients in any treatment group are summarized in Table 25.

**Table 25. Drug-Related* TESS Reported in ≥5% of Patients in Either Treatment Group**

| MedDRA System Organ Class/ Preferred Term† | Reboxetine N=43 | | Fluoxetine N=42 | |
|---|---|---|---|---|
| | n | % | n | % |
| Patients with at least one drug-related TESS | 34 | 79.1 | 28 | 66.7 |
| GASTROINTESTINAL DISORDERS | | | | |
| Dry mouth | 19 | 44.2 | 13 | 31.0 |
| Nausea | 7 | 16.3 | 5 | 11.9 |
| Constipation | 6 | 14.0 | 4 | 9.5 |
| NERVOUS SYSTEM DISORDERS | | | | |
| Hypoesthesia | 8 | 18.6 | 1 | 2.4 |
| Dizziness (exc vertigo) | 4 | 9.3 | 5 | 11.9 |
| Paraesthesia NEC | 4 | 9.3 | 2 | 4.8 |
| Taste disturbance | 3 | 7.0 | 1 | 2.4 |
| Tremor NEC | 1 | 2.3 | 3 | 7.1 |
| Somnolence | -- | -- | 3 | 7.1 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | | |
| Shivering | 7 | 16.3 | 4 | 9.5 |
| Feeling hot | 3 | 7.0 | -- | -- |
| Feeling cold | 1 | 2.3 | 3 | 7.1 |
| CARDIAC DISORDERS | | | | |
| Palpitations | 5 | 11.6 | 1 | 2.4 |
| Tachycardia NOS | 4 | 9.3 | -- | -- |
| RENAL AND URINARY DISORDERS | | | | |
| Urinary retention | 8 | 18.6 | 4 | 9.5 |
| VASCULAR DISORDERS | | | | |
| Postural hypotension | 5 | 11.6 | 1 | 2.4 |
| SKIN & SUBCUTANEOUS TISSUE DISORDERS | | | | |
| Sweating increased | 3 | 7.0 | -- | -- |

* TESS were considered to be drug-related if, in the opinion of the investigator, there was a reasonable possibility that the event was caused by the investigational medication.
† Arranged in decreasing order of frequency based on the reboxetine group.
-- No patients reported this event.
Abbreviations: NEC = not elsewhere classified, TESS = treatment-emergent signs and symptoms
Source: Table T24

In the reboxetine group, the most frequently reported drug-related TESS (reported in at least 10% of patients) were dry mouth, nausea, constipation, hypoesthesia, shivering, palpitations, urinary retention, and postural hypotension.

In the fluoxetine group, the most frequently reported drug-related TESS (reported in at least 10% of patients) were dry mouth, nausea, and dizziness.

All drug-related TESS are summarized by system organ class and preferred term in Table T24.

## 7.4.2. Deaths, Serious Adverse Events, and Other Significant Adverse Events

### 7.4.2.1. Deaths

No deaths were reported during this study (Table T27.4).

### 7.4.2.2. Serious Treatment-Emergent Signs and Symptoms

Serious TESS were reported in an equal number of patients (3 patients) in both of the treatment groups. The frequency of patients who experienced serious TESS is summarized in Table 26. Narrative summaries for patients who experienced serious TESS are provided in Section 7.4.2.4.

**Table 26. Frequency of Serious TESS**

| MedDRA System Organ Class/ Preferred Term* | Reboxetine N=43 | | Fluoxetine N=42 | |
|---|---|---|---|---|
| | n | % | n | % |
| Patients with at least one serious TESS | 3 | 7.0 | 3 | 7.1 |
| GASTROINTESTINAL DISORDERS | | | | |
| Appendicitis | 1 | 2.3 | -- | -- |
| Hemorrhoids | 1 | 2.3 | -- | -- |
| INVESTIGATIONS | | | | |
| Alanine aminotransferase increased | 1 | 2.3 | -- | -- |
| Aspartate aminotransferase increased | 1 | 2.3 | -- | -- |
| PSYCHIATRIC DISORDERS | | | | |
| Suicide attempt | -- | -- | 2 | 4.8 |
| RENAL AND URINARY DISORDERS | | | | |
| Calculus ureteric | -- | -- | 1 | 2.4 |

* Arranged in decreasing order of frequency based on the reboxetine group.
-- No patients reported this event.
Abbreviations: TESS = treatment-emergent signs and symptoms
Source: Table T26.1

Among the serious TESS that occurred during the study, 2 events (increased alanine aminotransferase [ALT] and increased aspartate aminotransferase [AST] in patient no. 297) were judged by the investigator to have been caused by the study medication. Narrative summaries for all patients who experienced serious TESS are provided in Section 7.4.2.4.

All serious TESS are summarized by system organ class and preferred term in Table T26.1. Patients who experienced serious TESS are listed in Tables T26.2 (by patient) and T26.3 (by system organ class and preferred term).

### 7.4.2.3. Discontinuations Due to Treatment-Emergent Signs and Symptoms

The percentage of patients who discontinued treatment due to TESS was slightly lower in the reboxetine group (11.6%; 5/43) than in the fluoxetine group (14.3%; 6/42) group. The TESS that led to discontinuation of treatment are summarized in Table 27.

**Table 27. Frequency of TESS That Led to Discontinuation of Treatment**

| MedDRA System Organ Class/ Preferred Term* | Reboxetine N=43 | | Fluoxetine N=42 | |
|---|---|---|---|---|
| | n | % | n | % |
| Patients with at least one TESS that led to discontinuation | 5 | 11.6 | 6 | 14.3 |
| PSYCHIATRIC DISORDERS | | | | |
| Hypomania | 1 | 2.3 | 2 | 4.8 |
| Suicide attempt | -- | -- | 2 | 4.8 |
| Mania | 1 | 2.3 | -- | -- |
| Panic attack | 1 | 2.3 | -- | -- |
| INVESTIGATIONS | | | | |
| Alanine aminotransferase increased | 1 | 2.3 | -- | -- |
| Aspartate aminotransferase increased | 1 | 2.3 | -- | -- |
| CARDIAC DISORDERS | | | | |
| Palpitations | 1 | 2.3 | -- | -- |
| NERVOUS SYSTEM DISORDERS | | | | |
| Headache NOS | -- | -- | 1 | 2.4 |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | | |
| Sexual dysfunction NOS | -- | -- | 1 | 2.4 |

* Arranged in decreasing order of frequency based on the reboxetine group.
-- No patients reported this event.
Abbreviations: NOS = not otherwise specified, TESS = treatment-emergent signs and symptoms
Source: Table T25.1

Most of the TESS that led to discontinuation of treatment were nonserious in nature. Serious TESS led to discontinuation of treatment in 2.3% (1/43) of reboxetine-treated patients (increased levels of ALT and AST in patient no. 297) and in 4.8% (2/42) of fluoxetine-treated patients (suicide attempt in patient nos. 223 and 299) (Table T27.3). Narrative summaries for all patients who experienced serious TESS are provided in Section 7.4.2.4.

Patients who discontinued treatment due to TESS are listed in Tables T25.2 (by patient) and T25.3 (by system organ class and preferred term). Patients who discontinued treatment due to serious TESS are listed in Table T27.2 (by patient) and T27.3 (by system organ class and preferred term).

### 7.4.2.4. Narrative Summaries

Narrative summaries for the patients who experienced serious TESS are presented below. Both the verbatim and MedDRA terms for each event are presented (MedDRA terms are shown in parentheses).

#### *7.4.2.4.1. Reboxetine*

*Patient No.:* *211*
*Investigator:* *Ru-Band Lu (No. 47044)*
*Treatment:* *Reboxetine, 8 mg daily*
*Event:* *Acute appendicitis and pelvic inflammatory disease (Appendicitis)*

This 51-year-old female patient (Tri-Service General Hospital, Taipei, Taiwan) developed acute appendicitis and pelvic inflammatory disease while enrolled in this clinical study. She had a 29-year history of depression. Other relevant medical history included treatment for a gastric ulcer approximately 2 years prior to enrollment in the study. The patient began treatment with reboxetine on 20 March 2001. On 19 April 2001, she developed acute appendicitis and pelvic inflammatory disease. She was hospitalized for an appendectomy on 21 April 2001, at which time her hemoglobin level was 12.1 g/dL and leukocyte count was 7,000/µL. At the time of the event, the patient was receiving concomitant treatment with scopolamine to relieve lower abdominal pain. She recovered from the event on 24 April 2001. Treatment with reboxetine was continued during the event. However, on 30 April 2001, the patient discontinued study medication because she refused to continue with the study. (Discontinuation was unrelated to the adverse event.) The investigator considered the adverse event to be unrelated to treatment with the study medication.

*Patient No.:* *235*
*Investigator:* *Shih-Ku Lin (No. 44699)*
*Treatment:* *Reboxetine, 8 mg daily*
*Event:* *Hemorrhoid (Hemorrhoids)*

This 43-year-old male patient (Taipei City Psychiatric Center, Taipei, Taiwan) experienced an exacerbation of hemorrhoids on 26 January 2001. He had a 5-year history of hemorrhoids and a 6-year history of depression. The patient began treatment with reboxetine on 15 December 2000. On 09 February 2001, he was hospitalized and underwent an operation for management of hemorrhoid exacerbation. The patient recovered from the event and operation. Treatment with reboxetine was continued during the hospitalization, and the patient completed the study. At the time of the event, the patient was receiving concomitant treatment with Serenal (oxazolam) and Inderal (propanolol) for anxiety, Eurodin (estazolam) and Mesyrel (trazodone) for sleep disturbance, and magnesium oxide as a laxative. The investigator considered the adverse event to be unrelated to treatment with the study medication.

*Patient No.:* *297*
*Investigator:* *Nein-Mu Chiu (No. 44700)*
*Treatment:* *Reboxetine, 8 mg daily*
*Event:* *Hepatitis (Increased ALT, Increased AST)*

This 53-year-old female patient (Chang-Gung Memorial Hospital Kaohsiung, Kaohsiung, Taiwan) suffered an acute exacerbation of hepatitis B. The patient's medical history showed that she had been a hepatitis carrier since childhood. Her liver function test results were borderline normal at the screen evaluation on 07 February 2001 (see table, below). The patient began treatment with reboxetine on 15 February 2001. On 22 March 2001 (day 28 of study treatment), the results of liver function tests showed elevated values for ALT and AST. The abnormal values were confirmed on 28 March 2001. On 01 April 2001, the study medication was discontinued due to the abnormal liver function values. On 05 April 2001, the patient was hospitalized due to poor appetite, weakness, and severe anxiety. She was discharged from the hospital on 07 April 2001. She was prescribed paroxetine for the treatment of MDD and intravenous fluids and vitamin complex (Silymarin, 150 mg) for the treatment of impaired liver function. A gastrointestinal specialist was consulted for further evaluation and management of the patient; the results of this follow-up evaluation were not reported. By 05 May 2001, the patient's liver function values had returned to levels similar to those observed at baseline. The investigator considered the adverse event to be unrelated to treatment with the study medication.

The results of liver function tests are shown below:

| Date | AST (U/L) | ALT (U/L) |
|---|---|---|
| 07 February 2001 (Screen) | 50 | 64 |
| 22 March 2001 (Day 28) | 140 | 187 |
| 28 March 2001 (Day 35) | 197 | 243 |
| 05 April 2001 | 269 | 367 |
| 12 April 2001 | 200 | 331 |
| 16 April 2001 | 250 | 380 |
| 19 April 2001 | 241 | 422 |
| 24 April 2001 | 125 | 272 |
| 28 April 2001 | 67 | 148 |
| 02 May 2001 | 49 | 85 |
| 05 May 2001 | 51 | 69 |

### *7.4.2.4.2. Fluoxetine*

*Patient No.:* *215*
*Investigator:* *Ru-band Lu (No. 47044*
*Treatment:* *Fluoxetine, 20 mg daily*
*Event:* *Ureteral stone (Calculus ureteric)*

This 53-year-old male patient (Tri-Service General Hospital, Taipei, Taiwan) developed a ureteral stone of the left ureter. He had a 2-year history of depression; no other relevant

medical history was noted. The patient began treatment with fluoxetine on 24 March 2001. On 10 May 2001, he began suffering intermittent right flank pain. On 11 May 2001, he went to the emergency room, where the following laboratory test results were noted:

| Assay | Value |
|---|---|
| **Hematology** | |
| Prothrombin time | 11.9 s / 11.3 s (international normalized ratio, 1.09) |
| Activated partial thromboplastin time | 34.2 s / 30.1 s |
| Hemoglobin | 14 g/dL |
| White blood cell count | 2820/μL |
| Platelets | 148,000/μL |
| **Chemistry** | |
| Aspartate aminotransferase | 19 IU/L |
| Alanine aminotransferase | 15 IU/L |
| Blood urea nitrogen | 18 mg/dL |
| Sodium | 136 meq/L |
| Potassium | 3.5 meq/L |
| Chloride | 108 meq/L |
| Glucose | 104 mg/dL |
| **Urinalysis** | |
| Red blood cells | 2 - 4 |
| White blood cells | 0 - 1 |
| Occult blood | 2+ |
| Protein | negative |

The patient was admitted to the genitourinary ward on 12 May 2001. The ureteral stone was managed using ureter renography, retrograde pyelography, and catheterization. The patient recovered from the event on 15 May 2001 and was discharged under stable condition on the same day. He was advised to return for outpatient follow-up. Relevant concomitant medications included Ativan (lorazepam) for insomnia, Buscopan (hyoscine) for release pain, magnesium oxide for constipation, and gentamicin for infection. Treatment with the study drug was not interrupted, and the patient completed the study. The investigator considered the adverse event to be unrelated to treatment with the study medication.

*Patient No.:* *223*
*Investigator:* *Ru-band Lu (No. 47044)*
*Treatment:* *Fluoxetine, 20 mg daily*
*Event:* *Suicide attempt (Suicide attempt)*

This 20-year-old male patient (Tri-Service General Hospital, Taipei, Taiwan) attempted suicide by slashing his left wrist with a shaving blade due to “emotional dysphoria.” He had a 2-year history of depression, with 2 previous episodes and no prior hospitalizations for depression. At baseline, his HAM-D Item-3 score was 2 (corresponding to “wishes he were dead or any thoughts of possible death to self”). He began treatment with fluoxetine on 16 April 2001. On 20 April 2001, he attempted suicide by inflicting a superficial slash wound (3 cm by 0.1 cm) to his left wrist. Medical management of the injury consisted of

covering the laceration with dressing; no sutures were required. The date of recovery of the adverse event was noted as 27 April 2001. The patient was withdrawn from the study due to the suicide attempt; his last dose of study medication was taken on 19 April 2001. At the time of the event, the patient was receiving concomitant treatment with Dalmadorm (flurazepam) for sleep disturbance, Relax Gel (mephenesin) and Surgam (tiaprofenic acid) for muscle strain, and Tarivid (ofloxacin) otic solution for otitis media. The investigator considered the adverse event to be unrelated to treatment with the study medication.

*Patient No.:* *299*
*Investigator:* *Nein-Mu Chiu (No. 44700)*
*Treatment:* *Fluoxetine, 20 mg daily*
*Event:* *Suicide attempt (Suicide attempt)*

This 23-year-old female patient (Chang-Gung Memorial Hospital Kaohsiung, Kaohsiung, Taiwan) attempted suicide by ingesting an overdose of concomitant medications that had been prescribed to her while enrolled in this clinical study. She had experienced 1 previous episode of depression within the previous year. The current episode of depression began approximately 2 months prior to the patient's admission to the study. She had no prior hospitalizations for depression. She began treatment with fluoxetine on 03 May 2001. She developed progressively worsening depression, loss of interest, loss of energy, anhedonia, poor appetite, insomnia, feelings of worthlessness, anxiety, and social withdrawal. Her HAM-D Item-3 scores increased from 1 at baseline to 3 on day 14 (16 May 2001) (see table, below). On 17 May 2001, she attempted suicide by swallowing 8 lorazepam pills, 6 flurazepam pills, and 3 estazolam pills. She was taken to the emergency room by her husband and was then admitted to the acute care ward on 18 May 2001. The patient was withdrawn from the study due to the suicide attempt; her last dose of study medication was taken on 21 May 2001. At the time of the event, the patient was receiving concomitant treatment with estazolam (4 mg, as needed) and flurazepam (60 mg, in the evening [hs]) for insomnia and lorazepam (1 mg, twice daily) for anxiety. The investigator considered the adverse event to be unrelated to treatment with the study medication.

The patient's HAM-D Item-3 scores are shown below:

| Date | HAM-D Item 3 Score | Definition of Item-3 Score |
|---|---|---|
| 02 May 2001 (Baseline) | 1 | "Feels life is not worth living" |
| 10 May 2001 (Day 7) | 2 | "Wishes he were dead or any thoughts of possible death to self" |
| 16 May 2001 (Day 14) | 3 | "Suicide ideas or gesture" |

## 7.4.3. Clinical Laboratory Evaluation

### 7.4.3.1. Hematology

#### *7.4.3.1.1. Mean Changes From Baseline*

Within the reboxetine group, no statistically significant changes from baseline were noted in the values for hemoglobin, leukocytes, platelets, or leukocyte differential (neutrophils, lymphocytes, monocytes, eosinophils, or basophils) at days 28 or 56 (Table T35). Statistically significant changes from baseline were noted in the values for erythrocytes (mean change of $0.086x10^6/\mu L$ at day 28) and hematocrit (mean changes of 1.16% and 1.34% at days 28 and 56, respectively). However, the mean values remained within normal ranges, and none of the changes was considered to be clinically meaningful.

Within the fluoxetine group, no statistically significant changes from baseline were noted in the values for hemoglobin, hematocrit, erythrocytes, or monocytes at days 28 or 56. Statistically significant changes from baseline were noted in the values for platelets (mean change of $-17{,}971/mm^3$ at day 28) and leukocytes (mean changes of -0.77 and $-0.59x10^3/\mu L$ at days 28 and 56, respectively). Statistically significant changes from baseline were also noted in the values for the following components of the leukocyte differential: segmented neutrophils (mean changes of -0.60 and $-0.62x10^3/\mu L$ at days 28 and 56, respectively), lymphocytes (mean change of 4.52% at day 56), eosinophils (mean changes of -0.054 and $-0.056x10^3/\mu L$ at days 28 and 56, respectively), and basophils (mean change of $-0.005x10^3/\mu L$ at day 56). However, the mean values remained within normal ranges, and none of the changes was considered to be clinically meaningful.

Table T35 provides summary statistics for each hematologic assay.

#### *7.4.3.1.2. Values Outside of Predefined Normal Ranges*

The majority of patients in each treatment group had postbaseline hematology values that were within the predefined normal ranges (Table T37). For all hematology assays except monocytes (absolute count), ≤25% of patients had values outside of normal ranges. Monocyte (absolute count) values that were below the predefined normal limit ($<0.20x10^3/\mu l$) were reported at day 56 in 43.5% (10/23) of the patients in the reboxetine group and 31.8% (7/22) of the patients in the fluoxetine group. However, monocyte (%) values were within normal limits in >96% of patients in each treatment group.

The frequency of patients who had hematology assay values outside of the predefined normal ranges is summarized in Table T37. Patients with postbaseline hematology assay values outside of the predefined normal ranges are listed in Appendix 3.8.4.

### 7.4.3.2. Chemistries

#### *7.4.3.2.1. Mean Changes From Baseline*

Within the reboxetine group, no statistically significant changes from baseline were noted in the values for the majority of the serum chemistry assays, including alkaline phosphatase, ALT, AST, bilirubin, blood urea nitrogen, carbon dioxide, creatinine, glucose, potassium, sodium, or uric acid at days 28 or 56 (Table T36). A statistically significant change from baseline was noted in the value for chloride, which showed a mean change of -0.74 milliequivalents/L at day 28. However, the mean value remained within the normal range, and the change was not considered to be clinically meaningful.

Within the fluoxetine group, no statistically significant changes from baseline were noted in the values for the majority of the serum chemistry assays, including ALT, AST, bilirubin, blood urea nitrogen, chloride, potassium, sodium, or uric acid. Statistically significant changes from baseline were noted in the values for alkaline phosphatase (mean change of -4.71 U/L at day 28), carbon dioxide (mean change of -1.81 milliequivalents/L at day 56), creatinine (mean change of -0.047 mg/dL at day 56), and glucose (mean change of -5.41 mg/dL at day 56). However, the mean values remained within normal ranges, and none of the changes was considered to be clinically meaningful.

Table T36 provides summary statistics for each chemistry assay.

#### *7.4.3.2.2. Values Outside of Predefined Normal Ranges*

The majority of patients in each treatment group had postbaseline chemistry values that were within the predefined normal ranges (Table T38). Fewer than 18% of patients in any treatment group had postbaseline chemistry values that were outside of normal ranges.

The percentage of patients who had renal or liver function tests that were normal at baseline but were outside the predefined limits at day 56 are summarized in Table 28.

**Table 28. Patients With Values Outside the Predefined Normal Limits* for Liver or Renal Function Tests at Day 56**

| Test | Reboxetine | | Fluoxetine | |
|---|---|---|---|---|
| | N† | n (%) | N† | n (%) |
| Alkaline phosphatase | 30 | 0 (0) | 32 | 0 (0) |
| ALT | 26 | 1 (3.8) | 29 | 1 (3.4) |
| AST | 28 | 2 (7.1) | 28 | 0 (0) |
| Total bilirubin | 29 | 2 (6.9) | 31 | 1 (3.2) |
| BUN | 29 | 1 (3.4) | 31 | 1 (3.2) |
| Creatinine | 29 | 0 (0) | 31 | 1 (3.2) |

* Predefined normal limits: alkaline phosphatase 20-225 U/L, depending on sex and age of patient; total bilirubin 0.0-1.3 mg/dL; ALT 0-48 U/L; AST 0-55 U/L, depending on age of patient; creatinine 0.5-1.4 mg/dL; BUN 7-30 mg/dL, depending on age of patient.

† No. of patients with a normal baseline value and at least one postbaseline measurement.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen

Source: Table T38

The elevated values for ALT and AST that were observed in patient no. 297 were reported as a serious TESS (see Section 7.4.2.4 for a narrative summary of this patient, who had a history of hepatitis B). With the exception of the elevated values that were reported in this patient, no clinically significant abnormal values (defined as values at least 3 times the upper limit of normal for ALT, AST, alkaline phosphatase, and bilirubin and creatinine values of at least 3.0 mg/dL) were observed.

The frequency of patients who had chemistry assay values that were outside of the predefined normal ranges is summarized in Table T38. Patients with postbaseline chemistry assay values outside of the predefined normal ranges are listed in Appendix 3.8.5.

## 7.4.4. Vital Signs

### 7.4.4.1. Mean Change From Baseline

Within both the reboxetine and fluoxetine groups, no statistically significant changes from baseline values for sitting systolic or diastolic blood pressure were observed at any postbaseline evaluation (Tables T28 and T29).

Statistically significant changes from baseline values for pulse rate were observed in both treatment groups at each postbaseline evaluation. These changes consisted of mean increases in pulse rate in the reboxetine group and mean decreases in pulse rate in the fluoxetine group. At the end of the study (day 56), the mean change from baseline pulse rate was +7.7 beats per minute in the reboxetine group and -6.4 beats per minute in the fluoxetine group (Table T30).

Within the reboxetine group, no statistically significant changes from the baseline value for body weight were observed at any postbaseline evaluation. Within the fluoxetine group, statistically significant changes from the baseline value for body weight were observed at days 21, 42, and 56. At the end of the study (day 56), the mean change from baseline body weight was +0.1 kg in the reboxetine group and -1.4 kg in the fluoxetine group (Table T31).

### 7.4.4.2. Values Outside of Predefined Normal Ranges

The majority of patients in each treatment group had values for systolic or diastolic blood pressure or pulse rate that were within the predefined normal limits. The number of patients who had values that were outside of the predefined limits for systolic or diastolic blood pressure or pulse rate is summarized in Table 29.

**Table 29. Patients With at Least One Postbaseline Blood Pressure or Pulse Rate Value Outside of the Predefined Limits**

| Variable | Predefined Limit | Reboxetine N=43 n (%)* | Fluoxetine N=42 n (%)* |
|---|---|---|---|
| Systolic BP | ≥180 mmHg | -- | -- |
| | ≤90 mmHg | 7 (16.3) | 3 (7.1) |
| Diastolic BP | ≥105 mmHg | -- | 1 (2.4) |
| | ≤50 mmHg | 1 (2.4) | 1 (2.4) |
| Pulse | ≥120 beats/min | 2 (4.7) | -- |
| | ≤50 beats/min | -- | -- |

-- No patients had a value outside of the specified predefined limit
* Percentages are based on the number of ITT patients.
Abbreviations: BP = blood pressure
Source: Tables T32, T33, T34 and Appendices 3.8.1, 3.8.2, 3.8.3

No clinically relevant differences were noted among the treatment groups in the frequency of patients who had vital sign values that were outside of the predefined limits. The majority of the patients in each treatment group who had a postbaseline vital sign that was outside of the predefined limit had only a single abnormal value.

The patients who had values that were outside of the predefined normal limits for vital signs are listed in Appendix 3.8.1 (systolic blood pressure), 3.8.2 (diastolic blood pressure) and 3.8.3 (pulse rate).

## 7.4.5. Electrocardiograms

### 7.4.5.1. ECG Abnormalities

The percentage of patients who had normal ECG findings at screen and abnormal ECG findings at day 56 was 27.6% (8/29) in the reboxetine group and 25.8% (8/31) in the

fluoxetine group (Table T47). The majority of these abnormal ECG findings met the predefined criteria for "abnormal, but not clinically relevant" ECG findings, as defined by Cardiac Alert, the central laboratory that evaluated the ECGs. Only 1 patient (patient no. 279 in the fluoxetine group) had a normal ECG at baseline and an abnormal ECG finding at day 56 that was classified as clinically relevant. The ECG abnormality that was observed at day 56 was first degree atrioventricular block.

Patients who had abnormal postbaseline ECG findings at any visit are listed in Appendix 3.8.11.

### 7.4.5.2. Effects of Treatment on Heart Rate, PR, QRS, and QT Intervals

#### *7.4.5.2.1. Mean Change from Baseline*

Within the reboxetine group, statistically significant changes from baseline were noted in the values for PR and QT intervals at day 28 and in the values for PR and QRS intervals at day 56. However, for the PR and QT intervals, the mean change in the reboxetine group represented a decrease from baseline values (ie, no prolongation of the intervals was observed). In addition, the mean values at days 28 and 56 remained within the normal ranges for each of the intervals.

Within the fluoxetine group, no statistically significant changes from baseline were noted in the values for PR or QRS intervals at days 28 or 56. Statistically significant changes from baseline were noted in the values for QT interval at days 28 and 56.

Table 30 summarizes the mean changes from baseline values for ECG intervals at day 56.

**Table 30. Mean Change From Baseline ECG Intervals at Day 56**

| | Reboxetine N=29† | | | Fluoxetine N=31† | | |
|---|---|---|---|---|---|---|
| | Baseline Mean | Mean Change | P Value‡ | Baseline Mean | Mean Change | P Value‡ |
| PR interval | 162.4 | -19.7 | 0.005* | 169.7 | -2.6 | 0.437 |
| QRS interval | 92.4 | 3.4 | 0.048* | 93.2 | 1.0 | 0.557 |
| QT interval | 390.3 | -12.4 | 0.070 | 391.0 | 13.5 | 0.025* |
| Heart rate | 67.3 | 10.8 | 0.001* | 65.5 | -6.1 | 0.001 |

* $p \leq 0.05$
† Number of intent-to-treat patients with the specified ECG measurement at screen and at day 56.
‡ Changes from baseline within each treatment group were tested using a paired t test.
Abbreviations: bpm = beats per minute, ECG = electrocardiogram,
Source: Tables T39, T40, T41, T42

Statistically significant changes from baseline values for ECG heart rate were observed in both treatment groups at days 28 and 56. These changes consisted of mean increases in ECG heart rate in the reboxetine group and mean decreases in ECG heart rate in the fluoxetine

group. At the end of the study (day 56), the mean change from baseline ECG heart rate was +10.8 beats per minute in the reboxetine group and -6.1 beats per minute in the fluoxetine group (Table 30).

Summary statistics for ECG intervals are provided in Tables T39 (heart rate), T40 (PR interval), T41 (QRS interval), and T42 (QT interval).

#### *7.4.5.2.2. Values Outside of Predefined Limits*

The majority of patients in each treatment group had values for ECG intervals that were within the predefined normal limits. The number of patients who had values that were outside of the predefined limits for heart rate, PR, QRS, or QT intervals is summarized in Table 31.

**Table 31. Patients With at Least One Postbaseline ECG Interval Outside of the Predefined Limits**

| Variable | Predefined Limit | Reboxetine N=43 n (%)* | Fluoxetine N=42 n (%)* |
|---|---|---|---|
| Heart Rate | ≤50 beats/min | 1 (2.3) | 8 (19.0) |
| | ≥120 beats/min | -- | -- |
| PR Interval | ≤110 msec | 2 (4.6) | -- |
| | ≥210 msec | -- | -- |
| QRS Interval | ≤30 msec | -- | -- |
| | ≥110 msec | 1 (2.3) | 2 (4.8) |
| QT Interval | ≥470 msec | 1 (2.3) | 2 (4.8) |

-- No patients had a value outside of the specified predefined limit
* Percentages are based on the number of ITT patients.
Abbreviations: ECG = electrocardiogram
Source: Tables T43, T44, T45, T46 and Appendices 3.8.7-3.8.10

Patients who had postbaseline values that exceeded the predefined limits for ECG intervals are listed in Appendices 3.8.7 (ECG heart rate), 3.8.8 (PR interval), 3.8.9 (QRS interval), and 3.8.10 (QT interval). The PR interval at day 56 for patient no. 201 which is noted as 0.0 in Appendix 3.8.8 is actually a missing value for that timepoint.

### 7.4.6. Exposure in Utero

No patients became pregnant during the study. One patient (patient no. 298 in the reboxetine group) had a positive serum pregnancy test at screen and at baseline. This patient had been pregnant and had undergone a dilatation and curettage procedure approximately 1 month before the screening visit. Before the patient was enrolled in the study, an ultrasound examination was performed, which confirmed that the pregnancy had been terminated. Therefore, the elevated HCG value was attributed to the previously terminated pregnancy, and the patient was enrolled in the study. At the end of the study (week 8), the pregnancy test result was negative for this patient.

## 7.4.7. Safety Conclusions

Treatment-emergent signs and symptoms were reported in 86.0% (37/43) of the reboxetine-treated patients and 78.6% (33/42) of the fluoxetine-treated patients. In the reboxetine group, the most frequently reported TESS (reported in at least 10% of patients) were dry mouth, nausea, constipation, hypoesthesia, dizziness, shivering, fatigue, palpitations, urinary retention, and postural hypotension. In the fluoxetine group, the most frequently reported TESS (reported in at least 10% of patients) were dry mouth, nausea, constipation, dizziness, headache, and fatigue.

Overall, the adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. Several adverse events, including hypoesthesia, shivering, palpitations, urinary retention, and postural hypotension, were reported at a higher frequency in this study than in the combined data from previous studies of reboxetine [23]. However, the relevance of these differences is not clear, due to the small sample size of this study.

Of the TESS that were reported in ≥2 male or female reboxetine-treated patients, sore throat, dizziness, fatigue, and feeling hot were reported at least 2 times more frequently (on a percentage basis) in the reboxetine-treated female patients than in the reboxetine-treated male patients, whereas hypoesthesia, insomnia, taste disturbance, palpitations, postural hypotension, and increased sweating were reported at least 2 times more frequently in the reboxetine-treated male patients than in the reboxetine-treated female patients.

Of the TESS that were reported in ≥2 male or female fluoxetine-treated patients, constipation, abdominal distension, dizziness, headache, fatigue, palpitations, blurred vision, decreased appetite, and back pain were reported at least 2 times more frequently (on a percentage basis) in the fluoxetine-treated female patients than in the fluoxetine-treated male patients, whereas feeling cold, urinary retention, and hypomania were reported at least 2 times more frequently in the fluoxetine-treated male patients than in the fluoxetine-treated female patients.

No deaths were reported during this study. Serious TESS were reported in an equal number of patients (3 patients) in both of the treatment groups.

The percentage of patients who discontinued treatment due to TESS was slightly lower in the reboxetine group (11.6%; 5/43) than in the fluoxetine group (14.3%; 6/42) group. No individual events led to discontinuation of treatment in more than 1 reboxetine-treated patient. Hypomania and suicide attempt each led to discontinuation of treatment in 2 fluoxetine-treated patients.

The majority of patients in each treatment group had postbaseline hematology and chemistry values that were within the predefined normal ranges. No evidence of a treatment-related effect was noted on any hematologic or chemistry assay.

No statistically significant changes from baseline values for sitting systolic or diastolic blood pressure were observed within either treatment group at any postbaseline evaluation. Likewise, no statistically significant changes from the baseline value for body weight were observed within the reboxetine group at any postbaseline evaluation. Within the fluoxetine group, statistically significant changes from the baseline value for body weight were observed at days 21, 42, and 56. At the end of the study (day 56), the mean change from baseline body weight was +0.1 kg in the reboxetine group and -1.4 kg in the fluoxetine group.

Statistically significant changes from baseline values for pulse rate and ECG heart rate were observed in both treatment groups at each postbaseline evaluation. At the end of the study (day 56), the mean change from baseline pulse rate was +7.7 beats per minute in the reboxetine group and -6.4 beats per minute in the fluoxetine group, whereas the mean change from baseline ECG heart rate was +10.8 beats per minute in the reboxetine group and -6.1 beats per minute in the fluoxetine group. However, only 2 reboxetine-treated patients had postbaseline values for pulse rate that were above the predefined limit (≥120 beats/min), and no reboxetine-treated patients had postbaseline values for ECG heart rate that were above the predefined limit (≥120 beats/min).

## 8. DISCUSSION AND OVERALL CONCLUSIONS

This phase III, multicenter, randomized, double-blind, active-controlled, parallel-group study was conducted in 85 patients aged 18 to 65 years who suffered from MDD without psychotic features, as diagnosed using criteria defined by DSM-IV. The primary objective of this study was to compare the antidepressant efficacy of reboxetine (administered at a dose of 8 to 10 mg/day for 8 weeks) with that of fluoxetine (administered at a dose of 20 to 40 mg/day for 8 weeks), as determined by the change from baseline in the 21-Item HAM-D total score at the last assessment in patients suffering from MDD.

A total of 85 patients were enrolled in the study and were randomized to receive treatment with reboxetine (43 patients) or fluoxetine (42 patients). All of the randomized patients received at least 1 dose of study medication. Therefore, the ITT population includes 43 reboxetine-treated patients and 42 fluoxetine-treated patients.

The patients in the study ranged in age from 19 to 64 years. All of the patients were Asian, and the majority (>60%) of the patients were female. No statistically significant differences were noted between the treatment groups in the severity of depression at baseline, as judged by the mean total scores for the HAM-D, the CGI Severity of Illness, or the SASS.

The results of this study demonstrate that the reboxetine and fluoxetine groups were comparable on the primary endpoint, the mean change from baseline in the HAM-D total score at day 56 in the LOCF analysis. Strong evidence of antidepressant activity was observed in both treatment groups, as demonstrated by mean change from baseline values in the HAM-D total score of -14.05 in the reboxetine group and -14.78 in the fluoxetine group (p=0.971). The difference between the treatment groups in the mean change values (0.72;

lower limit of 90% CI, -2.19) was not considered to be either clinically significant (because the difference was <2) or statistically significant (because the lower limit of the 90% CI was <0).

As summarized in Table 32, the results on the primary endpoint were supported by results on the secondary measures of antidepressant efficacy. No statistically significant differences were observed between the treatment groups in the HAM-D response or remission rates, the CGI Global Improvement response rate, or the mean change from baseline in the CGI Severity of Illness score at day 56 in the LOCF analysis. Thus, the results of both the primary and secondary measures of antidepressant efficacy were consistent in demonstrating the comparable efficacy of reboxetine and fluoxetine for the treatment of patients with depression.

**Table 32. Summary of Antidepressant Efficacy Measures at Day 56 (LOCF Analysis)**

| Variable | Reboxetine N=43 | Fluoxetine N=42 | P Value |
|---|---|---|---|
| **Primary Endpoint** | | | |
| HAM-D total score, mean change from baseline | -14.05 | -14.78 | 0.971 |
| **Secondary Endpoints** | | | |
| **% Responders or Remitters** | | | |
| HAM-D Response | 55.3 | 57.5 | 0.697 |
| HAM-D Remission | 36.8 | 40.0 | 0.593 |
| CGI Global Improvement Response | 71.1 | 70.0 | 0.905 |
| **Mean Change From Baseline** | | | |
| CGI Severity of Illness | -2.0 | -2.1 | 0.530 |
| SASS total score | 7.3 | 3.6 | 0.038* |

* $p \leq 0.05$ (reboxetine superior to fluoxetine)
Abbreviations: CGI = Clinical Global Impression, HAM-D = Hamilton Rating Scale for Depression, SASS = Social Adaptation Self-evaluation Scale
Source: Tables T12.1, 12.2, 13.1, 14.1, 17.1, 18.1, 18.2, 20.1, 20.2

The results of the final secondary endpoint, the SASS total score, demonstrated that reboxetine is superior to fluoxetine for the improvement of social function. The mean change from baseline in the SASS total score was significantly greater in the reboxetine group (mean change of 7.3) than in the fluoxetine group (mean change of 3.6) at day 56 in the LOCF analysis (p=0.038).

Treatment-emergent signs and symptoms were reported in 86.0% (37/43) of the reboxetine-treated patients and 78.6% (33/42) of the fluoxetine-treated patients. In the reboxetine group, the most frequently reported TESS (reported in at least 10% of patients) were dry mouth, nausea, constipation, hypoesthesia, dizziness, shivering, fatigue, palpitations, urinary retention, and postural hypotension. In the fluoxetine group, the most frequently reported TESS (reported in at least 10% of patients) were dry mouth, nausea,

constipation, dizziness, headache, and fatigue. The majority of TESS that were reported by patients in each treatment group were mild to moderate in intensity.

Overall, the adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. Several adverse events, including hypoesthesia, shivering, palpitations, urinary retention, and postural hypotension, were reported at a higher frequency in this study than in the combined data from previous studies of reboxetine [23]. However, the relevance of these differences is not clear, due to the small sample size of this study.

No deaths were reported during this study. Serious TESS were reported in an equal number of patients (3 patients) in both of the treatment groups.

The percentage of patients who discontinued treatment due to TESS was slightly lower in the reboxetine group (11.6%; 5/43) than in the fluoxetine group (14.3%; 6/42) group. No individual events led to discontinuation of treatment in more than 1 reboxetine-treated patient. Hypomania and suicide attempt each led to discontinuation of treatment in 2 fluoxetine-treated patients.

The majority of patients in each treatment group had postbaseline hematology and chemistry values that were within the predefined normal ranges. No evidence of a treatment-related effect was noted on any hematologic or chemistry assay.

No statistically significant changes from baseline values for sitting systolic or diastolic blood pressure were observed within either treatment group at any postbaseline evaluation.

Statistically significant changes from baseline values for pulse rate and ECG heart rate were observed in both treatment groups at each postbaseline evaluation. At the end of the study (day 56), the mean change from baseline pulse rate was +7.7 beats per minute in the reboxetine group and -6.4 beats per minute in the fluoxetine group, whereas the mean change from baseline ECG heart rate was +10.8 beats per minute in the reboxetine group and -6.1 beats per minute in the fluoxetine group. However, only 2 reboxetine-treated patients had postbaseline values for pulse rate that were above the predefined limit (≥120 beats/min), and no reboxetine-treated patients had postbaseline values for ECG heart rate that were above the predefined limit (≥120 beats/min).

In conclusion, this phase III, multicenter, randomized, double-blind, active-controlled, parallel-group study demonstrated that the reboxetine and fluoxetine groups were comparable on the primary endpoint, the mean change from baseline in the HAM-D total score at day 56 in the ITT patient population. Overall, the adverse-event profile that was observed for reboxetine in this study is consistent with the profile that was established in previous studies of reboxetine. Several adverse events, including hypoesthesia, shivering, palpitations, urinary retention, and postural hypotension, were reported at a higher frequency in this study than in the combined data from previous studies of reboxetine [23]. However, the relevance

of these differences is not clear, due to the small sample size of this study. No new safety concerns associated with the use of reboxetine were identified.

## 9. ACKNOWLEDGMENTS

The authors thank the following people for their contributions to the conduct of the study or to the preparation of the study report: Sharon S. Chang (Market Company Taiwan), Timothy D. Holt (Clinical Reporting Systems), Alice Huang (Market Company Taiwan), Jessica Lin (Market Company Taiwan), Patricia A. Smanik (Medical Writing), and Louise A. Wilson (Clinical Data Integration).

## 10. REFERENCES LIST

1. Merikangas KR, Kupfer DJ. Mood disorders: Genetic aspects. In: Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry. 6th ed. Baltimore, MD: Williams & Wilkins; 1995:1102-1116.

2. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC, American Psychiatric Association, 1994.

3. Post RM. Mood Disorders: Somatic treatment. In: Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry. 6th ed. Baltimore, MD: Williams & Wilkins; 1995:1152-1178.

4. Nierenberg A, Wright EC. Evolution of remission as the new standard in the treatment of depression. J Clin Psychiatry 1999;60(suppl 22):7-11.

5. Elkin I, Shea MT, Watkins JT, Sotsky SM, Collins JF, Glass DR, et al. National Institute of Mental Health Treatment of Depression Collaborative Research Program. General effectiveness of treatments. Arch Gen Psychiatry 1989;46(11):971-82.

6. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. Br Med J 1995;310(b992):1433-88.

7. Montgomery SA, Henry J, McDonald G, Dinan T, Lader M, Hindmarch I, et al. Selective serotonin reuptake inhibitors: meta-analysis of discontinuation rates. Int Clin Psychopharmaco 1994;9(1):47-53.

8. Song F, Freemantle N, Sheldon TA, House A, Watson P, Long A, Mason J. Selective serotonin reuptake inhibitors: Meta-analysis of efficacy and acceptability. Br Med J 1993(13);306(6879):683-7.

9. Montgomery SA. Reboxetine: additional benefits to the depressed patient. J Psychopharmacol 1997;11(suppl 4):S9-15.

10. Healy D, McMonagle T. The enhancement of social functioning as a therapeutic principle in the management of depression. J Psychopharmacol 1997;11(suppl 4):S25-31.

11. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122(5):509-22.

12. Wong EH, Sonders MS, Amara SG, Tinholt PM, Piercey MF, Hoffmann WP, et al. Reboxetine: a pharmacologically potent, selective, and specific norepinephrine reuptake inhibitor. Biol Psychiatry 2000;47(9):818-29.

13. Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997;340(2-3):249-58.

14. Dubini A, Ban TA, Money LC. Phase II controlled study of the activity and tolerability of reboxetine in comparison with placebo and desipramine in patients hospitalised for major depressive Disorder. Internal Report FCE 20124/702I, February 1991.

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

16. Brown MT, Brinkman SA, Reisner JK, Rowland CR. Reboxetine, placebo, and paroxetine comparison in patients with major depressive disorder (Protocol M/2020/0047). Pharmacia & Upjohn Study Report a0080877, 3 November 2000 (amended 6 February 2001).

17. Ban TA, Morey LC, Fjetland OK, Dubini A. Phase II placebo-controlled clinical study with reboxetine in major depression. Farmitalia Carlo Erba Internal Report FCE 201124/706i, November 1993.

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

19. Bosc M, Dubini A, Polin V. Development and validation of a social functioning scale, the Social Adaptation Self-Evaluation Scale. European Neuropsychopharmacology 1997;7(suppl 1):S57-70 (discussion, S71-73).

20. Prozac (fluoxetine hydrochloride) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2001.

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

22. Guy W. ECDEU assessment manual for psychopharmacology, Revised (DHEW Publication No. ADM. 76-338). Washington, DC: US Government Printing Office, 1976

23. New Drug Application 20-960 (Reboxetine mesylate). 2000 Safety Update Report. Pharmacia & Upjohn Document No. a0081901.