Studie 096

(950E-CNS-0005-096)

Studienbericht

Reboxetine augmentation of fluoxetine for Major Depressive Disorder: an 8-week open-label study

Project Code:	PHA-RBXA-0005
Final Report of the Study:	950E-CNS-0005-096
Previous Reports of the Study:	None
Date of First Subject Enrolled:	26 December 2000
Date of Last Subject Completed:	3 August 2001
Date of Last Follow-up (if applicable):	[not applicable]
Principal Investigator:	Mark Rapaport, MD Psychopharmacology Research Program University of California, San Diego La Jolla, CA 92037
Sponsor's Responsible Medical Officer:	Gerri Schwartz, PhD Global Director CNS, Psychiatry Pharmacia Inc, Peapack NJ 07977
Development Phase of Study:	3b

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.

Reboxetine augmentation of fluoxetine for Major Depressive Disorder: an 8-week open-label study

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.

1/23/03
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The approval signature of the principal Investigator is in Appendix 1.13

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SYNOPSIS

Name of Company: **Pharmacia** **Name of Finished Product:** **Reboxetine** **Name of Active Ingredient:** **Reboxetine methanesulphonate** **(reboxetine methylate)**	*(For National Authority Use only)*

Title of Study: Reboxetine augmentation of fluoxetine for Major Depressive Disorder: an 8-week open-label study

Protocol Number: 950ECNS0005-096

Investigators: 3 investigators enrolled 34 patients.
Jon Heiser, Pharmacology Research Institute, Newport Beach, CA;
Peter Londborg, Seattle Clinical Research Center, Seattle, WA;
Mark Rappaport, University of California San Diego, Psychopharmacology Research Program, La Jolla CA..

Study Centers: 3 centers

Publication Reference: None as of [date of report].

Studied Period (Years): 2000- 2001 **First patient enrolled:** 26 Dec 2000 **Last patient visit:** 3 Aug 2001	**Phase of Development:** **3b**

Objectives: The study was designed to determine the safety of treating fluoxetine partial responders with reboxetine to estimate augmentation effects.

Primary: To evaluate change from baseline in parameters relevant to efficacy and safety in patients meeting DSM-IV criteria for Major Depressive Disorder without Psychotic Features.

Secondary: [none listed in protocol]

Methodology: This study was an open-label, single-arm multicenter study conducted in the United States in outpatients diagnosed with Major Depressive Disorder. Patients were screened for up to 7 days prior to baseline assessments and initiation of treatment with reboxetine and fluoxetine. Therapy was continued up to 8 weeks. Safety and efficacy were evaluated during clinical visits at weeks 1, 2, 3, 4, 5, 6, and 8.

Number of Patients (Planned and Analyzed):

30 patients planned: 34 patients enrolled

Intent-to-treat population: 33 pts enrolled in the study, received at least one dose of study medication, and returned for at least one post-baseline visit.

Safety population: 33 patients enrolled in the study and received at least one dose of study medication.

Name of Company: **Pharmacia** **Name of Finished Product:** **Reboxetine** **Name of Active Ingredient:** **Reboxetine methanesulphonate** **(reboxetine methylate)**	*(For National Authority Use only)*

Diagnosis and Main Criteria for Inclusion: Male and female outpatients, aged 18 to 65 years, diagnosed with Major Depressive Disorder without Psychotic Features who have only partially responded to a 6-week treatment with fluoxetine 20 mg were eligible for this study. Patients with the following diagnoses were excluded from participating in this study: Major Depressive Disorder with Psychotic Features, Dysthymic or Cyclothymic Disorder, Bipolar I or II Disorder, Schizophrenia or other Psychotic Disorders,. In addition, patients at a high risk of suicide and patients who had a history of substance abuse (within the last 6 months) were also excluded from this study. Patients with a history of diseases which might interfere with absorption, distribution, metabolism, or excretion of drugs, with clinically significant illness, or seizures or brain injury were excluded from the study. See Section 6.2 for complete listing. In addition, patients were excluded who failed to respond to treatment with at least 2 different pharmacological classes of antidepressants given at full doses for more than one month were considered resistant to antidepressive therapy and were excluded from this study.

Test Product, Dose and Mode of Administration, Batch Number: Patients received reboxetine (2 mg tablets) at a daily dose of 4 to 8 mg, given twice daily in divided doses, Batch number: lot 28,923

Other Therapy, Dose and Mode of Administration, Batch Number: Patients received fluoxetine (Prozac® 20 mg tablets) at a daily dose of 20 mg, given once daily, Batch number: OL 10,271

Duration of Treatment: 8 weeks was the planned duration of this study.

Endpoints and Criteria for Evaluation:

Efficacy: The primary efficacy measure of depression was the mean change from baseline in the Hamilton Depression Rating Scale (HAM-D, 17-item) total score. Supportive secondary efficacy measures of depression were the Clinical Global Impression (CGI) and the Montgomery Asberg Depression Rating Scale (MADRS).

Safety: Safety was assessed by laboratory assays, vital sign measurements, and the frequency of reported adverse events over time.

Statistical Methods: Descriptive statistics were generated for the effectiveness and safety variables, including minimum, maximum, mean and standard error (deviation) for continuous variables. Proportions of patients in each category of interest were provided for categorical response variables. The intent-to-treat population was defined to include all patients enrolled into the trial who received at least one treatment dose with at least one post-baseline efficacy follow-up visit.

Name of Company: **Pharmacia** **Name of Finished Product:** **Reboxetine** **Name of Active Ingredient:** **Reboxetine methanesulphonate** **(reboxetine methylate)**	*(For National Authority Use only)*

SUMMARY OF RESULTS AND CONCLUSIONS:

Disposition of Subjects and Baseline Characteristics:

This study was conducted in 34 patients with major depressive disorder who were partial responders to fluoxetine treatment. There were 12 (35.3%) male patients and 22 (64.7%) female patients, the majority of whom were Caucasian. The mean age was 43.8 years (ranging from 20 to 61 years of age), and the mean age at the first depressive episode was 30.8 years (4 to 55 years) Most (64.7%) of the patients experienced previous episodes of depression (mean 2.3 episodes). Only one patient reported a history of hospitalization for this condition One-third of the patients had previously received other psychotropic treatment (benzodiazepines, 4 patients; lithium, 4 patients; other, 3 patients) for depression. In addition to fluoxetine therapy, the most commonly reported antidepressant therapies used prior to study entry were paroxetine, sertraline, and tricyclic antidepressants (TCAs). The depression episode at study entry was a recurrence for most patients but was the first episode for 8 patients. The mean duration of the present episode was 4.7 years, and a precipitating external stressor was implicated for 61.8% of the patients. The mean scores on depression rating scales were 18.3 (HAM-D), 26.2 (MADRS), and most patients were rated as "moderately ill" on the CGI Global Impression scale.

Efficacy Results: Decreases from baseline HAM-D 17-Item scores were noted throughout the 8-week treatment period, with the greatest decrease at week 8 (-7.3±6.1). A similar pattern of reduction in depression score with the addition of reboxetine was observed when patients were rated using the MADRS scale. The percentage of patients who were responders (defined as at least a <50% decrease from baseline score) after reboxetine augmentation was 39.4% of patients using the HAM-D score, and 36.4% were in remission by week 8. At week 8, more than half the patients were rated as responders (a score of ≤2 corresponding to "very much improved" or "much improved") using the CGI Global Improvement score.

All patients were ≥80% compliant with study medication; the mean dose at week 8 was 6.8±1.7mg/day.

Safety Results: Most (90.9%) patients reported at least one adverse event during the study. Insomnia (36.4%), dry mouth (30.3%), diaphoresis (24.2%), and constipation (24.2%) were the most frequently reported adverse events. Most adverse events were rated as mild or moderate in intensity. Drug-related adverse events were rated as severe in 6 patients: diaphoresis (2 patients), constipation (1 patient), insomnia (1 patient), dry mouth (1 patient), and tremor and sinus tachycardia (1 patient). Seven (21.2%, 7/33) patients discontinued from the study due to adverse events including unintended pregnancy (1 patient), diaphoresis (2 patients), tachycardia (1 patient), and 3 patients with multiple adverse events. No deaths were reported in this study.

Hematology and chemistry laboratory values for most patients were within normal limits at baseline and at the end of treatment. All changes observed in hematologic parameters were < 10% from baseline values, and none were clinically significant. Thyroid hormone levels (T4 and TSH) assessed at baseline were within normal limits for most patients in this study. The majority of patients had ECG findings that were normal at baseline and at the end of treatment. However, caution is indicated with administering Reboxetine to patients with compromised cardiovascular conditions. There were no major changes from baseline for supine systolic or diastolic blood pressure.

Name of Company: **Pharmacia** **Name of Finished Product:** **Reboxetine** **Name of Active Ingredient:** **Reboxetine methanesulphonate** **(reboxetine methylate)**	*(For National Authority Use only)*
CONCLUSION: Results from this 8-week, open-label pilot study conducted in 34 patients indicate that reboxetine appears to be safe when used in combination with fluoxetine in treating patients with major depressive disorder who were partial responders to fluoxetine treatment. Reboxetine augmentation decreased depression as measured by a 50% decrease in HAM-D score from baseline and a decrease to ≤ 2 in CGI score among partial responders with at least 6 weeks of previous fluoxetine therapy.	
Report Date: November 2002	

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IN-TEXT TABLES

1. ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
CGI	Clinician's Global Impression
CRF	case report form
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	electrocardiogram
ECT	electroconvulsive therapy
HAM-D	Hamilton Depression Rating Scale
ICH	International Conference on Harmonization
ITT	Intent-to-treat
LOCF	Last observation carried forward
MADRS	Montgomery Asberg Depression Rating Scale
NRI	noradrenaline reuptake inhibitor
OC	observed case
OTC	over the counter
SAE	serious adverse event
SSRI	selective serotonin reuptake inhibitor
T4	thyroxine
TCA	tricyclic antidepressant
TSH	thyroid-stimulating hormone

2. ETHICS

2.1. Institutional Review Board/Independent Ethics Committee

It was the responsibility of the investigator to obtain approval of the trial protocol from the Institutional Review Board (IRB). The protocol for this study was reviewed by an Independent Ethics Committee (IEC) prior to the initiation of the study. Copies of the IRB approval were to be sent to Pharmacia. All correspondence with the IRB was to be filed by the investigator. The investigator was responsible for reporting serious adverse events (SAEs), as defined in the protocol, to the IRB.

Appendix 1.1 contains a copy of the protocol, 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 IRBs 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.

2.3. Subject Information and Consent

It was the responsibility of the investigator to give each patient (or patient's acceptable representative) prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The patient was to be informed about their right to withdraw from the trial at any time. Written patient information was to be given to each patient before enrollment. The written patient information was not to be changed without prior discussion with Pharmacia. Furthermore, it was the responsibility of the investigator to obtain signed informed consent (or witnessed verbal consent according to applicable regulations) from all patients prior to inclusion in the trial.

Appendix 1.3 contains a copy of a sample informed consent form.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

3.1. Investigative Sites

This study enrolled patients at 3 study centers in the United States. The principal investigator was Dr. Mark Rapaport (University of California, San Diego; La Jolla, CA).

Appendix 1.4 lists the investigators and their affiliations. Appendix 1.5 provides a curriculum vitae for each. Appendix 1.13 contains the signature of the principal investigator.

3.2. Sponsor Information

Pharmacia was the sponsor for this study and coordinated the activities for initiating the study. Pharmacia developed the protocol, case report forms (CRFs), and a sample informed consent form. Copies of the protocol, blank CRF, and informed consent form are provided in Appendices 1.1 to 1.3. Pharmacia authorized the release of clinical supplies after receiving appropriate documentation. Study supplies were maintained in secure storage that was documented by the study monitor. Data were collected via internet using the Inform™ system (PhaseForward Inc., Waltham, MA). PhaseForward provided the Inform software, training, and data management during the study. Statistical Operations, Global Medical

Affairs performed the statistical analysis of the data. Pharmacia monitored the study and the data collection on an ongoing basis throughout the study.

3.3. Laboratory Testing

Laboratory testing for safety assessment was done at a central location, Quest Laboratories [Van Nuys, CA]. Electrocardiograms (ECGs) were assessed by eResearch Technologies [Philadelphia, PA].

4. INTRODUCTION

Even though many effective treatments exist for major depressive disorder including psychotherapy and electroconvulsive treatment, many experts consider antidepressant medications to be the standard treatment for this condition. However, results from studies suggest that 29% to 46% of depressed patients show only partial or no response to antidepressants [1]. Even among responders to antidepressant treatment, residual symptoms may be found. The presence of residual symptoms has been associated with a greater likelihood of relapse and, perhaps, a poorer prognosis. Augmentation offers a simple strategy of using a pharmacological agent to enhance the effect of an antidepressant. This strategy is especially attractive for use in patients refractile to therapy, in partial responders, or to accelerate the response. It offers the advantage of saving time by serving as a "bridge" to the new therapy, ie, eliminating the need to taper the first drug [2].

Reboxetine is a highly selective noradrenaline reuptake inhibitor (NRI), which has antidepressant activity. The efficacy and safety of reboxetine for the treatment of patients with depressive disorders were evaluated in clinical studies that were implemented in Europe, Latin America, Canada, and Australia [3-12]. Reboxetine tablets were approved for marketing in the United Kingdom in April 1997 and were entered into the Mutual Recognition process in Europe in July 1997. Reboxetine is now approved in 12 European countries.

For patients who have not fully responded to treatment with a serotonin reuptake inhibitor (SSRI), combination therapy with a noradrenergic compound may offer benefits. The mechanism of action of the 2 types of agents may be synergistic, raising the possibility that patients who have not responded to SSRI treatment alone may respond to combinations of SSRI and selected NRI therapy. Nelson hypothesized that combining drugs that affect both serotonin and norepinephrine may be uniquely helpful among non-responders to drugs that affect only the serotonergic system [13].

Coadministration of reboxetine with fluoxetine has been previously studied in a controlled trial of normal volunteers [14]. In this study, healthy volunteers were randomized into groups of 10-11 subjects: reboxetine 8 mg/day & placebo (n=11), placebo & fluoxetine 20 mg/day (n=10), and reboxetine 8 mg/day & fluoxetine 20 mg/day (n=10) for 8 days. Preliminary data analysis shows no evidence of any interaction between reboxetine and fluoxetine on any

clinical measure including adverse events. None of the treatments had a significant effect on the laboratory results or body temperature. In all treatments, performance on the Digit Symbol Substitution Test (DSST), a neuropsychological measure used for screening neurocognitive dysfunction, improved over time. No statistically significant pharmacokinetic or pharmacodynamic interaction was observed.

The first clinical pharmacology studies were begun in 1984 and the clinical program for reboxetine includes data from 39 studies: 23 clinical pharmacology studies, 14 phase 2/phase 3 studies in patients with depression, and 2 phase II studies in other indications (obsessive-compulsive disorder and panic disorder). A total of 3075 patients have participated in these studies; of these, 1926 were treated with reboxetine for periods ranging from 1 day in clinical pharmacology studies to 1 year in therapeutic trials. Of the 1926 patients who have been treated with reboxetine, 1622 were patients with depression who were treated with reboxetine at the recommended doses of 8 to 10 mg/day for adult (18 to 65 years) patients and 4 to 6 mg/day for elderly (>65 years) patients in short term (4, 6, or 8 weeks) or long-term (up to 1 year) phase 2/phase 3 depression studies [3-12].

The combined phase 2 and phase 3 safety data showed an adverse-event profile for reboxetine that was qualitatively similar to the safety profile demonstrated in the short-term, controlled studies. Dry mouth, constipation, nausea, insomnia, dizziness, headache, and sweating were among the most commonly reported adverse events. These events were generally mild to moderate in severity. Less than 2% of patients discontinued treatment due to adverse events in these clinical studies; <2% of patients reported serious adverse events. Deaths were infrequent (10/1622, 0.6%), and occurred mostly (8/10) in elderly patients (≥65 years of age). Suicide was the cause of death for 2 adult patients (>65 years old).

As of the 1 November 1997, data cut-off date for the US NDA, the adverse events that had been spontaneously reported in patients who have been treated with reboxetine in doses of 2 to 8 mg/day, are not different from those that were observed in the phase 2/phase 3 depression studies. Nausea, dizziness, and headache were the most commonly reported adverse events in addition to insomnia, urinary retention, constipation, agitation, and tachycardia. Thus, safety date from these sources failed to identify any new safety concerns associated with the use of reboxetine.

The most commonly reported adverse events associated with fluoxetine therapy in controlled studies of depression are anxiety, anorexia, asthenia, drowsiness, dry mouth, increased sweating, insomnia, nausea, nervousness, and tremor. Headache and diarrhea were also commonly reported in fluoxetine trials of other indications. [Prozac Package Insert, 28 February 2001].

Protocol 950E-CNS-0005-096 was designed for patients with Major Depressive Disorder who were partial responders to fluoxetine at a dose of 20 mg per day. This study was conducted to assess the safety of reboxetine augmentation in patients currently receiving fluoxetine, and to evaluate efficacy in the treatment of depressive disorder.

5. OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

The study was designed to determine the safety of treating fluoxetine partial responders with reboxetine to estimate augmentation effects, by evaluating the change from baseline in parameters relevant to efficacy and safety in patients meeting DSM-IV (Diagnostic and Statistical Manual for Mental Disorders, 4th edition) criteria for Major Depressive Disorder.

5.2. Endpoints

5.2.1. Primary Endpoint

The primary efficacy measure of depression was the mean change from baseline in Hamilton Depression Rating Scale (HAM-D, 17-item) total score [15]. All patients who received at least one dose of study medication were evaluated for safety by monitoring adverse events, laboratory assays, and vital signs over time.

5.2.2. Secondary Endpoints

Supportive secondary efficacy measures of depression were the Clinical Global Impression (CGI) [16] and the Montgomery Asberg Depression Rating Scale (MADRS) [17].

6. METHODS

6.1. Overall Study Design and Plan

This was an open-label, single-arm, multicenter study in outpatients, age 18-65, diagnosed with major depressive disorder who had only partially responded to a 6-week treatment with fluoxetine 20 mg. The 8-week study was conducted at 3 study centers in the United States.

Prior to enrollment, patients were screened for up to 7 days. Assessments at screening included diagnosis and rating severity of depression (HAM-D), medical history, physical examination, electrocardiogram (ECG), vital signs, and safety laboratory testing (thyroid tests, pregnancy test, and urine drug screen were performed only at screening). Eligible patients then underwent baseline testing (vital sign assessment and clinical response measures [HAM-D, MADRS, and CGI]). After safety results were reviewed and deemed acceptable by the investigator, treatment was initiated with reboxetine (up to 8 mg in 2 divided doses) to patients who had already been receiving fluoxetine for at least 6 weeks (20 mg once daily). The patient was requested to visit the hospital or clinic at weeks 1, 2, 3, 4, 5, 6, and 8. Measures of clinical response were repeated at each study visit. Vital signs and adverse events were monitored from the baseline visit throughout the study; ECG was repeated at week 8.

Data were collected via secure internet connections using the Inform system (internet connection was via Netscape Navigator or Microsoft Internet Explorer with password protection and extensive firewall protection.)

Fluoxetine was administered at 20 mg once daily (morning) for the duration of the study.

The starting dose of reboxetine was 4 mg/day (2 mg in morning and 2 mg in evening) and was to be maintained for at least 3 days prior to increasing dose. At the investigator's discretion, the dose could be increased to 6 mg/day (4 mg morning, 2 mg evening) and after an additional 3 days, could be further increased to 8 mg/day (4 mg morning, 4 mg evening). Any change in dose of reboxetine was to be based on clinical judgment of the patient's ability to tolerate the medication and on clinical response.

Treatment was to be administered orally in the morning and in the afternoon/evening, at approximately the same time each day, but at least 3 hours before bedtime. No study medication was dispensed on week 8.

Detailed study information is provided in Table 1 Schedule of Visit Activities.

Enrollment was targeted at 30 patients recruited from 3 study sites. Enrollment across centers was expected to take no longer than 7 months, therefore, the duration of the study was expected to be approximately 9 months from enrollment of first patient until the last clinic visit of the last patient enrolled. Enrollment was to be closely monitored at each study site.

Table 1--Schedule of Visit Activities

VISIT	Screening	Baseline							Final
Week	-1	0	1	2	3	4	5	6	8
Diagnosis DSM IV	X								
Medical history	X								
Physical Examination	X								X
Vital signs	X	X	X	X	X	X	X	X	X
ECG	X								X
Safety laboratory testing	X								X
Urine drug screen	X								
TSH, T4	X								
Pregnancy test	X								X
HAM-D (17-Item)	X	X	X	X	X	X	X	X	X
MADRS		X	X	X	X	X	X	X	X
CGI		X	X	X	X	X	X	X	X
Compliance			X	X	X	X	X	X	X
Dispensing medication		X	X	X	X	X	X	X	
Adverse events		(X)*	X	X	X	X	X	X	X

Abbreviations: CGI=Clinician's Global Impressions; DSM IV=Diagnostic and Statistical Manual of Mental Disorders, 4th ed; ECG=electrocardiogram; HAM-D=Hamilton Rating Scale for Depression; MADRS=Montgomery Asberg Depression Rating Scale; TSH=thyroid-stimulating hormone; T4=thyroxine

* Baseline 'adverse events'/pre-existing conditions. Adverse events were collected after study medication was taken.

6.2. Discussion of Study Design

For patients who have not fully responded to treatment with an SSRI, combination therapy with an NRI such as reboxetine may offer benefits. The mechanism of action of the 2 types of agents may be synergistic, ie, patients who have not responded to SSRI treatment alone may respond to combinations of SSRI and selected NRI therapy [2]. Nelson hypothesized that combining drugs which affect both serotonin and norepinephrine may be uniquely helpful among non-responders to drugs affecting only the serotonergic system [13].

Safety data for use of the combination of reboxetine and fluoxetine up to 8 days are available. No new safety concerns were identified when these drugs were administered concomitantly in normal volunteers [14].

Protocol 950ECNS0005-096 was designed to generate pilot data of treatment with reboxetine (4 to 8 mg/day) combined with fluoxetine (20 mg/day) in patients with major depressive disorder who were partial responders to fluoxetine therapy. Therefore, patients were required to have at least 6 weeks of previous fluoxetine treatment with documentation of partial response, ie, HAM-D 17 item total score $\geq$14. Since this was a single-arm pilot study, clinical judgment estimated that 20 to 30 patients treated in an open-label study with a

planned duration of 8 weeks should be adequate to provide appropriate safety and limited efficacy information for a larger, controlled, randomized trial.

6.3. Selection of Study Population

6.3.1. Inclusion Criteria

Participants meeting all of the following inclusion criteria at Screen could be included in the study:

1. Patient diagnosed with Major Depressive Disorder (DSM-IV, 296.2x single episode, or 296.3x recurrent episode) without Psychotic Features

2. Male or female between 18 to 65 years of age, inclusive

3. If the patient was female, she was required to be 2 years post-menopausal or, if of child-bearing potential, had to meet the following criteria:

   a) Agree to avoid pregnancy during the study

   b) Have a negative serum pregnancy test at Screen

   c) Regular use of an accepted means of birth control such as oral contraceptive (3 months), implants or injected contraceptives, intrauterine device, barrier method, or surgically sterilized

4. The patient must have received 20 mg/day fluoxetine daily for at least 6 weeks.

5. The patient had not responded to fluoxetine treatment, defined as: a current HAM-D 17 item score of $\geq$14 (and not more than 40% decrease in estimated pre-treatment HAM-D while on fluoxetine treatment).

6. The patient consented to participate voluntarily and signed a written Patient Informed Consent prior to any study procedures at Screen.

6.3.2. Exclusion Criteria

Participants meeting any of the following exclusion criteria at baseline were to be excluded from the study:

1. DSM-IV Diagnosis of Major Depressive Disorder with Psychotic Features

2. DSM-IV Diagnosis of Dysthymic or Cyclothymic Disorder

3. DSM-IV Diagnosis with Bipolar I or II Disorders

4. Schizophrenia or other Psychotic Disorders

5. DSM-IV Diagnosis of Substance Related Disorders for the last 6 months

6. Resistance to antidepressive treatment (defined as a lack of response to at least 2 different pharmacological classes of antidepressants given at full doses for more than 1 month)

7. History of Major Depressive Disorders associated with endocrine disorders: hypo- or hyper-thyroidism tested by thyroid-stimulating hormone (TSH) and thyroxine (T4); adrenal insufficiency, Cushing's syndrome, etc.

8. Positive pregnancy test (females of childbearing potential)

9. Lactating female patient

10. Participation in any clinical study with an investigational compound in the 4 weeks preceding the study

11. History or presence of gastrointestional, liver, or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism and excretion of drugs

12. History of seizures or brain injury (within the last 5 years, with sequelae); current evidence of clinically important hematopoietic, respiratory or cardiovascular diseases; current evidence of urinary retention or narrow angle glaucoma

13. Clinically significant illness in the 4 weeks preceding the study that might interfere with the conduct of the trial

14. Clinically relevant abnormal findings in the physical examination (including prostate enlargement), laboratory tests and ECG at admission

15. Electroconvulsive Therapy (ECT) in the previous 6 months

16. High risk of suicide in the Investigator's judgment, or HAM-D Item 3 score >2, or history of suicide attempt during the current depressive episode

17. Taking any of the following drugs, which are potent inhibitors of the drug metabolizing enzyme cytochrome p450-3A4: azole antifungals, macrolide antibiotics (such as erythromycin), and fluvoxamine

18. Taking oral coagulants (ie, warfarin) known to inhibit vitamin K coagulation factors, type 1C anti-arrhythmics (ie, flecainide), or inhibitors of p450-2D6 (ie, quinidine or cimetidine)

6.4. Treatments

Prior to enrollment, each patient was evaluated for eligibility according to the inclusion/exclusion criteria (ie, "screening visit"). Since the screening visit activities included assessment of safety laboratory values, no patient could be enrolled until the laboratory report was received and reviewed by the Investigator. Enrollment and the start of study treatment had to occur no later than 7 days after the Screen visit. Patients were required to continue taking fluoxetine (20 mg/day) during the screening period.

6.4.1. Treatments Administered

Fluoxetine: The fluoxetine dose was 20 mg/day for the duration of the study. Patients were instructed to take one fluoxetine 20-mg tablet in the morning every day during study participation. Adjustments to the timing of drug administration were permitted at the Investigator's discretion.

Reboxetine: The starting dose of reboxetine was 4 mg a day, given in divided doses. The dose of reboxetine could be increased from 4 mg to 6 mg, and then to 8 mg per day at the Investigator's discretion. Each dose regimen had to be maintained for at least 3 days prior to any dose increase. The dose change was to be based on clinical judgment of the patients' ability to tolerate the medication and on clinical response. The Investigator was permitted to decrease the dose of reboxetine to 4 or 6 mg/day at any time during the study.

6.4.2. Identity of Investigational Product

Table 2 shows the batch numbers of the medication used in this study.

Table 2. Study Medication Batch Number

Study Medication	Manufacturer	Batch Number
Reboxetine	Pharmacia	lot 28, 923
Fluoxetine	Eli Lilly	OL 10,271

Packages labeled with the trial name and number and patient number were provided for this open-label study by Pharmacia after receiving appropriate documentation from the study site. The study site was instructed to store drug supplies at room temperature under secure conditions. Drug storage conditions were to be assessed by the study monitor during site visits.

Reboxetine (2-mg tablets) and Fluoxetine (Prozac™ 20-mg tablets) were used in this study. Reboxetine was dispensed in bottles containing 40 tablets, and fluoxetine was dispensed in bottles containing 30 tablets. Depending on the patient's actual dose, a 40-tablet bottle of medication was expected to cover 2 to 3 weeks of treatment. Depending on dose, a 40 tablet

bottle of reboxetine would last from 1.9 weeks (8 mg/day) to 2.8 weeks (6 mg/day). The fluoxetine was provided in a 30 days supply. The investigator was to monitor the tablets at each visit to determine when more medication was to be provided to the patient.

Medication was dispensed at baseline and weeks 1, 2, 3, 4, 5, and 6. Patients were requested to return the empty packages from the previous week's supply along with any unused medication to allow the investigator to assess compliance by counting the remaining tablets. All unused medication was to be documented with the date, amount, and signature, and returned to the sponsor at the end of the study. The investigator was responsible for drug accountability and was instructed to keep a record of the test compounds received from the sponsor. Discrepancies between dispensed and returned study medications were to be recorded and explained on the accountability form.

6.4.3. Method of Assigning Subjects to a Treatment Group

Since this was a single-arm, open-label study, patients were enrolled into the treatment group at study site. After receiving assurance via secure internet connection from InForm (Phase Forward) that all entry criteria were met, the patient was assigned a patient number directly at the study center and enrolled into the study at that site.

6.4.4. Selection of Doses Used in the Study

The clinical program for reboxetine includes data from 39 studies, of which 14 trials were Phase 2 and Phase 3 studies conducted in patients with depression. In these studies, 1622 patients with depression were treated with reboxetine at the recommended doses of 8 to 10 mg/day for adults (18 to 65 years of age) and 4 to 6 mg/day for elderly (>65 years of age) patients in short-term (4, 6, or 8 weeks) or long-term (up to one year) phase 2 and phase 3 depression studies [3-12].

In patients who do not fully respond to treatment with an SSRI, combination therapy with an NRI may offer benefits. Combining 2 agents with different sites of action may enhance the activity of both agents. Safety data are available for the coadministration of reboxetine and fluoxetine for up to 8 weeks. [14] Results of preliminary data analysis showed no evidence of any interaction between reboxetine and fluoxetine on any clinical measure (adverse events or laboratory results).

The augmentation study described in this report was designed for patients with major depressive disorder who were partial responders to fluoxetine at a dose of 20 mg/day. This pilot study was undertaken to assess the safety of adding reboxetine to the regimen of patients already receiving fluoxetine (for at least 6 weeks). Based on the results of the short-term reboxetine/fluoxetine study in healthy volunteers, a reboxetine dosage of 4 mg to 8/mg per day with fluoxetine at 20 mg/day was chosen for this study.

6.4.5. Selection and Timing of Dose for Each Patient

Reboxetine. The starting dose of reboxetine was 4 mg given twice daily as divided doses (2 mg in the morning and 2 mg in the evening). After at least 3 days, at the discretion of the Investigator, the dose could be increased to 6 mg (given as 4 mg in the morning and 2 mg in the evening). After an additional 3 days at the discretion of the investigator, the dose could be increased to 8 mg (4 mg in the morning, 4 mg in the evening). At any time, the dose of reboxetine could be reduced (but not below 4 mg/day) at the discretion of the Investigator.

Study site personnel directed the patients to ingest the study treatment, in the morning and the afternoon/evening, at approximately the same time each day (eg, between 8 to 9 AM and 5 to 6 PM). The medication was to be taken at least 3 hours before bedtime.

Fluoxetine. The fluoxetine dose was to be maintained at a dose of 20 mg once daily to be given in the morning.

6.4.6. Blinding

This was an open-label study.

6.4.7. Prior and Concomitant Treatment

No concomitant psychotropic medication other than lorazepam 1 to 2 mg (maximum 2 mg/day), zolpidem 5 to10 mg (maximum 10 mg/day), or chloral hydrate 500 to 1000 mg (maximum 1000 mg/day), as a sleep inducer on an as-needed basis (up to 4 days/week) was permitted during the first 4 weeks of study treatment only. The administration of other psychotropic drugs was considered a protocol violation requiring exclusion of the patient from the study.

Other therapy considered necessary for the patient's well being could be given at the discretion of the Investigator and was to be recorded in the Concomitant Therapy Form. While enrolled in this study, patients were not permitted to use other investigational drugs nor participate in any other clinical study. Contraceptives were to be used by female patients of child-bearing potential (see Exclusion criteria Section 6.3.2.) Over-the-counter (OTC) medications were allowed as needed for symptomatic treatment, with the exception of St. John's Wort, Ginkgo, Valerian Root and S-adenosylmethionine (SAMe). Any OTC medications were to be recorded on the Concomitant Therapy Form along with other medications.

6.4.8. Treatment Compliance

Acceptable patient compliance was defined as an overall drug intake of at least 80% of the prescribed amount throughout the course of the trial. Compliance was monitored by the investigator and recorded in the appropriate CRF section at each scheduled visit.

6.4.9. Removal of Patients from Treatment or Assessment

A patient was to be withdrawn from the trial treatment if the investigator felt it was clinically necessary or if it was the wish of the patient.

Termination of study therapy prior to completion of the planned treatment period could be considered in case of adverse events, clinical deterioration, etc. In the case of pregnancy, a female patient would be withdrawn from the study.

The reasons for withdrawal of treatment were to be clearly described and, the patient was to be examined as soon as possible. Relevant safety and efficacy assessments (laboratory tests, ECG, and any diagnostic procedure necessary to define an adverse event leading to withdrawal) were to be obtained, and all relevant assessments completed. All case report forms were to be completed and forwarded to Pharmacia.

If the patient did not return for a scheduled visit, every effort was to be made to contact the patient and to document the patient's outcome, if possible.

6.5. Efficacy and Safety Variables

6.5.1. Efficacy and Safety Measures Assessed

Investigators assessed clinical efficacy by changes in the following scales: Primary variable, HAM-D; secondary variables, MADRS and CGI.

Safety of the combination regimen was monitored throughout the study by analysis of laboratory assays, measurement of vital signs, collection of adverse events, and the use of concomitant medications.

The study schedule is summarized in Table 1.

6.5.1.1. Efficacy Variables

The efficacy assessments used in this study included the HAM-D 17-item scale (primary variable), and MADRS and CGI scales (secondary variables). Each scale is a measure of depression rated by the clinician and is briefly described below.

No laboratory efficacy assessments were planned for this study.

6.5.1.1.1. Hamilton Depression Rating Scale (HAM-D 17 Item)

This observer-rated scale is based on a clinical interview and observations of behavior made by an experienced psychiatrist [15]. The items on the HAM-D are graded according to the severity on a 0 to 2 (3 points) or 0 to 4 (5 points) point scale. The total score ranges from 0 to 62. The protocol directed the HAM-D to be performed at every visit.

6.5.1.1.2. Montgomery Asberg Depression Rating Scale (MADRS)

The MADRS is based on a clinical interview [17]. This scale has been shown to distinguish satisfactorily between 5 grades of depression, and its overall performance was found to be equal to the HAM-D. The scale consists of 10 items, with each item scored on a 7-point scale, graded from 0 to 6. A score of 0 signifies absence of the symptom in question, while a score of 6 signifies the most extreme form of the symptom. Total scores range from 0 to 60. The protocol directed the MADRS to be performed at every visit except at screening.

6.5.1.1.3. Clinician's Global Impression (CGI)

The CGI consists of 2 parts: Severity of Illness and Global Improvement [16]. This scale is routinely used as an outcome measure in therapeutic trials. The Severity of Illness and Global Improvement scales are each 7 point scales, with lower scores indicating better health. The protocol directed the CGI to be performed at baseline and at all subsequent visits.

6.5.1.2. Safety Variables

The clinical safety assessments include the following:

- Standard medical history obtained at screening
- Standard clinical and physical examination obtained at screening and at the final visit
- Vital signs at screening, baseline, and every treatment visit
- Monitoring of treatment-emergent adverse events from baseline until the last study visit
- Clinical laboratory assessments at screening and at the final visit

6.5.1.2.1. Adverse Events

An adverse event (AE) was any untoward medical occurrence in a patient or trial subject administered a drug or biologic (medicinal product) or using a medical devise; the event did not necessarily have a causal relationship with that treatment or usage.

Adverse events included the following:

a. All suspected adverse medication reactions.

b. All reactions from medication overdose, abuse, withdrawal, sensitivity or toxicity.

c. Apparently unrelated illnesses, including the worsening of a preexisting illness (see Preexisting Conditions, below).

d. Injury or accidents. **Note** that if a medical condition was known to have caused the injury or accident (eg, a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) were reported as 2 separate adverse events. The outcome of the accident (eg, hip fracture secondary to the fall) was recorded under Comments.

e. Abnormalities in physiological testing or physical examination (findings that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).

f. Laboratory abnormalities that required clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (eg, elevated liver enzymes in a patient with jaundice) were to be described under Comments on the report of the clinical event rather than listed as a separate adverse event.

The adverse event reporting period for this trial began upon receipt of the first dose of investigational medication and ended at the final clinic visit/week 8.

In this trial, a preexisting condition (ie, a disorder present before the adverse event reporting period started and noted on the pretreatment medical history/physical examination form) was not to be reported as an adverse event unless the condition worsened or episodes increased in frequency during the adverse event reporting period (see also Symptoms of Depression).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, were not to be reported as adverse events. However, the medical condition for which the procedure was performed was to be reported if it met the definition of an adverse event. For example, an acute appendicitis that began during the adverse event reporting period was to be reported as the adverse event and the resulting appendectomy noted under Comments.

Except for worsening of depressed mood, worsening of other symptoms of depression were considered as adverse events in this protocol. Any increase in the intensity of depressed mood was to be reflected on the HAM-D (item 1). However, increases in the intensity of other symptoms of depression (eg, sleep difficulties, somatic symptoms, genital symptoms, weight change, anxiety, other psychiatric symptoms) were considered as an Adverse Event. It was recognized that such symptoms might be present prior to the start of study drug (ie, at baseline) and the importance of carefully recording the event as being present at that time was stressed. Only those symptoms whose intensity increased during the treatment period were counted as an Adverse Event.

Each adverse event was classified by the investigator as SERIOUS or NONSERIOUS. This classification of the gravity of the event determined the reporting procedures to be followed.

An adverse event that met one or more of the following criteria/outcomes was classified as serious:

- Death
- Life-threatening (ie, immediate risk of death)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity (any sight-threatening event with ophthalmic products was a significant incapacity)
- Congenital anomaly/birth defect
- Other, Medical/Scientific Judgment

Medical judgment was to be exercised in deciding whether a reaction was serious in other situations. Important adverse reactions that were not immediately life-threatening or did not result in death or hospitalization but possibly jeopardized the patient were to be considered serious. Also classified as serious was any other event that the investigator or company judged to be serious or which was defined as serious by the regulatory agency in the country in which the event occurred.

The Pharmacia monitor was to be notified using the designated form within 24 hours of awareness of the event by the investigator. The initial report was to be followed by submission of more detailed adverse event information within 5 working days of the event. If the serious event was unexpected, serious adverse events were also to be reported immediately to the responsible Institutional Review Board/Independent Ethics Committee.

The investigator was to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient. In addition, each trial patient was questioned about adverse events at each clinic visit following initiation of treatment. The question asked was "Since your last clinic visit" or "Since you began taking the investigational medication", have you had any health problems?"

If any female patient became or was found to be pregnant while receiving an investigational medication or within 30 days of discontinuing investigational medication, the investigator was instructed to submit an adverse event case report form that included the anticipated date of birth or pregnancy termination. The patient was then to be followed by the investigator until completion of the pregnancy. If the pregnancy ended for any reason before the anticipated date provided, the investigator was instructed to notify the Pharmacia monitor. If the outcome of the pregnancy met the criteria for immediate classification as a serious medical event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator was to follow the procedures for

reporting serious medical events. Additional information about pregnancy outcomes that were classified as serious medical events is provided in Section 8.5.10 of the Protocol.

All adverse events were to be followed until they resolved or the patient's participation in the trial ended, ie, until a final report was completed for that subject. In addition, all serious adverse events and those nonserious events assessed by the investigator as possibly related to the investigational medication/product were to be continued to be followed even after the patient's participation in the trial was over. Such events were to be followed until they resolved or until the investigator assessed them as "chronic" or "stable". Resolution of such events was to be documented on the appropriate CRF.

6.5.1.2.2. Clinical Laboratory Evaluations

The laboratory safety assessments included the ECG, and laboratory test assay results.

ECG (central reading and evaluation): at screening and week 8 (end of treatment). Analysis included assessment of normal or abnormal ECG patterns and measurement of appropriate intervals (eg, QT_c intervals).

Laboratory test assays (central analysis): complete blood count and differential, reticulocyte count, sodium, potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, and uric acid at screening and at the end treatment (week 8). Serum pregnancy test (females of childbearing potential) and urine drug screen (amphetamines, barbiturates, benzodiazepines, marijuana metabolites, cocaine metabolites, methadone, opiates, phencyclidine, propoxyphene, ethyl alcohol) were performed at screening and at the end of treatment. Thyroid tests TSH and T4 were performed only at screening.

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

Vital signs (blood pressure and heart rate) were measured and analyzed at screening, baseline, and at every treatment visit. Blood pressure (supine) and heart rate were to be measured at the same time of the day after 5 minutes of quiet rest at each visit.

Physical examinations were performed at screening and at the end of treatment. Changes in physical findings were to be documented.

6.5.2. Criteria for Effectiveness

6.5.2.1.1. Primary Efficacy Variable(s)

The primary efficacy variable is the change from baseline in HAM-D 17 item scale.

6.5.2.1.2. Secondary Efficacy Variables

The secondary efficacy variables are the MADRS and CGI scales.

6.6. Data Quality Assurance

To ensure that quality data were collected, the following actions were taken in conducting this trial.

The investigators received study manuals and attended an Investigator Meeting prior to initiating trial.

Data were collected using a password-protected web-based system shielded with extensive firewalls that provided data capture with all forms as on-line images. Data were inserted directly into the database.

Investigator descriptions of adverse events were coded using a standardized terminology (Coding Symbols for a Thesaurus of Adverse Reaction Terms [COSTART]).

The study sites underwent periodic monitoring visits by Pharmacia study monitors.

A central laboratory was used for analysis of safety laboratories, and a central facility performed all ECG assessments.

Source documents were reviewed by Pharmacia personnel to verify the correctness of the data collected on the CRFs.

The investigator or institution guaranteed Pharmacia representatives access to the source documents.

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, as documented in Appendix 1.8.

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

6.7.1. Statistical and Analytical Plans

Descriptive statistics were generated for the effectiveness and safety variables. These included minimum, maximum, mean and standard error (deviation) for continuous variables. For categorical variables, proportions of patients in each category of interest were provided.

6.7.2. Determination of Sample Size

Since this was a pilot study, clinical judgment estimated that 20 to 30 patients should be adequate to provide appropriate information for a larger controlled, randomized study. The purpose of the study was to generate safety data on the combined treatment with reboxetine 4

to 8 mg and fluoxetine 20 mg. If the safety information and the changes from baseline in the HAM-D, MADRS, and CGI observed in this study suggest that reboxetine augmentation may be beneficial to fluoxetine partial responders, a larger augmentation study might be conducted.

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

6.8.1. Protocol Amendments

This protocol was not amended.

6.8.2. Changes in the Statistical Plan

There were no changes to the statistical plan.

7. RESULTS

Important data displays are included in the text. More detailed, supportive tables are included in Appendix 2.

7.1. Study Subject Information

7.1.1. Disposition of Subjects

A total of 34 patients were enrolled in the 3 study centers. One patient was immediately lost to follow-up. It is unknown whether the patient ever took drug; this patient was excluded from all analyses. The remaining 33 patients received treatment with reboxetine.

A total of 33 patients were included in the safety analysis. The safety population consisted of all patients who received at least one dose of study medication. The ITT population consisted of 33 patients and included all patients who received at least one dose of study medication with at least one post-baseline efficacy measure.

Twenty-six (76.5%) patients completed the 8-week treatment period. The reasons for study discontinuation are summarized in Table 3.

Table 3. Patient Disposition

	n	%*
Number of patients		
Enrolled to reboxetine treatment	34	100
Safety population †	33	97.1
Intent-to-treat ‡	33	97.1
Completed 8-week study	26	76.5
Discontinued study	8	23.5
Reason for discontinuation		
Adverse event	7	20.6
Lost to follow-up	1	2.9

Abbreviation: ITT = intent-to-treat
*Percentages are based on the number of patients enrolled.
† The safety population includes all patients who received at least one dose of study medication.
‡ The intent-to-treat population includes all patients who received at least one dose of study medication with at least one post-baseline efficacy measure.
Source: Appendix 2, Table DS1

Eight patients discontinued the study early, 7 of these discontinuations were due to adverse events (see Section 2.5.2.3), and one patient was lost to follow-up. Diaphoresis (3 patients) was the most common reason for study discontinuation due to an adverse event. A list of patients who discontinued the study and the reasons for discontinuation is provided in Appendix 2, Table DS2.

The numbers of patients participating by visit are displayed in Appendix 2, Table DS3.

7.1.2. Protocol Deviations

7.1.2.1. Violations in Subject Inclusion/Exclusion Criteria

Post-study, one patient (No. 307) tested positive for marijuana at Screen but was enrolled anyway and completed the study. A complete summary of urine drug screen results is provided in Appendix 2, Table LAB6.

No other protocol violations were observed among the enrolled patients in this study.

7.1.2.2. Deviations from Planned Trial Conduct

No deviations from the planned trial conduct were reported.

7.1.3. Data Sets Analyzed

The efficacy analyses were based on the ITT population, which included all patients enrolled into the trial who received at least one treatment dose with at least one post-baseline efficacy follow-up. Of the 34 patients enrolled, 33 were included in the intent-to-treat efficacy analysis.

All patients who were enrolled and received at least one dose of the study drug were included in all safety analyses. Of the 34 patients who were enrolled into the study, 33 patients satisfied these criteria and were, therefore, included in all safety analyses.

Study days were numbered relative to the first day of dosing. The Study Manual clarified the study visit window to be ±3 days of the specified schedule.

7.1.4. Demographic and Other Baseline Characteristics

7.1.4.1. Patient Demographics

The patients in the study ranged in age from 20 to 61 years, and the majority of the patients were female and white. Demographic characteristics are summarized in Table 4.

Table 4. Patient Demographic Characteristics at Screen

Baseline Characteristic		Reboxetine N=34
Age, years	Mean ± SD	43.8 ± 11.5
	Range	20 - 61
Weight, pounds	Mean ± SD	187.4 ± 49.2
	Range	97 - 312
Height, inches	Mean ± SD	67.0 ± 3.6
	Range	60 - 74
Sex: n (%)	Male	12 (35.3%)
	Female	22 (64.7%)
Race: n (%)	Caucasian	27 (79.4%)
	Black	1 (2.9%)
	Asian	3 (8.8%)
	Other	3 (8.8%)

Abbreviations: SD=standard deviation
Source: Appendix 2, Tables DM1, DM2

Appendix 3.4 contains a listing of demographic data by subject.

7.1.4.2. Medical History

A listing of medical history findings for individual patients is presented in Appendix 2, Table DM10.

Headaches (ie, tension headaches and migraines) and gastrointestinal conditions (eg, gastroesophageal reflux, irritable bowel, constipation) were commonly reported as active or controlled conditions for patients in this study. Allergies (seasonal, environmental), drug allergies, and asthma were also frequently noted. Back pain/cervical back trouble was

reported by about one-fifth of the patients. One patient reported controlled hypothyroidism at study entry.

Antidepressant medication history is summarized for all 34 patients in Appendix 2, Table DM7. All patients in this study reported prior use of fluoxetine, 6 pts reported using paroxetine (Paxil™), 4 patients reported using sertraline (Zoloft™), 4 patients reported use of tricyclic antidepressants (1 each: amitryptyline, desipramine, doxepin, and protriptyline) and 3 patients reported using bupropion. There were 14 reports of patients involving 10 patients who received research or investigational drug in trials involving at least 5 individual research drugs.

7.1.4.3. Psychiatric History

Psychiatric history summaries can be found in Appendix 2, Tables DM4 and DM5. All patients were outpatients, and only one (1/34, 2.9%) had ever been hospitalized for this condition.

Eleven patients (32.4%) had been previously treated with psychotropic medications other than anti-depressants, including benzodiazepines and lithium (4 patients each); 3 patients had medications classified as "other." History of anti-depressant medications is summarized in Appendix 2, Table DM7.

All patients received fluoxetine throughout the study.

7.1.4.4. Diagnosis of Mental Disorder

On average, the patient in this study was 30.8 years old at his/her first depressive episode. The median duration of the present episode at screen was 52.2 weeks (range 10 to 2192 weeks).

The present episode was reported to be a first occurrence in only 8 patients (8/34, 23.5%). Patients for whom this episode was a recurrent event had 2.3 previous episodes (on average). Appendix 2, Table DM6 provides a complete summary of the diagnosis of mental disorder.

7.1.4.5. Laboratory Values

Most baseline laboratory values were within normal limits for hematology and chemistry assays. Laboratory tests performed are discussed in Section 6.5.1.2.2, and results are provided in Section 7.4.3.

7.1.4.6. Vital Signs

Baseline average blood pressure measurements were: 124±13 mmHg (systolic) and 79±10 mmHg (diastolic), and pulse rate was 70±11 beats per minute. Summaries of pre-treatment blood pressure and pulse are displayed in Appendix 2, Table DM3.

7.1.4.7. Efficacy Variables

Table 5 summarizes the efficacy variables at the baseline visit. All patients fulfilled the inclusion criterion of the HAM-D 17-Item Total Score ≥ 14. Most (97%) were rated by the clinician as moderately ill at baseline.

Table 5. Baseline Efficacy Variables

Efficacy Measure	Category or Statistic	Reboxetine N=34
HAM-D 17-Item Total score	Mean ± SD	18.3 ± 3.2
	Range	14 – 25
MADRS Total Score	Mean ± SD	26.2 ± 5.4
	Range	16 - 38
CGI Severity of Illness	Moderately ill	33 (97.1%)
	Markedly ill	1 (2.9%)

Abbreviation: CGI=Clinician's Global Impression, HAM-D=Hamilton Rating Scale for Depression, MADRS=Montgomery Asberg Depression Rating Scale
Source: Appendix 2, Tables DM8, DM9

7.1.5. Concomitant Medications and Other Therapies

All concomitant medications used during the course of the study, including those used within 30 days prior to the Screen visit, were recorded on the CRF. Concomitant medications were coded using the SUDDS dictionary, and a summary of coded medications was produced. Antipsychotic medications used before entering the study are described in Section 7.1.4.2 Medical History.

A descriptive summary of the number of patients using each concomitant medication before reboxetine treatment began is provided in Appendix 2, Table CM1, and a summary for during treatment can be found in Appendix 2, Table CM2.

The concomitant medications taken by more than 10% of the patients prior to treatment were multivitamins, aspirin, ibuprofen, and Claritin® (Table CM1). Ibuprofen and multivitamins were taken by more than 10% of patients during treatment (Table CM2). Most concomitant medications listed were taken by one patient each.

7.2. Dosage Information

7.2.1. Extent of Exposure

The mean daily, prescribed dose of study medication (reboxetine) is presented by visit in Table 6. These mean-dosing data suggest that patients complied with the dosing regimens that were specified in the protocol (ie, patients could be titrated from 4 to 6 mg/day, then 6 to

8 mg/day, with each dose regimen maintained for at least 3 days prior to dose increase). The average prescribed dose at the end of the 8 weeks was 6.8 ±1.7 mg/day.

Table 6. Mean Daily Dose of Reboxetine

Week	Reboxetine N=33	
	n	Mean Dose ± SD (mg/day)
Week 1	33	4.0 ± 0.0
Week 2	29	4.6 ± 0.9
Week 3	29	5.7 ± 1.5
Week 4	28	6.3 ± 1.4
Week 5	28	6.6 ± 1.5
Week 6	28	6.7 ± 1.6
Week 8	26	6.8 ± 1.7

Abbreviation: SD=standard deviation
Source: Appendix 2, Table SM2

Two patients had their dose reduced due to adverse events. Patient No. 113, a 45-year-old female, experienced moderate paresthesias of the extremities and had her dose reduced (day 17 to day 24). Patient No. 205, a 55 year-old-female, reported a mild insomnia and had her dose reduced (day 23 to day 30) but after 2 weeks at 6 mg, the dose was increased back to 8 mg/day. Both patients recovered from these adverse events and completed the study. In addition, 2 other patients had dose reductions: Patient No. 105, a 45-year-old male who initially received 4 mg (day 1 to day 15) increased to 6 mg (day 16 to day 23) and to 8 mg (day 23 to day 36), had a dose reduction to 4 mg (day 37 to day 42). This patient experienced sweating (initially moderate, increasing to severe [day 33]), withdrew from the study on day 42, and had recovered by day 44. Patient No. 301, a 54-year-old female, initially received 4 mg (day 1 to day 7) increased to 6 mg (day 7 to day 44), but the dose was reduced to 4 mg for the last 2 weeks of the study. The patient completed the study. No reason was given for the decreased dose.

7.2.2. Treatment Compliance

All patients were ≥80% compliant during the course of the study (Appendix 2, Table SM1).

Appendix 3 contains compliance and drug concentration data.

7.3. Efficacy Results

7.3.1. Primary Efficacy Variable

The primary efficacy variable in this study was the mean change from baseline in the HAM-D 17-Item score.

7.3.1.1. Primary Analysis

Table 7 shows results for the mean change from baseline in 17-Item HAM-D scores. Using the last observation carried forward (LOCF) methodology for missing data, decreases from baseline were noted in the mean 17-Item HAM-D total score throughout the entire 8 weeks of treatment. The greatest mean change from baseline HAM-D total scores occurred at week 8 (-7.3±6.1, with 95% confidence interval of -9.5, -5.2). The summary of LOCF mean scores of the HAM-D questionnaire by visit is provided in Appendix 2 Table EF1.

Table 7. Mean from Baseline in the HAM-D 17-Item Total Score ITT Population (LOCF)

Treatment Week*	Reboxetine N=33				
	Mean Values		Change from Baseline		
	Mean	SD	Mean	SD	95% CI
Baseline	18.2	3.1	--	--	--
Week 1	16.2	3.9	-2.0	3.2	(-3.1,-0.9)
Week 2	14.3	3.8	-3.9	3.6	(-5.2, -2.6)
Week 3	13.3	4.0	-4.9	4.2	(-6.4, -3.4)
Week 4	11.9	4.3	-6.2	4.8	(-8.0, -4.5)
Week 5	11.8	4.7	-6.3	5.2	(-8.2, -4.5)
Week 6	11.6	5.3	-6.5	5.7	(-8.6, -4.5)
Week 8	10.8	5.7	-7.3	6.1	(-9.5, -5.2)

Abbreviations: CI=confidence interval, HAM-D=Hamilton Rating Scale for Depression, ITT=intent-to-treat, LOCF=last observation carried forward, SD=standard deviation
* N=33 for every treatment week
Source: Appendix 2, Table EF1

An analysis of observed cases (OC) showed similar results (Appendix Table EF2).

7.3.2. Secondary Efficacy Variables

Secondary efficacy variables included the HAM-D response and remission rates, the mean change from baseline in MADRS total score, and the CGI Global Improvement responder rate.

7.3.2.1. HAM-D Response and Remission Rates

A decrease of at least 50% in the HAM-D 17-Item total score from baseline value was considered an index of response. The number of responders to reboxetine increased consistently over time with 13 (39.4%) responders at the end of treatment (Table 8).

A decrease to ≤8 in the HAM-D 17-Item score was considered an index of remission. The number of patients in remission consistently increased over time, with 12 (36.4%) patients in remission at end of treatment (Table 8).

Table 8. Number of Patients Responding to Reboxetine and the Number of Patients in Remission ITT Population (LOCF)

Week	Reboxetine			
	Responder * N=33		Remission † N=33	
	n	%	n	%
Week 1	0	0	0	0
Week 2	3	9.1	2	6.1
Week 3	5	15.2	4	12.1
Week 4	7	21.2	5	15.2
Week 5	8	24.2	7	21.2
Week 6	8	24.2	7	21.2
Week 8	13	39.4	12	36.4

Abbreviation: HAM-D=Hamilton Rating Scale for Depression, LOCF=last observation carried forward
* A decrease of at least 50% in the HAM-D 17-Item total score from baseline was considered an index of response
† A decrease to ≤8 in the HAM-D 17-Item score was considered an index of remission.
Source: Appendix 2, Table EF3, EF5

An analysis of observed cases showed a similar trend (Appendix 2, Tables EF4, EF6).

7.3.2.2. MADRS Total Score

In the LOCF analysis, decreases from baseline were shown in the mean MADRS total score throughout the entire 8 weeks of treatment (Table 9). The greatest mean change from baseline in the MADRS total score occurred at week 8 (-10.2±10.4, with 95% confidence interval of -13.8, -6.5.)

Table 9. Mean from Baseline in the MADRS Total Score ITT Population (LOCF)

Treatment Week*	Reboxetine N=33			
	Mean Values		Change from Baseline	
	Mean	SD	Mean	SD
Baseline	26.1	5.4	--	--
Week 1	24.0	5.8	-2.1	4.6
Week 2	21.1	6.4	-5.0	6.0
Week 3	19.3	7.3	-6.8	7.3
Week 4	16.5	7.6	-9.6	8.9
Week 5	16.2	8.0	-9.8	9.3
Week 6	15.7	8.2	-10.4	9.7
Week 8	15.9	9.1	-10.2	10.4

Abbreviations: ITT=intent-to-treat, LOCF=last observation carried forward, MADRS=Montgomery Asberg Depression Rating Scale, SD=standard deviation
* N=33 for every treatment week
Source: Appendix 2, Table EF7

The observed case analysis showed similar results (Appendix Table EF8).

7.3.2.3. CGI Global Impression

Improvements in the CGI Severity of Illness scale were consistently shown over time in both the LOCF and OC analyses. The distribution of patients by CGI Severity of Illness score over time is presented in Appendix 2, Tables EF9 and EF10.

A responder was defined as having a score of ≤2 (corresponding to "very much improved" or "much improved") on the CGI Global Improvement scale. As with the Severity of Illness scale, improvements were consistently shown over time in both the LOCF and OC analyses in the CGI Global Improvement scale (Appendix 2, Tables EF11 and EF12). The number of responders increased consistently over time until week 6, with a slight decrease at week 8 (Table 10).

**Table 10. CGI Global Improvement Responder Rate*
ITT Population (LOCF and OC)**

Treatment Week*	Reboxetine N=33			
	LOCF (N=33)		OC	
	n	%	n/N	%
Week 1	1	3.0	1/33	3.0
Week 2	6	18.2	6/29	20.7
Week 3	8	24.2	8/29	27.6
Week 4	17	51.5	17/28	60.7
Week 5	15	45.5	15/28	53.6
Week 6	18	54.5	18/28	64.3
Week 8	17	51.5	16/26	61.5

Abbreviations: CGI=clinician global impression scale, ITT=intent-to-treat, LOCF=last observation carried forward, OC=observed case
* A responder was defined as a score of ≤2 on the CGI Global Improvement scale. This score corresponds to assessments of "very much improved" or "much improved."
Source: Appendix 2, Table EF11, EF12

7.3.3. Efficacy Summary and Conclusions

Decreases from baseline HAM-D 17-Item scores were noted throughout the 8-week treatment period, with the greatest decrease at week 8. A similar pattern of reduction in depression score with the addition of reboxetine was observed when patients were rated using the MADRS scale. The percentage of patients identified as responders at week 8 after reboxetine augmentation was 39.4% of patients using the HAM-D score, and 36.4% were in remission. For those patients who were only partial responders to fluoxetine treatment, the fact that nearly 40% of patients were classified as being responders and as being in remission is a clinically important finding. At week 8, more than half the patients were rated as responders (very much improved or much improved) using the CGI Global Improvement score. Results for all measures were similar whether LOCF or OC analysis was used. These results show that short-term reboxetine augmentation improved the rates of response and remission among fluoxetine partial responders with at least 6 weeks of previous therapy.

7.4. Safety Results

Safety analyses are based on all patients who received at least one dose of study medication.

7.4.1. Treatment-Emergent Adverse Events

7.4.1.1. Brief Summary

Table 11 provides a summary of adverse events.

Table 11 Overall Summary of Adverse Events (AEs)

Adverse Event	Reboxetine N=33	
	n	%
Patients who reported ≥1 AE	30	90.9
Drug-related AEs*	29	87.9
Serious AE	1	3.0
Patients who discontinued due to AE	7	21.2

Abbreviation:
* AEs were considered drug-related, if, in the opinion of the investigator, there was a reasonable possibility that the event was caused by the investigational medication.
Source: Appendix 2, Tables AE1, AE3, AE4, AE8

Most (90.9%, 30/33) patients reported at least one adverse event while on study medication. Seven patients (21.2%) discontinued participation due to adverse events, mostly in the digestive, nervous, and skin systems.

The only serious AE reported in this study was an unintended pregnancy reported by one patient.

No deaths were reported in this study.

7.4.1.2. All Treatment-Emergent Adverse Events

The frequency of adverse events is summarized by COSTART body system in Table 12.

Table 12. Frequency of Adverse Events by Body System

COSTART Body System Classification	Reboxetine N=33	
	n	%*
Patients who reported ≥1 AE	30	90.9
Body systems		
Digestive	20	60.6
Nervous	17	51.5
Body as a whole	13	39.4
Skin	9	27.3
Urogenital	7	21.2
Special Senses	5	15.2
Cardiovascular	4	12.1
Respiratory	4	12.1
Metabolic and Nutritional	2	6.1

Abbreviation:
* Patients who reported more than one event in a given body system was counted only once for that body system.
Source: Appendix 2, Tables AE1

The most frequently reported adverse events were related to the digestive (60.5%) and nervous systems (51.5%).

Adverse events reported by at least 5% (>1 patient) are summarized in Table 13.

Table 13. Adverse Events Reported by ≥5% of Patients

COSTART Body System Preferred Term*	Reboxetine N=33	
	n	%*
Digestive		
Dry mouth	10	30.3
Constipation	8	24.2
Nausea	4	12.1
Nervous		
Insomnia	12	36.4
Anxiety	4	12.1
Dizziness	2	6.1
Libido decreased †	2	6.1
Tremor	2	6.1
Body as a whole		
Flu syndrome	4	12.1
Headache	4	12.1
Upper respiratory infection	2	6.1
Skin		
Diaphoresis	8	24.2
Urogenital		
Urination impaired ‡	3	9.1
Ejaculation abnormal	2	6.1
Special Senses		
Blurred vision	3	9.1
Tinnitus	3	9.1
Metabolic and Nutritional		
Weight decrease	2	6.1

Abbreviation:
* Patients who reported more than one event in a given body system was counted only once for that body system.
† Reported by 2 males.
‡ Reported by 2 males, 1 female.
Source: Appendix 2, Tables AE1

The most frequently reported adverse events were insomnia, dry mouth, diaphoresis, and constipation. Most adverse events were reported as mild to moderate in intensity. Adverse events rated as severe are summarized in Table 14.

All adverse events are summarized by maximum intensity in Appendix 2, Table AE2.

Table 14. Adverse Events Rated as Severe

COSTART Body System Preferred Term	Reboxetine N=33	
	n	%*
Skin		
Diaphoresis	2	6.1
Digestive		
Dry mouth	1	3.0
Constipation	1	3.0
Nervous		
Insomnia	1	3.0
Tremor	1	3.0
Cardiovascular		
Sinus tachycardia	1	3.0

Source: Appendix 2, Table AE2

All adverse events by body system and by COSTART preferred term are summarized in Appendix 2, Table AE1. The only patient associated with >1 severe adverse event was Patient No. 116, who reported severe tremor (onset day 1, recovered day 11) and severe sinus tachycardia (onset day 56, recovered one week after discontinuation). A complete listing of adverse events is presented in Appendix 2, Table AE5.

Appendix 2 lists the subjects for whom adverse events were reported.

7.4.1.3. Drug-Related Treatment-Emergent Adverse Events

Adverse events that were judged by the investigators as related to study medication were reported by 87.9% (29/33) of patients. Drug-related adverse events reported by at least 5% (more than one patient) are summarized in Table 15.

Table 15. Drug-Related* Adverse Events Reported by ≥5% of Patients

COSTART Body System Preferred Term*	Reboxetine N=33	
	n	%*
Digestive		
Dry mouth	10	30.3
Constipation	8	24.2
Nausea	4	12.1
Nervous		
Insomnia	11	33.3
Anxiety	3	9.1
Dizziness	2	6.1
Libido decreased †	2	6.1
Tremor	2	6.1
Skin		
Diaphoresis	8	24.2
Body as a whole		
Headache	4	12.1
Special Senses		
Blurred vision	3	9.1
Tinnitus	3	9.1
Urogenital		
Urination impaired ‡	3	9.1

* Drug-related adverse events judged by the investigator as caused by the study medication.
† Reported by 2 males
‡ Reported in 2 male, 1 female patient
Source: Appendix 2, Tables AE3

The most frequently reported drug-related adverse events were insomnia, dry mouth, diaphoresis, and constipation. Urinary impairment and decreased libido were reported more frequently by males. Most drug-related adverse events were rated as mild or moderate. Severe AEs were reported in 6 patients: diaphoresis (2 patients), constipation (1 patient), insomnia (1 patient), dry mouth (1 patient), and tremor and sinus tachycardia (1 patient).

Of the 29 patients with drug-related adverse events, half of the patients reported only 1 to 2 drug-related adverse events. Five (17.2%) patients reported 5 or more drug-related adverse events.

All drug-related adverse events are summarized by body system and COSTART preferred term in Appendix 2, Table AE3. A complete listing of drug-related adverse events is presented in Appendix 2, Table AE6.

Appendix 2 lists the subjects for whom adverse events were reported.

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

7.4.2.1. Deaths

No deaths were reported during this study.

7.4.2.2. Serious Adverse Events

The only serious adverse event reported in this study was an unintended pregnancy in one patient (3.0%, 1/33). Patient No. 104 experienced an unintended pregnancy and was withdrawn from the study (Appendix Table AE8).

7.4.2.3. Discontinuations Due to Adverse Events

Seven (21.2%, 7/33) patients discontinued from the study due to adverse events. These patients and the reasons for discontinuation are listed in Table 16.

Table 16. Discontinuations due to Adverse Events (AEs)

Patient No.	AEs Leading to Discontinuation*	Start/ stop dates	Intensity	Recovered?	Other AEs not leading to D/O
104	Unintended pregnancy	d28	Mild	no	insomnia
105	Diaphoresis	d33†	Sev	no	dry mouth, headache
109	Tachycardia	d1	Mod	no	dry mouth, anxiety, chest pain, excessive sweating, dyspnea
120	Diaphoresis	d2-d10	Sev	yes	Dry mouth, insomnia
308	*Dizziness* blurred vision, dry mouth, insomnia	d1-d7 (all)	*Mild* Mod Mod Mod	yes	
309	Nausea, hypesthesia, asthenia, headache *tinnitus, blurred vision*	d8-d17 (all)	Mod Mod *Mild*	yes (all)	flu syndrome
310	Diaphoresis, insomnia, anxiety, dry mouth headache, nausea	d1-24 d1-d24 d16-d24	Mod (all)	yes (all)	

Abbreviation: D/O=discontinuation, Mod=moderate, Sev=severe
* All events except the unintended pregnancy were considered drug-related. Only the unintended pregnancy was rated as serious.
† Moderate diaphoresis was reported on day 15, worsening to severe on day 33
Source: Appendix 2, Table AE7

Adverse events leading to discontinuation are summarized in Appendix Table AE4; a more detailed listing is provided in Table AE7.

7.4.3. Clinical Laboratory Evaluation

Laboratory normal ranges for hematology and biochemistry tests are shown in Appendix Table LAB1.

7.4.3.1. Hematology

Summary statistics for hematology assays by visit are presented in Appendix 2, Table LAB2.

Most hematology parameters were within normal range at screen and remained normal during treatment. Detailed shift frequencies for the hematology assays are in Appendix 2, Table LAB3. A listing of patients with post-baseline hematology values outside of the normal range is found in Appendix 2, Table LAB7. The changes observed for hemoglobin levels and hematocrits were all less than 10% change from baseline. None of these changes were clinically significant. One patient had a decline in absolute neutrophil count from 2,400 per mL to 1,500 per mL, a decrease in absolute eosinophils from 700 per mL to 400 per mL, and an increase in monocytes from 10.7% to 13.3%. None of these changes was associated with a related adverse event.

Appendix 3 lists laboratory values by patient.

7.4.3.2. Chemistries

Summary statistics for serum chemistry by visit are presented in Appendix Table LAB4.

Most serum chemistry parameters were normal at screen and remained normal during treatment. Detailed shift frequencies for the serum chemistry assays are in Appendix 2, Table LAB5. A listing of patients with post-baseline chemistry values exceeding the normal range is found in Appendix 2, Table LAB8. There were no clinically significant changes.

Appendix 3.8 lists laboratory values by patient.

7.4.3.3. Urine Drug Screen

Post-study, one patient (No. 307) was found to have tested positive for marijuana at Screen.

A complete summary of the urine drug screen results is located in Appendix 2, Table LAB6.

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

7.4.4.1. Vital Signs

There were no major changes from baseline for supine systolic or diastolic blood pressure. Changes in heart rate are listed in Section 7.4.4.2 Electrocardiograms.

7.4.4.2. Electrocardiograms (ECGs)

The majority of patients had ECG finding that were normal at baseline and at the end of treatment (Appendix 2, Table ECG1) These patients' ECG results are listed in Appendix 2, Table ECG3. One patient had a heart rate of 86 beats per minute at baseline, 128 beats per minute at the end of study visit, and 93 beats per minute at one week post-study. This was recorded as an adverse event. Another patient had a 1-mm ST depression observed in leads V3, V4, some of the V5, and parts of Lead II. This was not associated with any related adverse events.

Continuous ECG variables are summarized in Table 17. Two patients had end of study QTcB values exceeding 450 mSec. These values of 457 and 473 represented increases of 37 and 50 mSec, respectively, relative to baseline. While no serious adverse events were associated with the ECG changes in this study, caution should be exercised in patients with compromised cardiovascular conditions.

Table 17. Electrocardiogram Continuous Parameters

Parameter	Reboxetine N=33	
	Screen mean ±SD	End of Study Mean±SD
Heart rate mean (mSec)	65.2±9.8	80.6±14.4
PR interval mean (mSec)	151.9±19.7	146.1±17.6
QRS interval mean (mSec)	87.9±7.7	86.0±6.8
QT interval mean (mSec)	379.3±22.8	354.9±29.2
RR interval mean (mSec)	939.8±136.2	756.6±126.0
QTcB Interval mean (mSec)	394±23	407±26
QTcF Interval mean (mSec)	389±19	389±23

Abbreviation: SD=standard deviation
Source: Appendix 2, Table ECG

7.4.5. Exposure in Utero

Patient No. 104 experienced an unintended pregnancy and was withdrawn from the study. The patient had a therapeutic abortion.

7.4.6. Safety Summary and Conclusions

Most (90.9%) patients reported an adverse event during the study. Insomnia (36.4%), dry mouth (30.3%), diaphoresis (24.3%), and constipation (24.3%) were the most frequently reported adverse events. These were also the most frequently reported drug-related adverse events. Most adverse events were rated as mild or moderate in intensity. Drug-related adverse events were rated as severe in 6 patients: diaphoresis (2 patients), constipation (1 patient), insomnia (1 patient), dry mouth (1 patient), and tremor and sinus tachycardia (1 patient). The only serious adverse event reported in this study was an unintended pregnancy in one patient (3.0%, 1/33), who subsequently was withdrawn from the study. Seven (21.2%, 7/33) patients discontinued from the study due to adverse events including unintended pregnancy (1 patient), diaphoresis (2 patients), tachycardia (1 patient), and 3 patients with multiple adverse events. No deaths were reported in this study.

Hematology and chemistry laboratory values for most patients were within normal limits at baseline and at the end of treatment. Changes observed in hematologic parameters were all less than 10% change from baseline, and none were clinically significant. There were no major changes from baseline for supine systolic or diastolic blood pressure. The majority of patients had ECG finding that were normal at baseline and at the end of treatment. However, caution is indicated in patients with compromised cardiovascular conditions.

Results from this 8-week pilot study conducted in 33 patients indicate that reboxetine appears to be safe when used in combination with fluoxetine in treating patients with major depressive disorder.

8. DISCUSSION AND OVERALL CONCLUSIONS

This study was conducted to assess the safety of adding reboxetine to the regimen of patients who were partial responders on fluoxetine and to estimate augmentation effects in 34 patients with major depressive disorder. Reboxetine (4 mg to 8 mg/day) was added to the drug regimen of patients who were currently on fluoxetine (20 mg once daily) for at least 6 weeks. Reboxetine was initiated at 4 mg day in 2 divided doses, and after a minimum of 3 days, was escalated to 6 mg /day, then after at least 3 days, to 8 mg/day. The mean daily dose of reboxetine was 4 mg/day at week 1 and reached 6.8±1.7 mg/day on week 8. The majority (76.5%, 26/34) of patients completed the planned 8 weeks of treatment.

There were 12 (35.3%) males and 22 (64.7%) females enrolled in this study, and patients were mostly Caucasian. The mean age was 43.8 years (ranging from 20 to 61 years of age), and the mean age at the first depressive episode was 30.8 years. Two-thirds (65%) of the patients experienced previous episodes of depression (mean 2.3 episodes). Only one patient reported previous hospitalization for this condition. In addition to fluoxetine, the most commonly reported antidepressant therapies used prior to study entry were paroxetine, sertraline, and tricyclic antidepressants. One-third of the patients had previously received other psychotropic treatment.

The depression episode at study entry represented a recurrence of the condition for most patients but was the first episode for 8 patients. The mean duration of the present episode was 4.7 years, and a precipitating external stressor was implicated for 61.8% of the patients. The mean scores on depression rating scales were 18.3 (HAM-D) and 26.2 (MADRS), and most patients were rated as showing moderate illness (one as "markedly ill") on the CGI Global Impression scale.

Decreases from baseline HAM-D scores were noted throughout the 8-week treatment period, with the greatest decrease at week 8. A similar pattern of reduction in depression score with the addition of reboxetine was observed when patients were rated using the MADRS scale, which is believed to be a sensitive indicator of change in severity of depression. Using the HAM-D score to determine the percentage of patients who were responders after reboxetine augmentation, 39.4% of patients were responders, and 36.4% were in remission by week 8. This is a substantial improvement for these patients who are only partial responders to fluoxetine treatment. At week 8, more than half the patients were rated as responders (very much improved or much improved) using the CGI Global Improvement score.

Safety was monitored by reports of treatment-emergent adverse events, laboratory measures, vital signs, and ECGs. No clinically significant changes were noted in laboratory assay values, vital signs, or ECG results.

The most commonly reported drug-related adverse events in this study were dry mouth, constipation, sweating (diaphoresis), and insomnia. This is consistent with adverse events reported in the clinical trial database of short-term studies of reboxetine in patients with depression [1,18].

Results from this study appear to support Nelson's hypothesis that combining therapy with SSRI and NRI might be uniquely helpful among nonresponders to SSRI [2]. After 8 weeks of reboxetine augmentation, nearly 40% of the partial responders were classified as responders in this trial.

Nelson also raised the possibility that, although the use of SSRIs in combination with NRIs (particularly TCAs) might be particularly potent, the combination might result in an increase in the frequency of adverse events reported. It is interesting to note that combination treatment produced no new adverse events in this study.

However, Versiani states that since reboxetine has little affinity for muscarinic or adrenergic receptors and lacks affinity for serotonin and dopamine receptors, it may be free of adverse events noted with other NRIs like the TCAs [18].

Results from this 8-week, open-label pilot study conducted in 34 patients indicate that reboxetine appears to be safe when used in combination with fluoxetine in treating patients with major depressive disorder who were partial responders to fluoxetine treatment.

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TABLES AND FIGURES

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LIST OF APPENDICES