Studie 071

(950E-CNS-0005-071-SR)

Studienbericht

Open-label Reboxetine Rescue and Continuation Therapy

Project Code:	PNU-155950E / Reboxetine (Edronax™)
Final Report of the Study:	950E-CNS-0005-071
Previous Reports of the Study:	None
Date of First Subject Enrolled:	31 August 1999
Date of Last Subject Completed:	27 September 2002
Principal or Coordinating Investigator:	Multicenter
Sponsor's Responsible Medical Officer:	Charlotte Kremer, MD Medical Director, Team Leader US Medical Depression and Anxiety Disease Management Team
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.

Open-label Reboxetine Rescue and Continuation Therapy

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.

Charlotte Kremer, MD, Medical Director, Team Leader US Medical Date
Depression and Anxiety Disease Management Team
Pfizer Inc.

Dean Rutty, MSc, Biostatistician Date
Global Medical Affairs, Biostatistics and Data Management
Pfizer Inc.

SYNOPSIS

Name of Company: Pharmacia **Name of Finished Product:** **Reboxetine** **Name of Active Ingredient:** **Reboxetine**	*(For National Authority Use only)*
Title of Study: Open-label reboxetine rescue and continuation therapy.	
Protocol Number: 950E-CNS-0005-071	
Investigator: Multicenter	
Study Centers: 31 centers with subjects enrolled at 18 of the centers	
Publication Reference: None.	
Studied Period (Years): Date first subject enrolled: 31 August 1999 Date last subject completed: 27 September 2002	**Phase of Development:** 3
Objectives: **Primary:** To monitor the long-term safety of reboxetine (RBX) in subjects diagnosed with major depressive disorder (MDD) according to the Diagnostic and Statistical Manual for Mental Disorders, 4th Edition (DSM-IV) criteria. **Secondary:** To measure the efficacy of RBX in treating MDD.	
Methodology: This was an uncontrolled, open-label study of subjects treated with RBX, limited to subjects who had participated in a previous Pharmacia & Upjohn (PNU) supported or sponsored trial within 2 weeks of enrolling in this study. Potential subjects were to be screened for eligibility according to the inclusion/exclusion criteria, and then undergo a thorough assessment (medical and psychiatric history, physical examination, vital signs, height, weight, laboratory assessments, and electrocardiogram [ECG]). At the Screen/Day 1 visit, specific laboratory assessment tests, the physical examination, and the ECG could be waived if done within the last 14 days of the final visit from the previous RBX study. Subjects could enroll in the study once consent had been signed and the screening procedures were verified. Ideally, the subject's Final Visit for the previous RBX study was to be the Screen/Day 1 visit for this study. Thus, the final visit data could be used as the Screen/Day 1 data, with updates or additions as indicated, eliminating the need for duplicate labs and procedures. After clinical laboratory values had been checked, and other eligibility criteria verified, study drug could be administered. Subjects who were enrolled in this study, but whose RBX dose in the previous trial was not known, were to be started on RBX 4 mg BID; after 1 week the investigator could increase the dose up to 10 mg per day if necessary. All other subjects were to be started on their last known RBX dose. If subjects were started on RBX 10 mg/day, the dose could be lowered to 8 mg/day if AEs were reported. Treatment with RBX was to continue for up to 144 weeks.	
Number of Subjects (Planned and Analyzed): A total of 69 subjects were enrolled and all received at least one dose of study drug. The Modified Intent-to-Treat (MITT) population consisted of 68 subjects and included all subjects who received at least one dose of study drug with at least one post-baseline efficacy measure. A total of 37 subjects (53.6%) completed the initial 24-week treatment period, 17 subjects (24.6%) completed the 72-week treatment period, 9 subjects (13.0%) completed the 96-week treatment period, 7 subjects (10.1%) completed the 120-week treatment period, and 2 subjects (2.9%) completed the 144-week treatment period.	
Diagnosis and Main Criteria for Inclusion: Within 2 weeks prior to enrollment in this study, each subject	

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

must have participated in any clinical trial of RBX sponsored or supported by the U.S. Market Company division of PNU, for which the subject met all inclusion/exclusion criteria, including a diagnosis of MDD according to DSM-IV criteria (the subject's MDD could be in remission), and who signed the informed consent form for this study after full discussion.

Test Product, Dose and Mode of Administration, Batch Number: Reboxetine 4 mg scored tablets, 8 to 10 mg/day (total daily dose) administered by the oral route twice daily, Lot #28,588.

Duration of Treatment: Total duration of RBX treatment was up to 144 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: None (open-label study).

Endpoints and Criteria for Evaluation:

Efficacy Variables: Hamilton Rating Scale for Depression, 25-item version (HAMD-25) and Clinical Global Impression (CGI) scales (Severity of Illness, Global Improvement, and Efficacy Index).

Safety: Adverse events (AEs) occurring from baseline through the last visit were recorded; body weight and vital signs (respiration, pulse, blood pressure, temperature) were to be recorded at each visit; and clinical laboratory assessments and ECGs were to be done according to the predetermined schedule.

Statistical Methods: Descriptive statistics were to be generated for both the efficacy and safety variables. These were to include minimum, maximum, mean and standard deviation for continuous variables. For categorical response variables, proportions of subjects in each category of interest were to be provided. Efficacy measures were to be summarized by visit, and AEs were to be listed by subject. No interim analysis was performed.

Regarding changes to the planned analyses, efficacy measures were to be summarized by visit. Since the study was extended to 72 weeks, 96 weeks, 120 weeks, and 144 weeks, summary statistics were provided at the end of the original 24-week treatment period and each extension period instead, and last-observation-carried-forward (LOCF) methods were employed within each of these periods. For ease with terminology, from this point forward, "extension period" includes the initial 24-week treatment period. The version of the HAMD-25 scale used in this study allowed for a "can't rate" response. These responses were treated as missing data. LOCF methods were employed within each of the extension periods, for each of the individual questions. If a HAMD total score could not be derived within an extension period due to missing data within that extension period, then the last non-missing result from the previous extension was carried forward. Baseline values were not carried forward to any of the extension periods. A HAMD total score was derived based on the responses from all 25 questions. If a response was missing or "can't rate", then a total score could not be derived at that time point. For missing values, the LOCF methods were employed. In order to more easily compare the results of this study with those from other RBX studies using the standard 17-item HAMD score, a HAMD-17 equivalent was created using the following HAMD-25 items: HAMD-1, HAMD-6, HAMD-9 through HAMD-14, HAMD-16, and HAMD-18 through HAMD-25.

SUMMARY OF RESULTS AND CONCLUSIONS:

Disposition of Subjects and Baseline Characteristics:

A total of 69 subjects were enrolled and all received at least one dose of study drug and were included in all safety analyses. The Modified Intent-to-Treat (MITT) population consisted of 68 subjects and included all subjects who received at least one dose of study drug with at least one post-baseline efficacy measure.

A total of 37 subjects (53.6%) completed the initial 24-week treatment period, 17 subjects (24.6%) completed the 72-week treatment period, 9 subjects (13.0%) completed the 96-week treatment period, 7 subjects (10.1%)

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Name of Active Ingredient: **Reboxetine**	

completed the 120-week treatment period, and 2 subjects (2.9%) completed the 144-week treatment period.

Subjects in this study ranged in age from 20 to 66 years (mean = 46.7 years), and the majority were women (68.1%) and Caucasian (88.4%).

Efficacy Results:
For the main efficacy variable, HAMD-25, subject scores showed a continuous decrease from baseline through 144 weeks of treatment with RBX. The same can be said for the HAMD-17 scores, though the magnitude of the changes were smaller than those noted for the HAMD-25. The table below summarizes the change from baseline for HAMD-25 and HAMD-17 using LOCF methods.

Mean Change from Baseline in HAMD-25 and HAMD-17 Scores (MITT Population) (LOCF)

	HAMD-25			HAMD-17		
Study Visit	N	Mean Change from Baseline	SD of Change from Baseline	N	Mean Change from Baseline	SD of Change from Baseline
Week 24	65	-2.6	9.92	66	-1.3	6.65
Week 72	29	-3.7	12.63	30	-2.0	8.16
Week 96	11	-9.4	8.74	12	-5.3	5.82
Week 120	7	-11.9	11.94	7	-6.3	8.54
Week 144	5	-15.4	6.8	6	-8.5	5.09

Note: Three subjects had at least one HAMD item marked "can't rate" at baseline Therefore, the HAMD-25 total score could be derived for 65 subjects and the HAMD-17 total score could be derived for 66 subjects.

Based on the CGI Severity of Illness scale, the subjects also gradually improved over time. From Week 72 on, greater than half of the subjects were considered "normal, not at all ill." By 72 weeks there were no subjects considered "severely ill"; by 96 weeks, there were no subjects considered "mildly, moderately, or markedly ill." Results for the CGI Global Improvement scale using LOCF methods mirrored those of the CGI Severity of Illness scale—the subjects gradually demonstrated improvement over time. From Week 72 on, greater than half of the subjects were considered "much improved" and "very much improved" on the CGI Global Improvement scale.

Safety Results:
A total of 40 subjects (73%) previously treated with RBX had experienced AEs prior to entry into this study, as did 10 subjects (71%) previously treated with placebo. The most prevalent AEs experienced during previous studies were constipation (RBX group, 18%; placebo group, 21%), dry mouth (RBX group, 24%; placebo group, 14%), and insomnia (RBX group, 18%; placebo group, 29%).

Of the 69 subjects enrolled, 57 subjects (82.6%) reported at least one AE during this study, of which 45 subjects (65.2%) experienced at least one drug-related AE. Concerning maximum AE severity in the 57 subjects who experienced an AE while taking reboxetine: 15 subjects (21.7%) reported mild AEs; 25 subjects (36.2%) reported moderate AEs; and 17 subjects (24.6%) reported severe AEs. Nine subjects (13.0%) discontinued early due to treatment-emergent AEs. Four subjects (5.8%) experienced serious adverse events (SAEs), none of which were considered related to RBX treatment. No deaths occurred during the study.

Subjects reported AEs most frequently in the nervous (50.7%), body (47.8%), and digestive (42.0%) systems. The most commonly reported treatment-emergent AEs (i.e., those reported in at least 5% of the subjects) were

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headache (26.1%), insomnia (21.7%), and constipation (15.9%). The most frequently reported drug-related AEs were insomnia (15.9%), dry mouth (14.5%), headache (13.0%), and constipation (11.6%).

Most hematology, serum chemistry, and urinalysis parameters were inside the reference range at baseline and remained inside the reference range during treatment. All laboratory values outside the reference range were evaluated by a clinician and judged to be isolated incidences that were not clinically significant. In addition, no clinically relevant changes occurred in ECGs, vital signs, or weight during the study.

CONCLUSION:
Subjects continuously treated with open-label RBX for up to 144 weeks showed gradual improvement in their condition (i.e., MDD) as demonstrated by change from baseline results in HAMD-25, HAMD-17, CGI Severity of Illness, and CGI Global Improvement scales.

Reboxetine was well tolerated in this open-label rescue and therapy continuation study. The majority of AEs reported were mild or moderate in severity. The most frequently reported drug-related AEs during this extension study were insomnia, dry mouth, headache, and constipation, none of which were considered new or unexpected AEs with this class of compound.

Date of the Report: 30 January 2004

TABLE OF CONTENTS

IN-TEXT TABLES

1. ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
BID	Twice a day
CGI	Clinical Global Impression (scales)
CRF	Case report form
DMV-IV	Diagnostic and Statistical Manual for Mental Disorders, 4th Edition
ECG	Electrocardiogram
HAMD-17	Hamilton Rating Scale for Depression, 17-item version
HAMD-25	Hamilton Rating Scale for Depression, 25-item version
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MDD	Major Depressive Disorder
NEC	Not elsewhere classified
NOS	Not otherwise specified
NRI	Noradrenaline reuptake inhibitor
PNU	Pharmacia & Upjohn
RBX	Reboxetine
SAE	Serious adverse event
SD	Standard deviation
TSH	Thyroid stimulating hormone

2. ETHICS

2.1. Institutional Review Board/Independent Ethics Committee

It was the responsibility of the principal investigator at each study site to ensure that the protocol for this trial was reviewed by the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of the study. It was also the investigator's responsibility to inform the appropriate IRB/IEC of any serious adverse events (SAEs) that may have occurred. All IRB/IEC approvals and pertinent correspondence were filed by the investigators and copies forwarded to Pharmacia. Appendix 1.1 contains a copy of the protocol; Appendix 1.2 contains copies of the unique pages of the case report forms (CRFs); Appendix 1.3 contains a copy of a sample informed consent form; and Appendix 1.4 lists the IRBs/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.

2.3. Subject Information and Consent

It was the responsibility of the investigators to give each subject (or the subject'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 subjects were informed about their right to withdraw from the trial at any time. Written subject information (included as an appendix to the protocol; see Appendix 1.1) was given to each subject before enrollment. The written subject information was not changed without prior discussion with Pharmacia. Furthermore, it was the responsibility of the investigators to obtain signed informed consent from all subjects prior to inclusion in the trial.

Informed consent was obtained from each subject at the screening visit, which occurred 2 to 14 days prior to the start of this study. Appendix 1.3 contains a copy of a sample informed consent form.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

3.1. Investigators

The study was conducted at 31 study sites in the USA.

Appendix 1.4 lists the investigators and affiliations and Appendix 1.5 provides a curriculum vitae for each principal investigator.

3.2. Study Conduct

The study was conceived and planned by Pharmacia Corporation. The study sites were monitored by Pharmacia appointed monitors. Pharmacia Clinical Supply distributed treatments to the study sites.

3.3. Study Dates

The first subject was enrolled on 31 August 1999 and the last subject completed all study-related assessments on 27 September 2002.

4. INTRODUCTION

Reboxetine (Edronax™, PNU-155950E) is a highly selective noradrenaline reuptake inhibitor (NRI) that has been shown to be an effective and well-tolerated treatment for Major Depressive Disorder (MDD), both in inducing initial response and in reducing the rate of relapse.[1,2,3] Participation in this study was offered to subjects who had participated in other reboxetine (RBX) studies sponsored or supported by the Pharmacia & Upjohn (PNU) US Market Company (now Pfizer Corporation). This study was designed to generate important long-term safety data and to make RBX available to subjects while FDA approval was pending. In addition, treatment guidelines recommend continuing antidepressant medication for several months after remission of the symptoms of depression.[4,5] Reboxetine tablets were approved for marketing in the United Kingdom in April 1997, and the drug is now approved in 12 European countries.

5. OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

The primary objective of this study was to monitor the long-term safety of RBX (by monitoring clinical laboratory results, electrocardiograms [ECGs], and adverse events [AEs]) in subjects diagnosed with MDD according to DSM-IV criteria.[6]

5.1.2. Secondary Objectives

The secondary objectives were measurements of efficacy, as follows: the main efficacy measure was the 25-item Hamilton Rating Scale for Depression (HAMD-25)[7,8]; in addition, the Clinical Global Impression (CGI) Scales were used.[9] All efficacy measurements were to be administered according to the study flow chart (see Table 1, Schedule of Events).

6. METHODS

6.1. Overall Study Design and Plan

This was an uncontrolled, open-label study of subjects treated with RBX, limited to subjects who had participated in a previous PNU supported or sponsored trial within 2 weeks of enrolling in this study.

Potential subjects were to be screened for eligibility according to the inclusion/exclusion criteria. Subjects were then to undergo a thorough assessment (medical and psychiatric history, physical examination, vital signs, height, weight, laboratory assessments, and ECG). At the Screen/Day 1 visit, specific laboratory assessment tests, the physical examination, and the ECG could be waived if done within the last 14 days of the final visit from the previous reboxetine study. Subjects could enroll in the study once consent had been signed and the

screening procedures were verified. Screening/Day 1 activities were to be done within 14 days of the final visit for the previous reboxetine study. Ideally, the subject's Final Visit for the previous reboxetine study was to be the Screen/Day 1 visit for this study. Thus, the final visit data could be used as the Screen/Day 1 data, with updates or additions as indicated, eliminating the need for duplicate labs and procedures.

After clinical laboratory values had been checked, and other eligibility criteria verified, study drug could be administered. Subjects who were enrolled in this study, but whose RBX dose in the previous trial was not known, were to be started on RBX 4 mg BID; after 1 week the investigator could increase the dose up to 10 mg per day if necessary. All other subjects were to be started on their last known RBX dose. If subjects were started on RBX 10 mg/day, the dose could be lowered to 8 mg/day if AEs were reported.

Each subject was to be seen according to the study flow chart (see Table 1, Schedule of Events). Adverse events and concomitant medications were to be monitored at each visit. Clinical assessments, laboratory measurements, and ECG recordings were to be done according to a predetermined schedule (see Table 1, Schedule of Events).

Treatment with RBX was to continue for 144 weeks or until the following (whichever was sooner):

- Subject removed him/herself from the study.
- Site/investigator discontinued the subject for due cause (including, but not limited to, lack of efficacy or occurrence of unacceptable AEs).
- Subject became pregnant (or pregnancy was planned or suspected).
- Subject was non-compliant with the protocol (e.g., missed 2 consecutive visits).
- Site/investigator was non-compliant with the protocol (e.g., not monitoring or reporting AEs appropriately).

In addition, all of the following applied:

- No new subjects were to be enrolled in this study 3 months after RBX received US NDA approval.
- Subjects who were enrolled in this study at the time of US NDA approval of RBX could continue for 3 months after this event.
- This study was to be discontinued if PNU withdrew its US NDA (in some cases RBX would be continued for up to 3 months in this event).

At the end of 72 weeks of RBX treatment, the primary investigator or designee at each site was to interview the subject, review the subject's history, current mental and physical symptoms, and then determine if further RBX treatment was warranted. If it was decided that the subject should continue on RBX treatment, the investigator or designee was to complete the Continuation Assessment Case Report Form (for Week 72 extension). At this

time, subjects were to sign and date a revised informed consent document prior to inclusion in the study extension.

At the end of 96 weeks of RBX treatment, the primary investigator or designee at each site was again to interview the subject, review the subject's history, current mental and physical symptoms, and again determine if further RBX treatment was warranted. If it was decided that the subject should continue on RBX treatment, the investigator or designee was to complete the Continuation Assessment Case Report Form (for Week 96 extension). At this time, subjects were to sign and date a revised informed consent document prior to inclusion in the study extension.

At the end of 120 weeks of RBX treatment, the primary investigator or designee at each site was again to interview the subject, review the subject's history, current mental and physical symptoms, and again determine if further RBX treatment was warranted. If it was decided that the subject should continue on RBX treatment, the investigator or designee was to complete the Continuation Assessment Case Report Form (for Week 120 extension). At this time, subjects were to sign and date a revised informed consent document (Appendix 1.3) prior to inclusion in the study extension.

6.2. Selection of Study Population

All subjects had to meet the following inclusion criteria without exhibiting the exclusion criteria before participation in this study.

6.2.1. Inclusion Criteria

- Within 2 weeks prior to enrollment in this study, each subject must have participated in any clinical trial of RBX sponsored or supported by the U.S. Market Company division of PNU, for which the subject met all inclusion/exclusion criteria, including a diagnosis of MDD according to DSM-IV criteria.[6] The subject's MDD could be in remission.
- Signed an informed consent form.

6.2.2. Exclusion Criteria

- Any history of mania or hypomania.
- History of MDD associated with endocrine disorders: hypo- and hyper-thyroidism tested by thyroid stimulating hormone (TSH) and T4 levels (Note: TSH and T_4 results were to be obtained within the last 9 months); adrenal insufficiency, Cushing's Syndrome.
- Positive pregnancy test for women of childbearing potential (or pregnancy was planned or suspected).
- Females who were breastfeeding.
- Refusal by female subjects of potential childbearing age to use an accepted means of birth control, such as: oral contraceptives for an appropriate duration before study start,

implantable or injectable contraceptives, intrauterine devices, barrier methods, or if the subject had underwent surgical sterilization.

- Use of concomitant psychotropic medications except as specified by the protocol.
- History or presence of gastrointestinal, liver, or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, and excretion of drugs.
- History of seizures or brain injury; current evidence of clinically important hematopoietic, respiratory, or cardiovascular diseases. Current evidence of urinary retention or glaucoma.
- Any important clinical illness in the 2 weeks preceding this study which may have interfered with the conduct of the study.
- Clinically relevant abnormal findings in the physical examination, laboratory tests, and/or ECG at screening.

6.3. Treatments

6.3.1. Treatments Administered

Once the consent form had been signed and screening procedures were completed and reviewed, subjects could then receive study drug. Upon entering the study, subjects were to begin treatment according to the following schedule: 1) all previously blinded subjects enrolling in this study were to be started on RBX 4 mg BID, and at the investigator's discretion the dose could be increased after 1 week to 10 mg per day; or 2) subjects were to be started on their last known dose of RBX.

6.3.2. Identity of Investigational Products

6.3.2.1. Reboxetine Tablets

Trade name: Edronax™

Chemical name: (2RS,αRS)-[α-(2-ethoxphenoxy)benzyl]morpholine methanesulphonate

Laboratory code: PNU-155950E

Lot number: 28,588

Reboxetine 4 mg scored tablets were used.

6.3.3. Packaging, Labeling, and Storage

Reboxetine was provided as 4 mg scored tablets, packaged in bottles and labeled appropriately. Each bottle contained the medication necessary for either 12-15 days (total of

30 tablets), or 24-30 days (total 60 tablets), prepared according to a BID dosing regimen with one tablet for the "morning" dose and either 1 or 1½ tablets for the "evening" dose.

The appropriate number of bottles were dispensed by the site according to the visit schedule.

Drug supplies were to be stored at room temperature. All drug supplies were to be handled under the direct responsibility of the investigator. The study monitor checked drug storage conditions during site visits. The investigator was also responsible for drug accountability and kept a record of the test compounds received from the sponsor as well as of the dispensed and returned drug. Discrepancies between dispensed and returned study medication were to be explained and recorded.

Medication was to be dispensed to the subject on the occasion of each visit. On the same occasion, the bottle(s) of the previous supply were to be returned by the subject.

6.3.4. Method of Assigning Subjects to a Treatment Group

This was an open-label study.

6.3.5. Selection of Doses Used in the Study

Reboxetine 4 mg BID was approved for treatment of depression in the United Kingdom in 1997 and is now marketed in 12 European countries.

6.3.6. Selection and Timing of Dose for Each Subject

Subjects were instructed to take 1 tablet in the morning and 1 (if on 8 mg/day dosing) or 1½ (if on 10 mg/day dosing) tablets in the evening each day while participating in the study.

6.3.7. Blinding

The study was open-label.

6.3.8. Prior and Concomitant Treatment

Subjects were not allowed to take another investigational drug. No concomitant psychotropic medications other than temazepam (7.5 – 30 mg) or zolpidem tartrate (5 – 10 mg) as hypnotics on an "as needed" basis were allowed. Food supplements with prominent central nervous system effects, such as St. John's Wort, Kava Kava, Ginseng, and melatonin were not allowed in the study.

Caution was to be exercised in enrolling subjects who were taking drugs that were potent inducers or inhibitors of cytochrome p450 3A4 (see protocol Appendix 3 in Appendix 1.1).

Other therapy considered necessary for the subject's welfare could be given at the discretion of the investigator. Over-the-counter medications were allowed as needed for symptomatic

treatment and were to be recorded in the CRF. Subjects were not allowed to participate concurrently in any other clinical study. Women of childbearing potential had to use an effective means of contraception while on study (e.g., oral contraceptives, implantable or injectable contraceptives, intrauterine devices, barrier methods, or surgical sterilization).

6.3.9. Treatment Compliance

Open-label RBX treatment was administered. Subject compliance was strictly monitored. Dosing diaries were to be provided to the subject to record daily drug administration. The investigator's staff reviewed the diary for regular consumption of study drug. Diaries were source documents that were to be retained by the investigator. To assess compliance, pill counts were performed.

6.3.10. Removal of Subjects From Treatment or Assessment

A subject could be withdrawn from the study if, in the opinion of the investigator, it was medically necessary, or if it was the wish of the subject.

6.4. Efficacy and Safety Variables

6.4.1. Efficacy and Safety Measures Assessed and Flow Chart

The study schedule of events is presented in Table 1.

Table 1 Schedule of Events

Event	Screen (-2 to -14 days)	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wks 32/40	Wk 48	Wks 56/64	Wk 72	Wks 80/88	Wk 96	Wks 104/112	Wk 120	Wks 128/136	Wk 144 or Final Visit[1]
Sign informed consent	✓												✓		**X**				
Determine need to continue RBX via subject interview (Continuation Assessment)									✓				✓		**X**				
Medical history/ physical examination	✓																		**C**[2]
ECG (12-lead)	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Serum chemistry	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Hematology	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Urinalysis	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Serum pregnancy test	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Urine drug screen	✓																		
Vital signs and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**
HAMD-25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**
CGI or CGI-I	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**C**	**C**
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**
Adverse events	✓**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**
Dispense/return drug	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**[3]

Wk = week RBX = reboxetine ECG = electrocardiogram HAMD-25 = Hamilton Rating Scale for Depression, 25-item version CGI = Clinical Global Impression

NOTE: All Screen activities (except signing the Informed Consent) did not need to be repeated if done at the final study visit of the previous RBX protocol within a 14-day window.

1 Events listed for "Final Visit" were to be completed whenever a subject withdrew from the study.

2 At study end, only physical examination was performed.

3 All study medication, containers, and dosing diaries were to be collected at the final visit.

X = new assessments per Amendment B.

C = new assessments per Amendment C.

The Screen/Day 1 visit for this study was to take place within 14 days of the final visit of the previous reboxetine study. At the Screen/Day 1 visit, laboratory assessment tests, the physical examination, and the ECG could be waived if done within the last 14 days of the final visit from the previous reboxetine study. Potential subjects were to be screened for eligibility according to the inclusion/exclusion criteria at the screening visit. Subjects then underwent a thorough assessment (medical and psychiatric history, physical examination, vital signs, height, weight, laboratory assessments, ECG, HAMD-25, and CGI). Subjects could enroll in the study once consent had been signed and the screening procedures were verified.

After clinical laboratory values had been checked, and other eligibility criteria were verified, the subject could be administered study drug. Subjects who were enrolled in this study, but whose RBX dose in the previous trial was not known, were to be started on RBX 4 mg BID; after 1 week the investigator could increase the dose up to 10 mg per day if necessary. All other subjects were to be started on their last known RBX dose. If subjects were started on RBX 10 mg/day, the dose could be lowered to 8 mg/day if AEs were reported.

Each subject was to be seen according to the study flow chart (Table 1). Adverse events and concomitant medications were to be monitored at each visit. Clinical assessments, laboratory measurements, and ECG recordings were to be done according to the predetermined schedule (Table 1).

6.4.2. Appropriateness of Measurements

The safety assessments performed (AEs, physical examinations, vital signs, ECGs, and clinical laboratory evaluations) during this study were all standard and acceptable means of evaluating the safety profile of a study drug. The two efficacy measures, the HAMD-25 and the CGI scales, were also standard scales used for rating depression.

6.4.3. Efficacy Variables

6.4.3.1. Hamilton Rating Scale for Depression (25-item)

The main efficacy measure was the 25-item Hamilton Rating Scale for Depression (HAMD-25)[7,8], which was administered at each study visit as shown in Table 1.

The HAMD-25 is a standard scale used for rating severity of depression. It is a clinician-rated scale based on results of a subject interview. The individual items on the HAMD-25 are rated according to their severity either on a 0-2 or 0-4 point scale. The rating by the clinician is completed as a result of the clinician review (a structured interview is not required to complete this scale).

6.4.3.2. Clinical Global Impression Scales

The other efficacy measures in this study were the Clinical Global Impression (CGI) Scales.[9]

The CGI consists of three scales (Severity of Illness, Global Improvement, and Efficacy Index). The Global Improvement and Efficacy Index portions refer to changes since admission to the study. For this reason, there were no values assigned to these portions at the Screen/Day 1 visit. All three parts of this instrument were to be rated by the clinician at each subsequent study visit as shown in Table 1.

6.4.4. Safety Variables

Adverse events occurring from baseline through the last visit were recorded; body weight and vital signs (respiration, pulse, blood pressure, temperature) were to be recorded at each visit; and clinical laboratory assessments and ECGs were to be done according to the predetermined schedule (Table 1).

6.4.4.1. Adverse Events

The investigator was to report all directly observed AEs and all AEs spontaneously reported by subjects during this study. In addition, the occurrence of AEs was solicited from subjects at each clinic visit following initiation of treatment. Subjects were asked "Since your last clinic visit have you had any health problems?"

An AE was defined as any untoward medical occurrence in a subject administered study drug; the event did not necessarily have to have a causal relationship with the administered treatment. An AE could be any of the following:

- All suspected adverse medication reactions.
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness (see Pre-existing Conditions below).
- Injury or accidents. **Note:** if a medical condition was known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) were to be reported as two separate AEs. The outcome of the accident (e.g., hip fracture secondary to the fall) was to be recorded under "Comments" on the AE page of the CRF.
- Abnormalities in physiological testing or physical examination (findings that required clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that required clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they were associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a subject with jaundice) were to be described under "Comments" on the AE page of the CRF rather than listed as a separate AE.

- Pregnancy. Any pregnancy that occurred or was discovered during the treatment period or within 30 days of discontinuation of study treatment was to be reported as an AE (see Exposure *In Utero* below).

Pre-existing Conditions: A pre-existing condition (i.e., a disorder or symptom present before the AE reporting period started and noted on the pretreatment medical history/physical form) should not be reported as an AE unless the condition worsened or episodes increased in frequency and/or intensity during the AE reporting period (see also Symptoms of Depression below).

Procedures: Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, were not to be reported as AEs. However, the medical condition for which the procedure was performed was to be reported if it met the definition of an AE. For example, an acute appendicitis that began during the AE reporting period should have been reported as an AE and the resulting appendectomy should have been noted under "Comments" on the AE page of the CRF.

Symptoms of Depression: With the exception of worsening of depressed mood, worsening of symptoms of depression were to be considered as AEs during this study. Any increase in the intensity of depressed mood was to be reflected on the Hamilton Rating Scale for Depression (Item 1). However, increases in the intensity and/or frequency of other symptoms of depression (e.g., sleep difficulties, somatic symptoms, genital symptoms, weight change, anxiety, other psychiatric symptoms) were to be considered as AEs. It was recognized that such symptoms may be present prior to the start of study drug (i.e., at Day 1). Only those symptoms whose intensity and/or frequency increased during the treatment period were to be counted as AEs.

Intensity of AEs: Each AE was described by the investigator by its maximum intensity. The intensity grades were defined as follows:

MILD:	Did not interfere with subject's usual function.
MODERATE:	Interfered to some extent with subject's usual function.
SEVERE:	Interfered significantly with subject's usual function.

The distinction between the intensity and the gravity of an AE meant that a severe (intensity) AE was not necessarily a serious (gravity) one (see Section 6.4.4.2). The investigator also assessed the possible relationship between the AE and the study medication as well as any concomitant medications.

Adverse Event Reporting Period: The adverse event reporting period for this study began at Screen/Day 1 and ended at the final visit. Also, any known untoward event that occurred subsequent to the AE reporting period that the investigator assessed as possibly related to study drug was to be reported as an AE. The reporting requirements for AEs and SAEs can be found in the study protocol (Appendix 1.1).

Adverse Event Follow-Up: All AEs were to be followed until resolved or until the subject's participation in the study ended (i.e., until a final report was completed for that subject). Instructions for reporting changes in an ongoing AE during a subject's participation in the study were provided in the instructions that accompany the AE CRF.

In addition, all SAEs (see Section 6.4.4.2) and those nonserious AEs assessed by the investigator as possibly related to study drug were to be followed even after the subject'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." Any pregnant subject was to be followed by the investigator until completion of the pregnancy (see Exposure *In Utero* below). All follow-up and resolution of such events were to be documented in the CRF.

Exposure *In Utero*: If pregnancy was discovered during the treatment period, study medication was to be discontinued immediately and the subject withdrawn from the trial. Any pregnancy that occurred or was discovered during the treatment period or within 30 days of discontinuation of treatment was reported as an AE. The investigator was to note in the CRF the anticipated date of birth or pregnancy termination. The subject was 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 to notify Pharmacia.

If the outcome of the pregnancy that occurred or was discovered during treatment met the criteria for immediate classification as a serious medical event (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator was to follow the procedures for reporting SAEs (see Section 6.4.4.2). Pregnancy outcomes that were to be classified as SAEs included:

- Spontaneous abortion, including miscarriage and missed abortion.
- All neonatal deaths that occurred within 1 month of birth were to be reported, regardless of causality. In addition, any infant death after 1 month that the investigator assessed as possibly related to the *in utero* exposure to study drug.
- Congenital anomaly, including that in an aborted fetus. The "normality" of a newborn was assessed at the time of birth. The "normality" of an aborted fetus was to be assessed by gross visual inspection, unless there were pre-abortion laboratory findings suggestive of a congenital anomaly.

6.4.4.2. Serious Adverse Events

Each AE was classified by the investigator as either serious or nonserious. The classification of the gravity of the event determined the reporting procedures to be followed.

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

- Death.

- Life-threatening (i.e., immediate risk of death).
- In-subject hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity (e.g., any sight-threatening event with ophthalmic products is a significant incapacity).
- Congenital anomaly/birth defect.
- Other medically relevant condition judged/defined as serious (see below).

Medical judgment was to be exercised in deciding whether a reaction was serious in other situations. Important medical events that were not immediately life-threatening or did not result in death or hospitalization, but that jeopardized the subject or required medical or surgical intervention to prevent one of the outcomes listed above, were to be considered as serious.

Serious adverse events were to be reported to the Pharmacia monitor using the designated form within 24 hours of the investigator's awareness of the event, regardless of proximity to the occurrence of the event. The initial report was to be followed by submission of more detailed adverse event information within 5 working days of the event. If the SAE was unexpected, it was also to be reported immediately to the responsible IRB/IEC. Serious adverse events were to be reported on both the adverse event page and the serious adverse event page of the CRF.

6.4.4.3. Clinical Laboratory Assessments

Serum chemistries, hematology, serum pregnancy tests (for women of childbearing potential), and urinalysis (a complete listing of assessments can be found in protocol Appendix 2 in Appendix 1.1) were to be performed according to the predetermined schedule (Table 1). A urine drug screen was to be performed only at screening. Each subject's screening laboratory assessments were to take place within 14 days prior to receiving the first dose of study drug in this study. Laboratory assessment tests could be waived if done within the last 14 days of the final visit from the previous reboxetine study (investigator's discretion).

6.4.4.4. Vital Sign and Weight Measurements

Vital signs (respiration, pulse, systolic and diastolic blood pressure, and temperature) were to be measured with the subject in a sitting position at screening and each subsequent study visit. Body weight was also measured at all visits.

6.4.4.5. Electrocardiograms

Electrocardiograms were to be performed according to the predetermined schedule (Table 1). Analysis of ECGs included abnormal ECG patterns and measurements of appropriate intervals (i.e., heart rate, PR interval, QRS interval, QT interval, and QT_c interval).

6.5. Data Quality Assurance

Pharmacia was responsible for independent internal quality assurance audits of the clinical study processes at company sites worldwide. An independent audit of this clinical study was not performed, as documented in Appendix 1.8.

Monitoring visits to the study site were made periodically during the trial to ensure that all aspects of the protocol were followed. Source documents were reviewed for verification of agreement with data on the CRFs.. The investigator/institution guaranteed access to source documents by Pharmacia and appropriate regulatory agencies.

A CRF was required and completed for each included subject. Data were entered directly onto original CRF pages. The completed original CRFs were the sole property of Pharmacia and were not to be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Pharmacia. To enable evaluations and/or audits from Health Authorities/Pharmacia and to comply with international regulations, the investigator agreed to keep pertinent records for 15 years. Pertinent records included the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs, and detailed records of drug disposition.

All data were entered into the database and checked for accuracy with logical checks. Standard Pharmacia database release checks were performed prior to database lock. All data handling procedures were conducted according to Pharmacia standard operating procedures.

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

6.6.1. Statistical and Analytical Plans

This was an uncontrolled, open-label observational study of subjects treated with reboxetine to generate important long-term safety data on the treatment with 8-10 mg reboxetine daily. The study was limited to subjects who participated in a PNU supported or sponsored trial within the previous 2 weeks.

Appendix 1.9 contains further documentation of the statistical methods. Appendix 1.10 includes documentation of inter-laboratory standardization methods.

6.6.1.1. Analysis of Efficacy and Safety Variables

Descriptive statistics were to be generated for both the efficacy and safety variables. These were to include minimum, maximum, mean and standard deviation for continuous variables. For categorical response variables, proportions of subjects in each category of interest were to be provided. Efficacy measures were to be summarized by visit, and AEs were to be listed by subject.

6.6.1.2. Interim Analysis

No interim analysis was performed.

6.6.2. Determination of Sample Size

Not applicable.

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

6.7.1. Protocol Amendments

The original protocol (dated 11 May 1999) was amended 6 times (amendments dated 7 July 1999, 10 March 2000, 7 February 2001, 10 May 2001, 13 September 2001, and 15 February 2002); the final protocol and amendments can be found in Appendix 1.1.

Amendment No. 1 (7 July 1999) made the following changes to the protocol: in study procedures changes were made to allow for a smooth transition of subjects from the previous reboxetine study into the open-label study without a break in reboxetine treatment or the inconvenience to the subject of having the same visit activities repeated over a short period of time. Some of the changes were simply corrections and clarifications. The main changes included the following:

- Data from the final visit activities of the previous reboxetine study could now be used for the Screen/Day 1 visit if the Screen/Day 1 activities occurred within 14 days of the final visit of the previous reboxetine study.
- New Appendix 2 was added detailing safety laboratory assessments.
- A cautionary note regarding concomitant use of inducers and inhibitors of cytochrome p450-3A4 was added; a list of inhibitors and inducers of cytochrome p450 3A4 was also added for reference (i.e., new Appendix 3).
- Allowed for the use of thyroid function (TSH and T_4) test results done within 9 months of Screen/Day 1 for this study in determining subject eligibility at Screen/Day 1.
- CGI at Screen/Day 1 now included only the “Severity of Illness” portion.

Amendment No. 2 (10 March 2000) can be summarized as follows: the original protocol was written to allow subjects previously enrolled in another reboxetine trial to continue reboxetine treatment for an additional 24 weeks or until 3 months after reboxetine received FDA approval, whichever occurred first. Due to the delay in FDA approval, some subjects were going to exceed the allowed 24-week treatment period. Therefore, this amendment was written to allow site physicians to assess the need for continued reboxetine therapy on a case-by-case basis. If both the physician and the subject agreed that continued therapy with reboxetine was warranted, reboxetine treatment for an additional 48 weeks and continued routine safety assessments could now be provided (up to 72 weeks total treatment per

subject). The other stipulations for subject termination in the original protocol still applied. It was the responsibility of the investigator to obtain signed and dated consent from subjects prior to inclusion in this study extension (i.e., for Amendment No. 2). A new consent form was provided at this time (Appendix 1.3). In addition, Amendment No. 2 documented some changes in study personnel.

Amendment No. 3 (7 February 2001) was written to update changes in study personnel and to define the visit windows for the extension protocol.

Amendment No. A (10 May 2001) can be summarized as follows: the original protocol, as modified by Amendment 2, was written to allow subjects previously enrolled in another reboxetine trial to continue reboxetine treatment for an additional 72 weeks or until 3 months after reboxetine received FDA approval, whichever occurred first. This amendment was written to allow site physicians to assess the need for continued reboxetine therapy on a case-by-case basis. If both the physician and the subject agreed that continued therapy with reboxetine was warranted, reboxetine treatment for an additional 24 weeks and continued routine safety assessments could now be provided (up to 96 weeks total treatment per subject). The other stipulations for subject termination in the original protocol still applied. It was the responsibility of the investigator to obtain signed and dated consent from subjects prior to inclusion in this second study extension (i.e., for Amendment No. A). A new consent form, allowing reboxetine treatment for up to 96 weeks, was provided at this time (Appendix 1.3). In addition, Amendment No. A documented some changes in study personnel.

Amendment No. B (13 September 2001) can be summarized as follows: the original protocol, as modified by Amendments No. 2 and A, was written to allow subjects previously enrolled in another reboxetine trial to continue reboxetine treatment for an additional 72 weeks and 96 weeks, respectively, or until 3 months after reboxetine received FDA approval, whichever occurred first. This amendment was written to further extend the study period from 96 weeks to 120 weeks. Site physicians were again to assess the need for continued reboxetine therapy on a case-by-case basis. If both the physician and the subject agreed that continued therapy with reboxetine was warranted, reboxetine treatment for an additional 24 weeks and continued routine safety assessments were to be provided (up to 120 weeks total treatment per subject). The other stipulations for subject termination in the original protocol still applied. It was the responsibility of the investigator to obtain signed and dated consent from subjects prior to inclusion in this third study extension (i.e., for Amendment No. B). A new consent form, allowing reboxetine treatment for up to 144 weeks, was provided at this time (Appendix 1.3).

Amendment No. C (15 February 2002) can be summarized as follows: The original protocol, which was modified by Amendment 2, Amendment A, and Amendment B was written to allow subjects previously enrolled in another reboxetine trial to continue reboxetine treatment for an additional 72 weeks, 96 weeks, and 120 weeks respectively or until 3 months after reboxetine received FDA approval, whichever occurred first. This amendment would further extend of the protocol period from 120 weeks to 144 weeks. Site physicians will again assess

the need for continued reboxetine therapy on a case-by-case basis. If both the physician and the subject agree that continued therapy with reboxetine is warranted, reboxetine treatment for an additional 24 weeks and continued routine safety assessments may be provided (up to 144 weeks total treatment per subject). The other stipulations for subject termination in section 5.1 of the protocol still apply. It is the responsibility of the Investigator to obtain signed and dated consent from subjects prior to inclusion in this fourth study extension (Amendment #C). After IRB approval of this amendment, all subjects who enter the study at the site should sign the most recent version of the informed consent form (allowing reboxetine treatment for up to 144 weeks).

6.7.2. Changes in the Statistical Plan

Efficacy measures were to be summarized by visit. Since the study was extended to 72 weeks, 96 weeks, 120 weeks, and 144 weeks, summary statistics were provided at the end of the original 24-week treatment period and each extension period instead, and last-observation-carried-forward (LOCF) methods were employed within each of these periods. For ease with terminology, from this point forward, "extension period" includes the initial 24-week treatment period.

Appendix 1.9 contains further documentation of the statistical methods.

6.7.2.1. Handling of Missing Data

The version of the HAMD scale used in this study allowed for a "can't rate" response. These responses were treated as missing data. LOCF methods were employed within each of the extension periods, for each of the individual questions. If a HAMD total score could not be derived within an extension period due to missing data within that extension period, then the last non-missing result from the previous extension was carried forward. Baseline values were not carried forward to any of the extension periods.

6.7.2.2. Derived Variables

A HAMD total score was derived based on the responses from all 25 questions. If a response was missing or "can't rate", then a total score could not be derived at that time point. For missing values, the LOCF methods were employed.

In order to more easily compare the results of this study with those from other RBX studies using the standard 17-item HAMD score, a HAMD-17 equivalent was created using the following HAMD-25 items: HAMD-1, HAMD-6, HAMD-9 through HAMD-14, HAMD-16, and HAMD-18 through HAMD-25.

7. RESULTS

7.1. Study Subject Information

7.1.1. Disposition of Subjects

Table 2 summarizes the subject disposition and reasons for study discontinuation. Further information on subject disposition can be found in Section 11.1, Table T1.1; and a by-subject listing of reasons for early termination can be found in Appendix 3.1, Listing 3.1.1.

A total of 69 subjects were enrolled at 18 study sites in this study and all subjects received at least one dose of study drug and were therefore included in all safety analyses (i.e., Safety Population). The Modified Intent-to-Treat (MITT) population consisted of 68 subjects and included all subjects who received at least one dose of study drug with at least one post-baseline efficacy measure. Subject #231042 had no post-baseline efficacy measure, and discontinued due to a protocol violation (non-compliance with office visits).

A total of 37 subjects (53.6%) completed the initial 24-week treatment period, 17 subjects (24.6%) completed the 72-week treatment period, 9 subjects (13.0%) completed the 96-week treatment period, 7 subjects (10.1%) completed the 120-week treatment period, and 2 subjects (2.9%) completed the 144-week treatment period.

Table 2 Subject Disposition

Subject Disposition	Reboxetine (N=69) n %
Enrolled in open-label study	69 (100%)
Safety population[1]	69 (100%)
Modified Intent-to-Treat (MITT) population[2]	68 (98.6%)
Completed 24 weeks	37 (53.6%)
Completed 72 weeks	17 (24.6%)
Completed 96 weeks	9 (13.0%)
Completed 120 weeks	7 (10.1%)
Completed 144 weeks	2 (2.9%)
Total Subjects who Discontinued	55 (79.7%)

Subject Disposition	Reboxetine (N=69) n %
Reasons for discontinuation:	
Adverse event	11 (15.9%)
Protocol violation	7 (10.1%)
Consent withdrawn	6 (8.7%)
Lost to follow-up	4 (5.8%)
Protocol specific withdrawal criteria	2 (2.9%)
Lack of efficacy	12 (17.4%)
Progression of disease	1 (1.4%)
Improvement	1 (1.4%)
Other	11 (15.9%)

[1] Safety population included all subjects who received at least one dose of study drug.

[2] MITT population included all subjects who received at least one dose of study drug with at least one post-baseline efficacy measure.

Source: Section 11.1, Table T1.1

Section 11.1, Table T1.1 details subject disposition through the several study extensions. Subjects had the option of continuing RBX treatment through 72, 96, 120, or 144 weeks. A subject could decline to continue in the study at any of these time points without being considered an early discontinuation. Of the subjects who continued, 55 (79.7%) subsequently terminated the study prematurely. The most common reasons for these later discontinuations were lack of efficacy (12 subjects, 17.4%), AEs (11 subjects, 15.9%), and other (11 subjects, 15.9%. Details regarding each of these subjects and the specific reasons for discontinuation can be found in Appendix 3.1, Listing 3.1.1.

7.1.2. Protocol Deviations

A summary of protocol deviations can be found in Section 11.1, Table T1.2. A total of 8 subjects were noted to have protocol deviations. Six of these subjects were discontinued because of protocol violations involving non-compliance with either dosing or study visits; one subject was discontinued for taking concomitant Klonopin (clonazepam) for anxiety; and one subject answered “yes” to exclusion criterion No. 7 (history or presence of gastrointestinal, liver, or kidney disease, or other conditions known to interfere with the absorption, distribution, metabolism, and excretion of drugs), however, this subject was enrolled in the study and subsequently discontinued due to progression of disease.

7.1.3. Data Sets Analyzed

The Safety Population (n=69) was used for all safety analyses (i.e., AEs, clinical laboratory assessments, vital signs, and ECGs). All 69 subjects enrolled in the study received at least one dose of study drug and were therefore included in the Safety Population. The MITT Population (n=68) was used for all efficacy analyses (i.e., HAMD-25, HAMD-17, and CGI)

and included all subjects who received at least one dose of study drug with at least one post-baseline efficacy measure. See Table 2 above.

7.1.4. Demographic and Other Baseline Characteristics

Summary tables regarding subject sex and race, age, marital status, current employment status, and occupational group (All Enrolled Subjects) can be found in Section 11.1, Tables T2 through T6, respectively. Statistical summaries of baseline vital signs and height/weight (All Enrolled Subjects) can be found in Section 11.1, Tables T7 and T8, respectively. Summary tables regarding medical history, physical examination findings, treatment status, hospitalization for this condition, and mood disorders (All Enrolled Subjects) can be found in Section 11.1, Tables T9, T10, T12.1, T12.2, and T12.3, respectively. Serum pregnancy test results at baseline for all enrolled female subjects can be found in Section 11.1, Table T11.

Subjects in this study ranged in age from 20 to 66 years (mean = 46.7 years), and the majority were women (68.1%) and Caucasian (88.4%). Table 3 summarizes subject demographics at baseline.

Table 3 Subject Demographics at Baseline (All Subjects Enrolled)

Demographic Variable		Reboxetine (N=69)
Age (years)	Mean ± SD	46.7 ± 10.35
	Range	20 – 66
Weight (pounds)	Mean ± SD	173 ± 39.3
	Range	112 – 300
Height (inches)	Mean ± SD	66.8 ± 3.9
	Range	60 – 76
Sex [n (%)]	Male	22 (31.9%)
	Female	47 (68.1%)
Race [n (%)]	Caucasian	61 (88.4%)
	Black	6 (8.7%)
	Hispanic	2 (2.9%)

Source: Section 11.1, Tables T2, T3, and T8

Regarding other baseline characteristics: 37.7% of subjects were currently married (Section 11.1 Table T4); most (53.6%) were employed full-time(Section 11.1 Table T5); 33.3% were in technical, sales, and administrative support occupations (Section 11.1 Table T6); nothing remarkable was noted for medical histories or physical examinations (Section 11.1 Table T9 and T10, respectively); all enrolled subjects (100%) were being treated as outpatients for their condition (Section 11.1 Table T12.1); the majority (92.8%) had never been hospitalized for

their condition (Section 11.1 Table T12.2); and 24.6% had recurrent moderate depressive disorder (Section 11.1 Table T12.3).

7.1.4.1. Efficacy Variables at Baseline

Statistical summaries of baseline efficacy variables for the MITT Population can be found in Section 11.1, Tables T15.1 through T15.4, and Table T16.

Table 4 summarizes the HAMD-25, HAMD-17, and CGI Severity of Illness scales at baseline.

Table 4 HAMD-25, HAMD-17, and CGI Severity of Illness Mean ± SD Scores at Baseline (All Enrolled Subjects)

Efficacy Variable		Reboxetine (N=69)
HAMD-25 Total Score	N	65
	Mean ± SD	13.7 ± 8.3
	Range	0 – 36
HAMD-17 Total Score	N	66
	Mean ± SD	9.2 ± 5.2
	Range	0 – 23
CGI Severity of Illness [n (%)]	Normal, not at all ill	9 (13.0%)
	Borderline ill	21 (30.4%)
	Mildly ill	18 (26.1%)
	Moderately ill	19 (27.5%)
	Markedly ill	2 (2.9%)

Note: Three subjects had at least one HAMD item marked “can’t rate” at baseline. Therefore, the HAMD-25 total score at baseline could be derived for 65 subjects and the HAMD-17 total score at baseline could be derived for 66 subjects.

Source: Section 11.1, Tables T15.1, T15.3, and T16

Mean HAMD-17 and HAMD-25 total scores by previous treatment group are summarized in Table 5.

Table 5 HAMD-25 and HAMD-17 Mean ± SD Total Scores at Baseline by Previous Treatment Group (MITT Population)

Previous Treatment Group		HAMD-25	HAMD-17
Reboxetine	N	52	53
	Mean ± SD	13.2 ± 8.56	8.9 ± 5.31
Placebo	N	13	13
	Mean ± SD	15.5± 7.15	10.1± 4.75

Source: Section 11.1, Tables T15.2 and T15.4

7.1.5. Concomitant Medications and Other Therapies

All concomitant medications used during the study were to be recorded. Concomitant medications were coded using the SUDDS dictionary. A summary of the number of subjects using each concomitant medication can be found in Section 11.1, Table T14.

The majority of subjects (68 of 69, or 98.6%) were taking, or had recently taken, some sort of concomitant medication. The concomitant medications taken by more than 20% of the subjects during treatment were Advil (24.6%), ibuprofen (23.2%), multivitamins (23.2%), and aspirin (20.3%).

A summary of subject history of other psychoactive drug therapy can be found in Section 11.1, Table T13. Eight subjects (11.6%) had been treated with psychotropic medications other than antidepressants, as follows: three subjects (4.3%) had used alcohol; four subjects (5.8%) had been prescribed Ambien (zolpidem); and one subject (1.4%) had been prescribed two different strengths (15 and 30 mg) of Restoril (temazepam).

7.2. Dosage Information

7.2.1. Extent of Exposure

Statistical summaries of the extent of study drug exposure (in days) by extension period for the safety population can be found in Section 11.4, Table T39; and a listing of the extent of study drug exposure by subject can be found in Appendix 3.5, Listing 3.5.1. The minimum number of days on treatment was 7 days, and the maximum was 673 days.

7.2.2. Treatment Compliance

The overall compliance with the dosing regimen is summarized for the MITT population in Section 11.4, Table T40. The majority of subjects (81%) were in the dosing compliance range of <70% to 79% during the study.

7.3. Efficacy Results

Statistical summaries of all efficacy variables (including HAMD-25, HAMD-17, and CGI) for the MITT population can be found in Section 11.2, Tables T17 through T22.

7.3.1. Hamilton Rating Scale for Depression

Three subjects had at least one HAMD item marked “can’t rate” at baseline and therefore a total score could not be derived for these subjects. All change from baseline HAMD-25 comparisons were based on 65 subjects. An equivalent to the usual HAMD-17 score was

calculated using 17 of the 25 items found in the HAMD-25; 66 subjects had all 17 of these items at baseline and were included in the change from baseline HAMD-17 comparisons.

Table 6 summarizes the change from baseline for HAMD-25 and HAMD-17 using LOCF methods.

Table 6 Mean Change from Baseline in HAMD-25 and HAMD-17 Scores (MITT Population) (LOCF)

Study Visit	HAMD-25			HAMD-17		
	N	Mean Change from Baseline	SD of Change from Baseline	N	Mean Change from Baseline	SD of Change from Baseline
Week 24	65	-2.6	9.92	66	-1.3	6.65
Week 72	29	-3.7	12.63	30	-2.0	8.16
Week 96	11	-9.4	8.74	12	-5.3	5.82
Week 120	7	-11.9	11.94	7	-6.3	8.54
Week 144	5	-15.4	6.8	6	-8.5	5.09

Note: Three subjects had at least one HAMD item marked "can't rate" at baseline Therefore, the HAMD-25 total score could be derived for 65 subjects and the HAMD-17 total score could be derived for 66 subjects.

Source: Section 11.2, Tables T18 and T20

For the main efficacy variable, HAMD-25, subject scores showed a continuous decrease from baseline through 144 weeks of treatment with RBX. The same can be said for the HAMD-17 scores, though the magnitude of the changes were smaller than those noted for the HAMD-25.

7.3.2. Clinical Global Impression Scales

Table 7 summarizes the change from baseline for the CGI Severity of Illness scale using LOCF methods. As can be seen in Table 7, based on the CGI Severity of Illness scale, the subjects in this study gradually improved over time. From Week 72 on, greater than half of the subjects were considered "normal, not at all ill." By 72 weeks there were no subjects considered "severely ill"; by 96 weeks, there were no subjects considered "mildly, moderately, or markedly ill."

Table 7 Change in CGI Severity of Illness During the Study (MITT Population) (LOCF)

	Reboxetine (N=68)									
	Week 24		Week 72		Week 96		Week 120		Week 144	
CGI Severity Level	n	%	n	%	n	%	n	%	n	%
Normal, not at all ill	23	33.8%	17	54.8%	11	91.7%	7	87.5%	5	83.3%
Borderline ill	20	29.4%	5	16.1%	1	8.3%	0	0.0%	0	0.0%
Mildly ill	12	17.6%	3	9.7%	0	0.0%	1	12.5%	1	16.7%
Moderately ill	9	13.2%	5	16.1%	0	0.0%	0	0.0%	0	0.0%
Markedly ill	2	2.9%	1	3.2%	0	0.0%	0	0.0%	0	0.0%
Severely ill	2	2.9%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Total	68	100%	31	100%	12	100%	8	100%	6	100%

Source: Section 11.2, Table T21

Table 8 summarizes the change from baseline for the CGI Global Improvement scale using LOCF methods. The results for this CGI scale mirrored those presented above for the CGI Severity of Illness scale—the subjects gradually demonstrated improvement over time. From Week 72 on, greater than half of the subjects were considered "much improved" and "very much improved."

Table 8 Change in CGI Global Improvement During the Study (MITT Population) (LOCF)

	Reboxetine (N=68)									
	Week 24		Week 72		Week 96		Week 120		Week 144	
CGI Improvement Level	n	%	n	%	n	%	n	%	n	%
Very much improved	17	25.0%	13	41.9%	9	75.0%	7	87.5%	5	83.3%
Much improved	12	17.6%	6	19.4%	1	8.3%	0	0.0%	1	16.7%
Minimally improved	10	14.7%	3	9.7%	0	0.0%	1	12.5%	0	0.0%
No change	16	23.5%	3	9.7%	2	16.7%	0	0.0%	0	0.0%
Minimally worse	10	14.7%	4	12.9%	0	0.0%	0	0.0%	0	0.0%
Much worse	2	2.9%	1	3.2%	0	0.0%	0	0.0%	0	0.0%
Very much worse	1	1.5%	1	3.2%	0	0.0%	0	0.0%	0	0.0%
Total	68	100%	31	100%	12	100%	8	100%	6	100%

Source: Section 11.2, Table T22

7.3.3. Drug Dose, Drug Concentration, and Relationships to Response

No data were collected during this open-label continuation study regarding relationships between drug dose, serum drug concentration, and clinical response.

7.3.4. Drug-Drug and Drug-Disease Interactions

No data were collected during this open-label continuation study regarding drug-drug or drug-disease interactions.

7.3.5. Efficacy Conclusions

Subjects continuously treated with open-label RBX for up to 144 weeks showed gradual improvement in their condition (i.e., MDD) as demonstrated by change from baseline results in HAMD-25, HAMD-17, CGI Severity of Illness, and CGI Global Improvement scales.

7.4. Safety Results

7.4.1. Adverse Events Noted at Baseline

A summary table regarding AEs noted at screening by previous treatment group can be found in Section 11.3, Table T23.

A total of 40 subjects (73%) previously treated with reboxetine had experienced AEs prior to entry into this study, as did 10 subjects (71%) previously treated with placebo (Section 11.3, Table T23). The most prevalent AEs experienced during previous studies were constipation (RBX group, 18%; placebo group, 21%), dry mouth (RBX group, 24%; placebo group, 14%), and insomnia (RBX group, 18%; placebo group, 29%).

7.4.2. Treatment-Emergent Adverse Events

All AEs experienced during the course of the study were recorded and coded using the COSTART coding dictionary. Summary tables regarding treatment-emergent AEs, treatment-emergent AEs by maximum severity, treatment-emergent AEs considered related to study drug, SAEs, and AEs resulting in early termination can be found in Section 11.3, Tables T24 through T28, respectively.

7.4.2.1. Brief Summary

Of the 69 subjects enrolled, 57 subjects (82.6%) reported at least one AE during the study, of which 45 subjects (65.2%) experienced at least one drug-related AE. Concerning maximum AE severity in the 57 subjects who experienced an AE while taking reboxetine: 15 subjects (21.7%) reported mild AEs; 25 subjects (36.2%) reported moderate AEs; and 17 subjects (24.6%) reported severe AEs. Nine subjects (13.0%) discontinued early due to treatment-emergent AEs, and four subjects (5.8%) experienced SAEs. No deaths occurred during the study.

Table 9 presents an overview of the number and percentage of subjects who had at least one treatment-emergent AE (overall, drug-related, or serious) or who discontinued due to an AE during the treatment period.

Table 9 Overall Summary of Treatment Emergent Adverse Events (Safety Population)

	Reboxetine (N=69)	
	n	%
Subjects reporting at least one AE	57	82.6%
Subjects reporting at least one drug-related AE[1]	45	65.2%
Subjects reporting at least one SAE	4	5.8%
Subjects who discontinued due to an AE	9	13.0%

[1] An AE was considered drug-related if, in the opinion of the investigator, there was a reasonable possibility that the event was related to the study drug.

Source: Section 11.3, Tables T24, T26, T27, and T28

7.4.2.2. All Treatment-Emergent Adverse Events

The 57 subjects (82.6%) with at least one AE during the study reported a total of 265 events. The frequency of treatment-emergent AEs is summarized by COSTART body system in decreasing order of frequency in Table 10. Subjects reported AEs most frequently in the nervous (50.7%), body (47.8%), and digestive (42.0%) systems.

Table 10 Number (%) of Subjects Reporting Treatment-Emergent Adverse Events by COSTART Body System Arranged in Decreasing Order of Frequency (Safety Population)

	Reboxetine (N=69)	
COSTART Body System	n	%
Nervous	35	50.7%
Body as a Whole	33	47.8%
Digestive	29	42.0%
Cardiovascular	14	20.3%
Respiratory	13	18.8%
Skin	12	17.4%
Urogenital	10	14.5%
Special Senses	8	11.6%
Musculo-Skeletal	7	10.1%
Metabolic and Nutritional	4	5.8%
Endocrine	1	1.4%
Hemic and Lymphatic	1	1.4%

Source: Section 11.3, Table T24

The most commonly reported treatment-emergent AEs (i.e., those reported in at least 5% of the subjects) are summarized in Table 11. The most frequently reported AEs were headache (26.1%), insomnia (21.7%), and constipation (15.9%).

Table 11 Most Commonly Reported (in ≥5% of Subjects) Treatment-Emergent Adverse Events by COSTART Body System and Preferred Term (Safety Population)

COSTART Body System/Preferred Term[1]	Reboxetine (N=69) n	%
BODY AS A WHOLE		
Headache	18	26.1%
Upper respiratory infection	10	14.5%
Localized pain	6	8.7%
Trauma	4	5.8%
DIGESTIVE		
Constipation	11	15.9%
Dry mouth	10	14.5%
Diarrhea	4	5.8%
Nausea	4	5.8%
Vomiting	4	5.8%
NERVOUS		
Insomnia	15	21.7%
Anxiety	10	14.5%
RESPIRATORY		
Sinusitis	6	8.7%
SKIN		
Diaphoretic	6	8.7%
CARDIOVASCULAR		
Palpitation	4	5.8%

[1] Arranged in decreasing order of frequency within a body system.

Source: Section 11.3, Table T24

Most of the 265 reported AEs were mild to moderate (235 AEs, or 88.7%) in intensity. There were 30 AEs (or 11.3%) reported as severe by 17 subjects (24.6%).

7.4.2.3. Drug-Related Treatment-Emergent Adverse Events

An AE was considered drug-related if, in the opinion of the investigator, there was a reasonable possibility that the event was related to the study drug. Adverse events that were judged by the investigators to have been related to the study medication were reported by 45 subjects (65.2%). The most frequently reported (i.e., those reported in at least 5% of the subjects) drug-related AEs are summarized in Table 12.

Table 12 Treatment-Emergent Adverse Events Considered Related[1] to Study Drug as Reported in ≥5% of Subjects by COSTART Body System and Preferred Term (Safety Population)

COSTART Body System/Preferred Term[2]	Reboxetine (N=69) n	%
DIGESTIVE		
Dry mouth	10	14.5%
Constipation	8	11.6%
NERVOUS		
Insomnia	11	15.9%
Anxiety	6	8.7%
BODY AS A WHOLE		
Headache	9	13.0%
SKIN		
Diaphoretic	6	8.7%
CARDIOVASCULAR		
Palpitation	4	5.8%

[1] An AE was considered drug-related if, in the opinion of the investigator, there was a reasonable possibility that the event was related to the study drug.

[2] Arranged in decreasing order of frequency within a body system.

Source: Section 11.3, Table T26

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

7.4.3.1. Deaths

No deaths were reported during this study.

7.4.3.2. Serious Adverse Events

Serious adverse events were reported by 4 subjects (5.8%) and these are summarized by COSTART body system and preferred term in Table 13.

Table 13 Number (%) of Subjects Reporting Serious Adverse Events by COSTART Body System and Preferred Term (Safety Population)

COSTART Body System/Preferred Term	Reboxetine (N=69) n	%
CARDIOVASCULAR		
Atrial Fibrillation	1	1.4%
NERVOUS		
Depressive Symptoms	1	1.4%
Suicidal Tendency	1	1.4%
UROGENITAL		
Menorrhagia	1	1.4%

Source: Section 11.3, Table T27

Subject #51041 was hospitalized for depression, but later recovered. Subject #361035 reported suicidal ideation and was discontinued from the study. Subject #361065 experienced atrial fibrillation with rapid atrial response and was referred to a cardiologist; the subject subsequently recovered from this event. Subject #361056 was hospitalized for excessive menstrual bleeding, from which she subsequently recovered. None of these SAEs were considered by the investigator as related to treatment with RBX. Brief narratives for each SAE can be found in Section 7.4.3.4.

7.4.3.3. Discontinuations Due to Adverse Events

A total of 11 subjects (15.9%) were listed in the database as having discontinued early from the study due to AEs (Appendix 3.1, Listing 3.1.1); however, two of these subjects (#361066 and #361069) discontinued due to AEs that began during their previous study and prior to the current study, and therefore these two subjects were not included in Section 11.3, Table T28. For the sake of completeness, all 11 subjects who discontinued early from the study because of AEs are listed in Table 14.

Table 14 Subjects Who Discontinued Due to Adverse Events (Safety Population)

Subject	Study Week	Adverse Event(s) Leading to Discontinuation
#41021	120	Nervousness
#81016	24	Constipation; urinary retention
#131032	72	Weight increase
#151023	24	Insomnia
#181050	72	Choking
#361056	72	Dyspnea
#361059	24	Appetite decreased; dry mouth
#361064	72	Headache
#361066*	24	Constipation
#361068	72	Reaction unevaluable
#361069*	24	Chills; palpitation; nausea; insomnia; dyspnea

* Adverse event began during the previous study and prior to the current study.

Source: Appendix 3.1, Listing 3.1.1 and Section 11.3, Table T28

7.4.3.4. Narrative Summaries of Deaths, Serious Adverse Events, and Other Significant Adverse Events

Subject #361035 was a 22-year-old woman with concurrent asthma and insomnia, who developed new onset suicidal ideation while receiving RBX 4 mg BID for approximately 8 months in this study. Concomitant medications included albuterol, aspirin, and zolpidem tartrate. The subject was hospitalized and discontinued from the study. The physician reported that the event was not related to RBX treatment.

Subject #361056 was a 50-year-old woman with a history of heavy menstrual bleeding, and she was hospitalized for excessive menstrual bleeding. The subject was receiving RBX 4 mg BID for approximately 3 months in this study. Concomitant medications included Provera, Chromagen, and Lo/Ovral. RBX was discontinued, and the subject underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy. No complications occurred and the subject recovered. The physician reported that the event was not related to RBX treatment.

Subject #361065 was a 78-year-old woman with concurrent hypertension and a history of intermittent arrhythmia absoluta with atrial fibrillation and myocardial infarction. She developed pulmonary hypertension while receiving RBX 4 mg BID for approximately 2 years. Concomitant medications included citalopram, metoprolol, furosemide, captopril, and amlodipine. RBX was discontinued, however, the subject did not improve. Subsequently, she was diagnosed with CREST syndrome (i.e., **C**alcinosis, **R**aynaud's disease, **E**sophageal dysmotility, **S**clerodactyl, and **T**elangiectasia). The physician reported that the event was not related to RBX treatment.

Subject #51041 was a 30-year-old woman with concurrent insomnia who developed worsening depressive symptoms while receiving RBX 10 mg/day for approximately 5 months

in this study. Concomitant medications included zolpidem tartrate. RBX was discontinued and the subject was hospitalized. She subsequently recovered, and the physician reported that the event was not related to RBX treatment.

7.4.4. Clinical Laboratory Evaluation

The laboratory normal ranges can be found in Section 11.3, Table T29. Shift tables from screening through the treatment period for hematology, serum chemistry, and urinalysis assays can be found in Section 11.3, Tables T30 through T32. Individual listings of subjects with laboratory values outside the normal range are presented in Appendix 3.2, Listings 3.2.1, 3.2.2, and 3.2.3 for hematology, serum chemistry, and urinalysis, respectively.

The reference range for evaluation of laboratory values (i.e., from hematology, serum chemistry, and urinalysis assays) was defined as the lower limit of the normal range minus 20% to the upper limit of the normal range plus 20%.

All laboratory values outside the reference range were evaluated by a clinician and judged to be isolated incidences that were not clinically significant.

7.4.4.1. Hematology

Most hematology parameters were within the reference range at baseline and remained within the reference range during treatment with RBX. Treatment-emergent hematology values inside the reference range at baseline but outside the reference range during treatment are summarized in Table 15.

Table 15 Treatment-Emergent Hematology Values Outside the Reference Range (Safety Population)

Hematology Parameter	Number[1] (%[2]) of Subjects
Hematocrit	0 (0.0%)
Hemoglobin	0 (0.0%)
Mean Corpuscular Volume	0 (0.0%)
Reticulocyte	6 (11.5%)
Total Neutrophils	0 (0.0%)
Lymphocytes	0 (0.0%)
Monocytes	0 (0.0%)
Eosinophils	1 (1.9%)
Basophils	0 (0.0%)
Leukocytes (WBC)	0 (0.0%)
Erythrocytes (RBC)	0 (0.0%)
Platelet Count	1 (1.9%)

[1] Number of subjects who had values inside the reference range at baseline but outside the reference range during treatment.

[2] Percent = (number of subjects who had values inside the reference range at baseline but outside the reference range during treatment) / (total number of subjects who had a baseline value and treatment value for this particular assay).

Source: Section 11.3, Table T30

7.4.4.2. Serum Chemistry

Most serum chemistry parameters were inside the reference range at baseline and remained inside the reference range during treatment. Treatment-emergent serum chemistry values inside the reference range at baseline but outside the reference range during treatment are summarized in Table 16.

Table 16 Treatment-Emergent Serum Chemistry Values Outside the Reference Range (Safety Population)

Serum Chemistry Parameter	Number[1] (%[2]) of Subjects
ALT/SGPT	1 (1.9%)
AST/SGOT	0 (0.0%)
Alkaline Phosphatase	1 (1.9%)
Bilirubin, Total	0 (0.0%)
Blood Urea Nitrogen (BUN)	0 (0.0%)
Carbon Dioxide	0 (0.0%)
Chloride	0 (0.0%)
Creatinine	0 (0.0%)
Glucose	8 (15.1%)
Potassium	0 (0.0%)
Sodium	0 (0.0%)
Uric Acid	2(3.8%)
T4	0 (0.0%)
TSH	0 (0.0%)

[1] Number of subjects who had values inside the reference range at baseline but outside the reference range during treatment.

[2] Percent = (number of subjects who had values inside the reference range at baseline but outside the reference range during treatment) / (total number of subjects who had a baseline value and treatment value for this particular assay).

Source: Section 11.3, Table T31

7.4.4.3. Urinalysis

There appeared to be a greater effect on urinalysis parameters than other laboratory values since more subjects showed shifts to values outside the reference range among urinalysis parameters than among the hematology or serum chemistry assays. However, as noted above, all laboratory values outside the reference range were evaluated by a clinician and judged to be isolated incidences that were not clinically significant. Treatment-emergent urinalysis values that were inside the reference range at baseline but outside the reference range during treatment are summarized in Table 17.

Table 17 Treatment-Emergent Urinalysis Values Outside the Reference Range (Safety Population)

Urinalysis Parameter	Number[1] (%[2]) of Subjects
Appearance	18 (34.0%)
Bilirubin	1 (1.9%)
Blood	10 (18.9%)
Color	8 (15.1%)
Glucose	2 (3.8%)
Leukocytes	9 (17.0%)
Nitrite	1 (1.9%)
Protein	10 (18.9%)
Ketone	4 (7.5%)
pH	0 (0.0%)
Specific Gravity	0 (0.0%)
Urobilinogen	0 (0.0%)

[1] Number of subjects who had values inside the reference range at baseline but outside the reference range during treatment.

[2] Percent = (number of subjects who had values inside the reference range at baseline but outside the reference range during treatment) / (total number of subjects who had a baseline value and treatment value for this particular assay).

Source: Section 11.3, Table T32

7.4.5. Electrocardiograms

Summary statistics for continuous ECG variables at screen and at the end of each extension period (LOCF) can be found in Section 11.3, Table T33. Global ECG results by visit can be found in Section 11.3, Table T34. An individual listing of subjects with abnormal ECG results is presented in Appendix 3.3, Listing 3.3.1.

Global ECG results are summarized in Table 18. Most subjects had normal ECGs at baseline that remained normal during treatment. Only two subjects (#321044 and #361065) had clinically relevant ECG abnormalities. Subject #321044 was a 55-year-old male whose ECG was abnormal at screening and remained abnormal throughout the study. Subject #361065 was a 50-year-old male whose ECG was normal until the Week 120 visit. See Appendix 3.3, Listing 3.3.1, for details regarding these two subjects' ECG results.

Table 18 ECG Global Results (Safety Population)

Study Visit	Normal ECG n (%)	Abnormal ECG; Not Clinically Relevant n (%)	Abnormal ECG; Clinically Relevant n (%)
Screen (n=64)	59 (92.2%)	4 (6.3%)	1 (1.6%)
Week 24 (n=59)	53 (89.8%)	5 (8.5%)	1 (1.7%)
Week 72 (n=34)	27 (79.4%)	6 (17.6%)	1 (2.9%)
Week 96 (n=9)	8 (88.9%)	1 (11.1%)	0 (0.0%)
Week 120 (n=12)	10 (83.3%)	1 (8.3%)	1 (8.3%)
Week 144 (n=4)	4 (100.0%)	0 (0.0%)	0 (0.0%)

Source: Section 11.3, Table T34

7.4.6. Vital Signs and Body Weight

Statistical summaries of baseline vital signs and height/weight (All Enrolled Subjects) can be found in Section 11.1, Tables T7 and T8, respectively. Statistical summaries of change from baseline for systolic blood pressure, diastolic blood pressure, pulse, and body weight can be found in Section 11.3, Tables T35 through T38, respectively. An individual listing of subjects with significant changes in vital signs or weight is presented in Appendix 3.4, Listing 3.4.1.

No clinically relevant mean changes from baseline occurred in vital signs or weight during treatment with RBX. While the mean change from baseline for weight shows a decrease of approximately 19 pounds by Week 144, this outcome was based on a very small number of subjects (i.e., <12 subjects after Week 96). As can be seen in Appendix 3.4, Listing 3.4.1, only two subjects (#41021 and #361035, both female) experienced what was considered to be significant weight loss during the study, one by Week 20 and the other by Week 32, and one of these subjects was actually dieting. Another subject (#131032, female) actually experienced what was considered to be a significant weight gain by Week 24.

Mean (SD) changes from baseline in vital signs and weight during the study are summarized in Table 20.

Table 20 Change from Baseline in Vital Signs and Weight (Safety Population)

Vital Sign	Study Visit	N	Mean Change from Baseline	SD of Change from Baseline
Systolic Blood Pressure (mmHg)	Week 24	68	1.9	12.58
	Week 72	31	1.9	17.47
	Week 96	12	6.9	17.58
	Week 120	7	8.1	20.71
	Week 144	6	7.3	21.08
Diastolic Blood Pressure (mmHg)	Week 24	68	0.1	9.74
	Week 72	31	-1.7	9.81
	Week 96	12	0.7	9.04
	Week 120	7	2.0	6.63
	Week 144	6	1.3	7.76
Pulse (bpm)	Week 24	68	1.9	12.75
	Week 72	31	0.0	15.67
	Week 96	12	6.3	8.30
	Week 120	7	0.0	15.36
	Week 144	6	-2.7	19.70
Weight (lbs)	Week 24	68	-3.4	7.83
	Week 72	31	-6.0	14.55
	Week 96	12	-14.3	12.93
	Week 120	7	-15.7	18.57
	Week 144	6	-19.3	18.39

Source: Section 11.3, Tables T35 through T38

7.4.7. Safety Conclusions

Reboxetine was well tolerated in this open-label rescue and therapy continuation study. The majority of AEs reported were mild or moderate in severity. Nine subjects (13.0%) discontinued early due to treatment-emergent AEs, and four subjects (5.8%) experienced SAEs. No deaths occurred during the study. Adverse events that were judged by the investigator to have been related to study drug administration were reported in the majority (65%) of subjects while taking RBX. The most frequently reported drug-related AEs during this extension study were insomnia, dry mouth, headache, and constipation, none of which were considered new or unexpected AEs with this class of compound.

Most hematology, serum chemistry, and urinalysis parameters were inside the reference range at baseline and remained inside the reference range during treatment. All laboratory values outside the reference range were evaluated by a clinician and judged to be isolated incidences that were not clinically significant. In addition, no clinically relevant changes occurred in ECGs, vital signs, or weight during the study.

8. DISCUSSION AND OVERALL CONCLUSIONS

This was an uncontrolled, open-label, rescue and continuation therapy study of subjects treated with RBX, limited to subjects who had participated in a previous PNU supported or sponsored trial within the previous 2 weeks. This study was originally designed to generate important long-term safety data and to make RBX available to subjects while FDA approval was pending. In addition, treatment guidelines recommend continuing antidepressant medication for several months after remission of the symptoms of depression.[4,5] Subsequently, the study protocol was amended six times to allow for continued RBX treatment for up to 144 weeks.

A total of 69 subjects were enrolled at 18 study sites, and all subjects received at least one dose of study drug and were therefore included in all safety analyses. The MITT population (for efficacy analyses) consisted of 68 subjects and included all subjects who received at least one dose of study drug with at least one post-baseline efficacy measure. A total of 37 subjects (53.6%) completed the initial 24-week treatment period, 17 subjects (24.6%) completed the 72-week treatment period, 9 subjects (13.0%) completed the 96-week treatment period, 7 subjects (10.1%) completed the 120-week treatment period, and 2 subjects (2.9%) completed the 144-week treatment period. Subjects ranged in age from 20 to 66 years (mean = 46.7 years), and the majority were women (68.1%) and Caucasian (88.4%).

Reboxetine was well tolerated in this open-label study. The majority of AEs reported were mild or moderate in severity. Nine subjects (13.0%) discontinued early due to treatment-emergent AEs, and four subjects (5.8%) experienced SAEs. No deaths occurred during the study. Adverse events that were judged by the investigator to have been related to study drug administration were reported in the majority (65%) of subjects while taking RBX. The most frequently reported drug-related AEs during this extension study were insomnia, dry mouth, headache, and constipation, none of which were considered new or unexpected AEs with this class of compound. No clinically relevant changes occurred in clinical laboratory assessments, ECGs, vital signs, or weight during the study.

Regarding the secondary assessments of efficacy in this open-label study, subjects continuously treated with RBX for up to 144 weeks showed gradual improvement in their condition (i.e., MDD) as demonstrated by change from baseline results in HAMD-25, HAMD-17, CGI Severity of Illness, and CGI Global Improvement scales.

9. ACKNOWLEDGEMENTS

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11. TABLES AND FIGURES

11.1. Subject Disposition, Demographics, and Baseline Characteristics Summary Tables

11.2. Efficacy Data Summary Tables

11.3. Safety Data Summary Tables

11.4. Extent of Exposure and Dosing Compliance Summary Tables

LIST OF APPENDICES

TABLE T17
HAMD-25 Total Scores: Mean Change from Baseline at Week 24 By Previous Treatment Group
MITT Population (LOCF)
Date Produced: August 25, 2003

		Placebo	Reboxetine
HAMD-25 Total Score	N	13	52
	Baseline Mean	15.5	13.2
	Mean	10.2	11.3
	Mean Change	-5.3	-1.9
	SD of Change	13.54	8.83
	Min of Change	-24	-22
	Max of Change	21	15

Program: ef1.sas

TABLE T18
HAMD-25 Total Scores: Mean Change from Baseline
MITT Population (LOCF)
Date Produced: August 25, 2003

		Reboxetine (N=68)				
		Week 24	Week 72	Week 96	Week 120	Week 144
HAMD-25 Total Score	N	65	29	11	7	5
	Baseline Mean	13.7	13	13.5	16	19
	Mean	11.1	9.3	4.2	4.1	3.6
	Mean Change	-2.6	-3.7	-9.4	-11.9	-15.4
	SD of Change	9.92	12.63	8.74	11.94	6.8
	Min of Change	-24	-25	-20	-23	-21
	Max of Change	21	23	6	12	-4

NOTE: A total of three subjects were excluded because total score could not be derived due to item(s) marked "Can not rate."

Program:ef2.sas

TABLE T19
HAMD-17 Total Scores: Mean Change from Baseline at Week 24 By Previous Treatment Group
MITT Population (LOCF)
Date Produced: August 25, 2003

		Placebo	Reboxetine
HAMD-17 Total Score	N	13	53
	Baseline Mean	10.1	8.9
	Mean	7.6	8
	Mean Change	-2.5	-1
	SD of Change	8.85	6.07
	Min of Change	-15	-16
	Max of Change	14	12

Program: ef3.sas

TABLE T20
HAMD-17 Total Scores: Mean Change from Baseline
MITT Population (LOCF)
Date Produced: August 25, 2003

		Reboxetine (N=68)				
		Week 24	Week 72	Week 96	Week 120	Week 144
HAMD-17 Total Score	N	66	30	12	7	6
	Baseline Mean	9.2	8.5	8.8	9.7	11.2
	Mean	7.9	6.6	3.6	3.4	2.7
	Mean Change	-1.3	-2	-5.3	-6.3	-8.5
	SD of Change	6.65	8.16	5.82	8.54	5.09
	Min of Change	-16	-16	-13	-15	-15
	Max of Change	14	14	7	10	-2

NOTE: Two subjects were excluded because total score could not be derived due to item(s) marked "Can not rate."

Program:ef4.sas

TABLE T21
Clinical Global Impressions: Severity of Illness
MITT Population (LOCF)
Date Produced: August 25, 2003

	Reboxetine (N=68)									
	Week 24		Week 72		Week 96		Week 120		Week 144	
	# of Pts	%	# of Pts	%	# of Pts	%	# of Pts	%	# of Pts	%
Normal, not at all ill	23	33.8	17	54.8	11	91.7	7	87.5	5	83.3
Borderline ill	20	29.4	5	16.1	1	8.3	0	0	0	0
Mildly ill	12	17.6	3	9.7	0	0	1	12.5	1	16.7
Moderately ill	9	13.2	5	16.1	0	0	0	0	0	0
Markedly ill	2	2.9	1	3.2	0	0	0	0	0	0
Severely ill	2	2.9	0	0	0	0	0	0	0	0
Total	68	100.0	31	100.0	12	100.0	8	100.0	6	100.0

Program: ef5.sas

TABLE T23
Adverse Events at Screening by Previous Treatment Group
All Enrolled Subjects
Date Produced: August 25, 2003

Body System	COSTART Term	Placeb (N=14)			Reboxetine (N=55)		
		n	%	# of Reports	n	%	# of Reports
Subjects with at least one AE in system		10	71.4	21	40	72.7	131
BODY	Any Adverse Events	3	21.4	4	17	30.9	22
	ABDOMINAL DISTENSION	0	0	0	2	3.6	2
	ABDOMINAL PAIN LOCALIZED	0	0	0	2	3.6	2
	ALLERGIC REACTION	1	7.1	1	0	0	0
	CHEST PAIN	0	0	0	1	1.8	1
	CHILLS	1	7.1	1	4	7.3	4
	ENVIRONMENTAL ALLERGY	0	0	0	1	1.8	1
	GENERALIZED EDEMA	0	0	0	1	1.8	1
	GENERALIZED PAIN	0	0	0	1	1.8	1

NOTE: N = Number of subjects enrolled.
n = Number of subjects reporting adverse events at screening.
% = Percentage based on number of subjects enrolled.
Each subject is counted once per COSTART term.
Each subject is counted once per body system

Program: dm14.sas

TABLE T23
Adverse Events at Screening by Previous Treatment Group
All Enrolled Subjects
Date Produced: August 25, 2003

Body System	COSTART Term	Placebo (N=14)			Reboxetine (N=55)		
		n	%	# of Reports	n	%	# of Reports
BODY	HEADACHE	0	0	0	6	10.9	6
	LOCALIZED PAIN	1	7.1	1	0	0	0
	NECK PAIN	1	7.1	1	1	1.8	1
	TRAUMA	0	0	0	2	3.6	2
	UPPER RESPIRATORY INFECTION	0	0	0	1	1.8	1
CARDIOVASCULAR	Any Adverse Events	2	14.3	2	7	12.7	7
	HYPERTENSION	0	0	0	1	1.8	1
	PALPITATION	0	0	0	1	1.8	1
	TACHYCARDIA	0	0	0	2	3.6	2
	VASODILATION	2	14.3	2	3	5.5	3

NOTE: N = Number of subjects enrolled.
n = Number of subjects reporting adverse events at screening.
% = Percentage based on number of subjects enrolled.
Each subject is counted once per COSTART term.
Each subject is counted once per body system

Program: dm14.sas

TABLE T23
Adverse Events at Screening by Previous Treatment Group
All Enrolled Subjects
Date Produced: August 25, 2003

Body System	COSTART Term	Placebo (N=14)			Reboxetine (N=55)		
		n	%	# of Reports	n	%	# of Reports
DIGESTIVE	Any Adverse Events	6	42.9	6	24	43.6	30
	APPETITE DECREASED	0	0	0	2	3.6	2
	CONSTIPATION	3	21.4	3	10	18.2	10
	DRY MOUTH	2	14.3	2	13	23.6	13
	DYSPEPSIA	1	7.1	1	2	3.6	2
	NAUSEA	0	0	0	1	1.8	1
	RECTAL BLEEDING	0	0	0	1	1.8	1
	THROAT DRY	0	0	0	1	1.8	1
METABOLIC AND NUTRITIONAL	Any Adverse Events	0	0	0	3	5.5	3
	HYPERCHOLESTEREMIA	0	0	0	1	1.8	1

NOTE: N = Number of subjects enrolled.
n = Number of subjects reporting adverse events at screening.
% = Percentage based on number of subjects enrolled.
Each subject is counted once per COSTART term.
Each subject is counted once per body system

Program: dm14.sas

TABLE T23
Adverse Events at Screening by Previous Treatment Group
All Enrolled Subjects
Date Produced: August 25, 2003

Body System	COSTART Term	Placebo (N=14)			Reboxetine (N=55)		
		n	%	# of Reports	n	%	# of Reports
METABOLIC AND NUTRITIONAL	PERIPHERAL EDEMA	0	0	0	2	3.6	2
MUSCULO-SKELETAL	Any Adverse Events	1	7.1	1	2	3.6	4
	ARTHRALGIA SINGLE AND MULTIPLE JOINT	0	0	0	1	1.8	3
	MYALGIA	1	7.1	1	1	1.8	1
NERVOUS	Any Adverse Events	6	42.9	6	22	40.0	31
	AGITATION	0	0	0	1	1.8	1
	ANXIETY	0	0	0	2	3.6	2
	CHANGE IN DREAMS	0	0	0	3	5.5	3
	CONCENTRATION IMPAIRED	0	0	0	1	1.8	1
	DIZZINESS	1	7.1	1	0	0	0

NOTE: N = Number of subjects enrolled.
n = Number of subjects reporting adverse events at screening.
% = Percentage based on number of subjects enrolled.
Each subject is counted once per COSTART term.
Each subject is counted once per body system

Program: dm14.sas

TABLE T23
Adverse Events at Screening by Previous Treatment Group
All Enrolled Subjects
Date Produced: August 25, 2003

Body System	COSTART Term	Placebo (N=14)			Reboxetine (N=55)		
		n	%	# of Reports	n	%	# of Reports
NERVOUS	EMOTIONAL LABILITY	0	0	0	1	1.8	1
	HYPERTONIA	0	0	0	1	1.8	1
	INSOMNIA	4	28.6	4	10	18.2	10
	LIBIDO DECREASED	1	7.1	1	2	3.6	2
	NERVOUSNESS	0	0	0	3	5.5	3
	NIGHTMARES	0	0	0	1	1.8	1
	PARESTHESIA	0	0	0	2	3.6	2
	RESTLESSNESS	0	0	0	1	1.8	1
	VERTIGO	0	0	0	3	5.5	3
RESPIRATORY	Any Adverse Events	1	7.1	1	4	7.3	5

NOTE: N = Number of subjects enrolled.
n = Number of subjects reporting adverse events at screening.
% = Percentage based on number of subjects enrolled.
Each subject is counted once per COSTART term.
Each subject is counted once per body system

Program: dm14.sas

TABLE T23
Adverse Events at Screening by Previous Treatment Group
All Enrolled Subjects
Date Produced: August 25, 2003

Body System	COSTART Term	Placebo (N=14)			Reboxetine (N=55)		
		n	%	# of Reports	n	%	# of Reports
RESPIRATORY	COUGH	1	7.1	1	1	1.8	1
	DYSPNEA	0	0	0	2	3.6	2
	PHARYNGITIS	0	0	0	1	1.8	1
	SINUSITIS	0	0	0	1	1.8	1
SKIN	Any Adverse Events	0	0	0	5	9.1	9
	DIAPHORETIC	0	0	0	4	7.3	4
	ECZEMA	0	0	0	1	1.8	1
	ERYTHEMA	0	0	0	1	1.8	2
	HAIR LOSS	0	0	0	1	1.8	1
	NODULE SKIN	0	0	0	1	1.8	1

NOTE: N = Number of subjects enrolled.
n = Number of subjects reporting adverse events at screening.
% = Percentage based on number of subjects enrolled.
Each subject is counted once per COSTART term.
Each subject is counted once per body system

Program: dm14.sas

TABLE T23
Adverse Events at Screening by Previous Treatment Group
All Enrolled Subjects
Date Produced: August 25, 2003

Body System	COSTART Term	Placebo (N=14)			Reboxetine (N=55)		
		n	%	# of Reports	n	%	# of Reports
SPECIAL SENSES	Any Adverse Events	1	7.1	1	8	14.5	9
	BLURRED VISION	0	0	0	4	7.3	4
	TASTE PERVERSION	0	0	0	1	1.8	1
	TINNITUS	0	0	0	3	5.5	4
	VISION ABNORMAL	1	7.1	1	0	0	0
UROGENITAL	Any Adverse Events	0	0	0	7	12.7	11
	DISORDER PENIS	0	0	0	1	1.8	1
	DYSURIA	0	0	0	1	1.8	1
	EJACULATION ABNORMAL	0	0	0	2	3.6	2
	IMPOTENCE	0	0	0	2	3.6	2

NOTE: N = Number of subjects enrolled.
n = Number of subjects reporting adverse events at screening.
% = Percentage based on number of subjects enrolled.
Each subject is counted once per COSTART term.
Each subject is counted once per body system

Program: dm14.sas

TABLE T23
Adverse Events at Screening by Previous Treatment Group
All Enrolled Subjects
Date Produced: August 25, 2003

Body System	COSTART Term	Placebo (N=14)			Reboxetine (N=55)		
		n	%	# of Reports	n	%	# of Reports
UROGENITAL	NOCTURIA	0	0	0	1	1.8	1
	POLYURIA	0	0	0	1	1.8	1
	SEXUAL FUNCTION ABNORMAL	0	0	0	1	1.8	1
	URINATION IMPAIRED	0	0	0	1	1.8	1
	URINE ABNORMAL	0	0	0	1	1.8	1

NOTE: N = Number of subjects enrolled.
n = Number of subjects reporting adverse events at screening.
% = Percentage based on number of subjects enrolled.
Each subject is counted once per COSTART term.
Each subject is counted once per body system

Program: dm14.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
Subjects with at least one AE		57	82.6	265
BODY	Any Event in Body System	33	47.8	81
	ABDOMINAL CRAMP	1	1.4	1
	ABDOMINAL PAIN LOCALIZED	1	1.4	1
	ALLERGIC REACTION	2	2.9	2
	CHEST PAIN	1	1.4	1
	FATIGUE	1	1.4	1
	FLU SYNDROME	3	4.3	3
	HEADACHE	18	26.1	38
	HERNIA	1	1.4	1
	HERNIATED DISC	1	1.4	1
	INFECTION FUNGAL NOS	2	2.9	3
	LOCALIZED EDEMA	1	1.4	1

Program: ae1.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
BODY	LOCALIZED PAIN	6	8.7	8
	REACTION UNEVALUABLE	2	2.9	2
	TRAUMA	4	5.8	6
	UPPER RESPIRATORY INFECTION	10	14.5	12
CARDIOVASCULAR	Any Event in Body System	14	20.3	15
	ATRIAL FIBRILLATION	1	1.4	1
	CARDIAC RHYTHM ABNORMAL	1	1.4	1
	DISORDER RAYNAUD	1	1.4	1
	HYPERTENSION	2	2.9	2
	MIGRAINE	2	2.9	2
	PALPITATION	4	5.8	4
	SYNCOPE	1	1.4	1
	TACHYCARDIA	2	2.9	2

Program: ae1.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
CARDIOVASCULAR	VASODILATION	1	1.4	1
DIGESTIVE	Any Event in Body System	29	42.0	45
	ABSCESS PERIODONTAL	1	1.4	2
	APPETITE DECREASED	1	1.4	1
	BLOODY STOOL	1	1.4	1
	CHOKING	1	1.4	1
	CONSTIPATION	11	15.9	11
	DIARRHEA	4	5.8	4
	DRY MOUTH	10	14.5	10
	DYSPEPSIA	2	2.9	2
	GASTROESOPHAGEAL REFLUX	1	1.4	1
	HEMORRHOID	1	1.4	1
	NAUSEA	4	5.8	4
	RECTAL BLEEDING	1	1.4	1

Program: ae1.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
DIGESTIVE	TOOTH CARIES	1	1.4	1
	TOOTHACHE	1	1.4	1
	VOMITING	4	5.8	4
ENDOCRINE	Any Event in Body System	1	1.4	1
	DISORDER THYROID	1	1.4	1
HEMIC AND LYMPHATIC	Any Event in Body System	1	1.4	1
	ANEMIA	1	1.4	1
METABOLIC AND NUTRITIONAL	Any Event in Body System	4	5.8	4
	HYPERCHOLESTEREMIA	1	1.4	1
	PERIPHERAL EDEMA	1	1.4	1
	WEIGHT DECREASE	1	1.4	1
	WEIGHT INCREASE	1	1.4	1
MUSCULO-SKELETAL	Any Event in Body System	7	10.1	8

Program: ae1.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
MUSCULO-SKELETAL	ARTHRALGIA SINGLE AND MULTIPLE JOINT	1	1.4	1
	ARTHRITIS SINGLE AND MULTIPLE JOINT	1	1.4	1
	MUSCLE TWITCH	1	1.4	1
	MYALGIA	3	4.3	4
	OSTEOPOROSIS	1	1.4	1
NERVOUS	Any Event in Body System	35	50.7	52
	AMNESIA	1	1.4	1
	ANXIETY	10	14.5	11
	CHANGE IN DREAMS	2	2.9	2
	DEPRESSIVE SYMPTOMS	2	2.9	2
	DIZZINESS	2	2.9	2
	HYPESTHESIA	3	4.3	3
	HYPOREFLEXIA	1	1.4	1

Program: ae1.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
NERVOUS	INSOMNIA	15	21.7	18
	MYOCLONUS	1	1.4	1
	NERVOUSNESS	3	4.3	3
	NYSTAGMUS	1	1.4	1
	SOMNOLENCE	3	4.3	3
	SUICIDAL TENDENCY	1	1.4	1
	TREMOR	1	1.4	1
	VERTIGO	2	2.9	2
RESPIRATORY	Any Event in Body System	13	18.8	19
	BRONCHITIS	2	2.9	3
	COUGH	2	2.9	2
	DYSPNEA	1	1.4	1
	LARYNGITIS	1	1.4	1
	PHARYNGITIS	3	4.3	3

Program: ae1.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
RESPIRATORY	RHINITIS	1	1.4	1
	SINUSITIS	6	8.7	8
SKIN	Any Event in Body System	12	17.4	16
	ACNE	1	1.4	1
	DIAPHORETIC	6	8.7	7
	DRY SKIN NON-APPLICATION SITE	1	1.4	1
	ERYTHEMA	1	1.4	1
	HERPES SIMPLEX DERM	1	1.4	1
	RASH	2	2.9	4
	SKIN TEST REACTION	1	1.4	1
SPECIAL SENSES	Any Event in Body System	8	11.6	9
	BLURRED VISION	3	4.3	4
	CONJUNCTIVITIS	1	1.4	1

Program: ae1.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
SPECIAL SENSES	DISORDER EAR	1	1.4	1
	DISORDER EYE	1	1.4	1
	HEMORRHAGE EYE	1	1.4	1
	TINNITUS	1	1.4	1
UROGENITAL	Any Event in Body System	10	14.5	14
	BREAST PAIN	1	1.4	1
	DISORDER PENIS	1	1.4	1
	DISORDER TESTICLE	1	1.4	1
	DYSMENORRHEA	1	1.4	1
	FREQUENCY URINARY	2	2.9	2
	IMPOTENCE	2	2.9	2
	INFECTION URINARY TRACT	1	1.4	1
	MENORRHAGIA	1	1.4	1
	NEOPLASM BREAST	1	1.4	1

Program: ae1.sas

TABLE T24
Treatment-Emergent Adverse Events
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
UROGENITAL	PYELONEPHRITIS	1	1.4	1
	RETENTION URINARY	1	1.4	1
	URINATION IMPAIRED	1	1.4	1

Program: ae1.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
Subjects with at least one AE		15	21.7	148	25	36.2	87	17	24.6	30
BODY	Any Event in Body System	15	21.7	46	11	15.9	23	7	10.1	12
	ALLERGIC REACTION	1	1.4	1	0	0	0	1	1.4	1
	CHEST PAIN	1	1.4	1	0	0	0	0	0	0
	FATIGUE	1	1.4	1	0	0	0	0	0	0
	HEADACHE	11	15.9	26	5	7.2	7	2	2.9	5
	HERNIA	1	1.4	1	0	0	0	0	0	0
	INFECTION FUNGAL NOS	0	0	1	2	2.9	2	0	0	0
	LOCALIZED PAIN	2	2.9	3	2	2.9	3	2	2.9	2
	TRAUMA	2	2.9	4	2	2.9	2	0	0	0
	UPPER RESPIRATORY INFECTION	6	8.7	8	2	2.9	2	2	2.9	2
	ABDOMINAL CRAMP	0	0	0	1	1.4	1	0	0	0

Program: ae5.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
BODY	FLU SYNDROME	0	0	0	2	2.9	2	1	1.4	1
	HERNIATED DISC	0	0	0	1	1.4	1	0	0	0
	LOCALIZED EDEMA	0	0	0	1	1.4	1	0	0	0
	REACTION UNEVALUABLE	0	0	0	2	2.9	2	0	0	0
	ABDOMINAL PAIN LOCALIZED	0	0	0	0	0	0	1	1.4	1
CARDIOVASCULAR	Any Event in Body System	9	13.0	10	3	4.3	3	2	2.9	2
	CARDIAC RHYTHM ABNORMAL	1	1.4	1	0	0	0	0	0	0
	DISORDER RAYNAUD	1	1.4	1	0	0	0	0	0	0
	HYPERTENSION	2	2.9	2	0	0	0	0	0	0
	PALPITATION	4	5.8	4	0	0	0	0	0	0
	TACHYCARDIA	2	2.9	2	0	0	0	0	0	0
	MIGRAINE	0	0	0	1	1.4	1	1	1.4	1
	SYNCOPE	0	0	0	1	1.4	1	0	0	0

Program: ae5.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
CARDIOVASCULAR	VASODILATION	0	0	0	1	1.4	1	0	0	0
	ATRIAL FIBRILLATION	0	0	0	0	0	0	1	1.4	1
DIGESTIVE	Any Event in Body System	15	21.7	28	9	13.0	12	5	7.2	5
	ABSCESS PERIODONTAL	1	1.4	2	0	0	0	0	0	0
	BLOODY STOOL	1	1.4	1	0	0	0	0	0	0
	CONSTIPATION	8	11.6	8	2	2.9	2	1	1.4	1
	DIARRHEA	2	2.9	2	2	2.9	2	0	0	0
	DRY MOUTH	7	10.1	7	2	2.9	2	1	1.4	1
	GASTROESOPHAGEAL REFLUX	1	1.4	1	0	0	0	0	0	0
	NAUSEA	3	4.3	3	0	0	0	1	1.4	1
	RECTAL BLEEDING	1	1.4	1	0	0	0	0	0	0
	TOOTHACHE	1	1.4	1	0	0	0	0	0	0
	VOMITING	2	2.9	2	1	1.4	1	1	1.4	1

Program: ae5.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
DIGESTIVE	APPETITE DECREASED	0	0	0	1	1.4	1	0	0	0
	CHOKING	0	0	0	1	1.4	1	0	0	0
	DYSPEPSIA	0	0	0	2	2.9	2	0	0	0
	HEMORRHOID	0	0	0	1	1.4	1	0	0	0
	TOOTH CARIES	0	0	0	0	0	0	1	1.4	1
ENDOCRINE	Any Event in Body System	1	1.4	1	0	0	0	0	0	0
	DISORDER THYROID	1	1.4	1	0	0	0	0	0	0
HEMIC AND LYMPHATIC	Any Event in Body System	1	1.4	1	0	0	0	0	0	0
	ANEMIA	1	1.4	1	0	0	0	0	0	0
METABOLIC AND NUTRITIONAL	Any Event in Body System	3	4.3	3	1	1.4	1	0	0	0
	HYPERCHOLESTEREMIA	1	1.4	1	0	0	0	0	0	0
	WEIGHT DECREASE	1	1.4	1	0	0	0	0	0	0
	WEIGHT INCREASE	1	1.4	1	0	0	0	0	0	0

Program: ae5.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
METABOLIC AND NUTRITIONAL	PERIPHERAL EDEMA	0	0	0	1	1.4	1	0	0	0
MUSCULO-SKELETAL	Any Event in Body System	4	5.8	5	1	1.4	1	2	2.9	2
	ARTHRALGIA SINGLE AND MULTIPLE JOINT	1	1.4	1	0	0	0	0	0	0
	MUSCLE TWITCH	1	1.4	1	0	0	0	0	0	0
	MYALGIA	2	2.9	3	1	1.4	1	0	0	0
	ARTHRITIS SINGLE AND MULTIPLE JOINT	0	0	0	0	0	0	1	1.4	1
	OSTEOPOROSIS	0	0	0	0	0	0	1	1.4	1
NERVOUS	Any Event in Body System	15	21.7	22	14	20.3	22	6	8.7	8
	AMNESIA	1	1.4	1	0	0	0	0	0	0
	ANXIETY	3	4.3	3	5	7.2	6	2	2.9	2
	CHANGE IN DREAMS	1	1.4	1	1	1.4	1	0	0	0

Program: ae5.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
NERVOUS	DIZZINESS	1	1.4	1	1	1.4	1	0	0	0
	HYPESTHESIA	2	2.9	2	1	1.4	1	0	0	0
	HYPOREFLEXIA	1	1.4	1	0	0	0	0	0	0
	INSOMNIA	7	10.1	8	6	8.7	7	2	2.9	3
	MYOCLONUS	1	1.4	1	0	0	0	0	0	0
	NYSTAGMUS	1	1.4	1	0	0	0	0	0	0
	SOMNOLENCE	2	2.9	2	1	1.4	1	0	0	0
	TREMOR	1	1.4	1	0	0	0	0	0	0
	DEPRESSIVE SYMPTOMS	0	0	0	2	2.9	2	0	0	0
	NERVOUSNESS	0	0	0	2	2.9	2	1	1.4	1
	VERTIGO	0	0	0	1	1.4	1	1	1.4	1
	SUICIDAL TENDENCY	0	0	0	0	0	0	1	1.4	1
RESPIRATORY	Any Event in Body System	5	7.2	7	8	11.6	12	0	0	0

Program: ae5.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
RESPIRATORY	BRONCHITIS	0	0	1	2	2.9	2	0	0	0
	PHARYNGITIS	2	2.9	2	1	1.4	1	0	0	0
	RHINITIS	1	1.4	1	0	0	0	0	0	0
	SINUSITIS	3	4.3	3	3	4.3	5	0	0	0
	COUGH	0	0	0	2	2.9	2	0	0	0
	DYSPNEA	0	0	0	1	1.4	1	0	0	0
	LARYNGITIS	0	0	0	1	1.4	1	0	0	0
SKIN	Any Event in Body System	9	13.0	10	3	4.3	6	0	0	0
	ACNE	1	1.4	1	0	0	0	0	0	0
	DIAPHORETIC	4	5.8	4	2	2.9	3	0	0	0
	DRY SKIN NON-APPLICATION SITE	1	1.4	1	0	0	0	0	0	0
	ERYTHEMA	1	1.4	1	0	0	0	0	0	0

Program: ae5.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
SKIN	HERPES SIMPLEX DERM	1	1.4	1	0	0	0	0	0	0
	RASH	1	1.4	1	1	1.4	3	0	0	0
	SKIN TEST REACTION	1	1.4	1	0	0	0	0	0	0
SPECIAL SENSES	Any Event in Body System	6	8.7	7	2	2.9	2	0	0	0
	BLURRED VISION	3	4.3	4	0	0	0	0	0	0
	DISORDER EAR	1	1.4	1	0	0	0	0	0	0
	DISORDER EYE	1	1.4	1	0	0	0	0	0	0
	HEMORRHAGE EYE	1	1.4	1	0	0	0	0	0	0
	CONJUNCTIVITIS	0	0	0	1	1.4	1	0	0	0
	TINNITUS	0	0	0	1	1.4	1	0	0	0
UROGENITAL	Any Event in Body System	5	7.2	8	4	5.8	5	1	1.4	1
	BREAST PAIN	1	1.4	1	0	0	0	0	0	0
	DISORDER PENIS	1	1.4	1	0	0	0	0	0	0

Program: ae5.sas

TABLE T25
Treatment-Emergent Adverse Events by Maximum Severity
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)								
		Mild			Moderate			Severe		
		# of Pts	%	# Reported	# of Pts	%	# Reported	# of Pts	%	# Reported
UROGENITAL	DISORDER TESTICLE	1	1.4	1	0	0	0	0	0	0
	FREQUENCY URINARY	2	2.9	2	0	0	0	0	0	0
	IMPOTENCE	2	2.9	2	0	0	0	0	0	0
	URINATION IMPAIRED	1	1.4	1	0	0	0	0	0	0
	DYSMENORRHEA	0	0	0	1	1.4	1	0	0	0
	INFECTION URINARY TRACT	0	0	0	1	1.4	1	0	0	0
	NEOPLASM BREAST	0	0	0	1	1.4	1	0	0	0
	PYELONEPHRITIS	0	0	0	1	1.4	1	0	0	0
	RETENTION URINARY	0	0	0	1	1.4	1	0	0	0
	MENORRHAGIA	0	0	0	0	0	0	1	1.4	1

Program: ae5.sas

TABLE T26
Subjects with Treatment Emergent Adverse Events Related to Study Medication by Body System and COSTART Preferred Term
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
Subjects with at least one AE		45	65.2	113
BODY	Any Event in Body System	12	17.4	23
	ABDOMINAL CRAMP	1	1.4	1
	ABDOMINAL PAIN LOCALIZED	1	1.4	1
	HEADACHE	9	13.0	19
	LOCALIZED EDEMA	1	1.4	1
	UPPER RESPIRATORY INFECTION	1	1.4	1
CARDIOVASCULAR	Any Event in Body System	11	15.9	11
	CARDIAC RHYTHM ABNORMAL	1	1.4	1
	HYPERTENSION	2	2.9	2
	MIGRAINE	1	1.4	1
	PALPITATION	4	5.8	4

NOTE: Table includes Subject #151034 who had an AE on the 11 Jul 2001 and relation to medication was noted as unknown.

Program: ae3.sas

TABLE T26
Subjects with Treatment Emergent Adverse Events Related to Study Medication by Body System and COSTART Preferred Term
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
CARDIOVASCULAR	TACHYCARDIA	2	2.9	2
	VASODILATION	1	1.4	1
DIGESTIVE	Any Event in Body System	21	30.4	26
	APPETITE DECREASED	1	1.4	1
	CONSTIPATION	8	11.6	8
	DIARRHEA	2	2.9	2
	DRY MOUTH	10	14.5	10
	DYSPEPSIA	2	2.9	2
	HEMORRHOID	1	1.4	1
	NAUSEA	1	1.4	1
	RECTAL BLEEDING	1	1.4	1
METABOLIC AND NUTRITIONAL	Any Event in Body System	2	2.9	2
	WEIGHT DECREASE	1	1.4	1

NOTE: Table includes Subject #151034 who had an AE on the 11 Jul 2001 and relation to medication was noted as unknown.

Program: ae3.sas

TABLE T26
Subjects with Treatment Emergent Adverse Events Related to Study Medication by Body System and COSTART Preferred Term
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
METABOLIC AND NUTRITIONAL	WEIGHT INCREASE	1	1.4	1
MUSCULO-SKELETAL	Any Event in Body System	1	1.4	1
	MUSCLE TWITCH	1	1.4	1
NERVOUS	Any Event in Body System	22	31.9	29
	AMNESIA	1	1.4	1
	ANXIETY	6	8.7	6
	CHANGE IN DREAMS	2	2.9	2
	DEPRESSIVE SYMPTOMS	1	1.4	1
	DIZZINESS	1	1.4	1
	INSOMNIA	11	15.9	12
	MYOCLONUS	1	1.4	1
	NERVOUSNESS	2	2.9	2
	SOMNOLENCE	2	2.9	2

NOTE: Table includes Subject #151034 who had an AE on the 11 Jul 2001 and relation to medication was noted as unknown.

Program: ae3.sas

TABLE T26
Subjects with Treatment Emergent Adverse Events Related to Study Medication by Body System and COSTART Preferred Term
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
NERVOUS	VERTIGO	1	1.4	1
RESPIRATORY	Any Event in Body System	1	1.4	1
	SINUSITIS	1	1.4	1
SKIN	Any Event in Body System	7	10.1	7
	DIAPHORETIC	6	8.7	6
	ERYTHEMA	1	1.4	1
SPECIAL SENSES	Any Event in Body System	3	4.3	4
	BLURRED VISION	2	2.9	3
	TINNITUS	1	1.4	1
UROGENITAL	Any Event in Body System	6	8.7	9
	BREAST PAIN	1	1.4	1
	DISORDER PENIS	1	1.4	1
	DISORDER TESTICLE	1	1.4	1

NOTE: Table includes Subject #151034 who had an AE on the 11 Jul 2001 and relation to medication was noted as unknown.

Program: ae3.sas

TABLE T26
Subjects with Treatment Emergent Adverse Events Related to Study Medication by Body System and COSTART Preferred Term
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
UROGENITAL	FREQUENCY URINARY	2	2.9	2
	IMPOTENCE	2	2.9	2
	RETENTION URINARY	1	1.4	1
	URINATION IMPAIRED	1	1.4	1

NOTE: Table includes Subject #151034 who had an AE on the 11 Jul 2001 and relation to medication was noted as unknown.

Program: ae3.sas

TABLE T27
Subjects with Serious Treatment Emergent Adverse Events by Body System and COSTART Preferred Term
Safety Population
Date Produced: August 25, 2003

Body System	COSTART Term	Reboxetine (N=69)		
		# of Pts	%	# Reported
Subjects with at least one AE		4	5.8	4
CARDIOVASCULAR	Any Event in Body System	1	1.4	1
	ATRIAL FIBRILLATION	1	1.4	1
NERVOUS	Any Event in Body System	2	2.9	2
	DEPRESSIVE SYMPTOMS	1	1.4	1
	SUICIDAL TENDENCY	1	1.4	1
UROGENITAL	Any Event in Body System	1	1.4	1
	MENORRHAGIA	1	1.4	1

Program: ae2.sas

DataFax #153 **Plate #015** **Seq. #032**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*

Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min*

Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐

Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

DataFax #153 **Plate #018** **Seq. #072**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

Date of last dose of study medication: ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Did patient complete 24/72 weeks of treatment? ☐ *Yes* ☐ *No*

*If **No**, choose **one** primary reason for withdrawal:*

☐ 1 *Adverse event* → ***Fill in / update Adverse Event page***

☐ 2 *Protocol violation* → ***Explain in Comments section below***

☐ 3 *Consent withdrawn* → ***Explain in Comments section if necessary***

☐ 4 *Lost to follow-up*

☐ 5 *Protocol specific withdrawal criteria* → ***Explain in Comments section below***

☐ 6 *Lack of efficacy*

☐ 7 *Progression of disease*

☐ 8 *Improvement*

☐ 9 *Other, specify:* _____

COMMENTS

Investigator's Signature: _____

Pharmacia & Upjohn

Protocol 950ECNS0005-071
Principal Monitor: Saeeduddin Ahmed, M.D.

CONTINUATION ASSESSMENT
CASE REPORT FORM

DataFax #153 **Plate #028** **Seq. #024**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

1. I interviewed the subject today, reviewed the subject's history, current mental and physical symptoms and am of the opinion that continuation of Reboxetine treatment is indicated at this time:

   ☐ *Yes* *(go to item 2)*

   ☐ *No* *(perform the ORIGINAL End of Week 24 Final Visit activities and Study Termination Report)*

2. I discussed the possible benefits, risks and alternatives of continuing Reboxetine treatment with the subject, and the subject concurs with my decision:

   ☐ *Yes* *(go to item 3)*

   ☐ *No* *(perform the ORIGINAL End of Week 24 Final Visit activities and Study Termination Report)*

3. If the responses to items 1 and 2 are "Yes", has the amendment #2 informed consent been presented to and signed by the subject?

   ☐ *Yes* *(perform the NEW End of Week 24 Visit activities listed on NEW End of Week 24 tab)*

   ☐ *No* *(perform the ORIGINAL End of Week 24 Final Visit activities and Study Termination Report)*

Signature of person who performed this evaluation *(must be licensed physician who is noted on 1572)*:

Signature: _____ **Date:** ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Signature of primary investigator if assessment was performed by designee: ☐ ***N/A***
(NOTE: If same as above, please check "N/A")

Signature: _____ **Date:** ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

SAMPLE
PATIENT CONSENT FORM

Protocol No. 950ECNS0005-071 Name of Investigator _____

IND Number 53,206

Name of Study: Open-label Reboxetine Rescue and Continuation Therapy

IRB Approval Date _____

Version #_____

You are being asked if you wish to take part in a research study of an experimental drug. Your decision to take part in this study is voluntary. Deciding not to participate will not cause you to lose any benefits associated with your health care.

If you decide to participate, your involvement with the study will last for **up to** 6 months (24 weeks or less of which involve taking medication), although in practice it may be shorter. After you meet study qualifications, you will be taking study drug each day you are in the study.

Please read this consent form carefully and ask as many questions as you like before deciding whether you want to participate. It is anticipated that about three to five subjects will be involved with this study at this office.

If you decide to participate, you may quit the study at any time without losing any benefits that you would otherwise have. Quitting the study early will not affect your present or future medical care.

PURPOSE OF STUDY

The purpose of this research study is to make the drug reboxetine available to subjects who have previously participated in clinical trials with this agent, and for whom it is determined by their physician or psychiatrist that continuing on reboxetine would be beneficial. A major objective of this study is to monitor the safety and efficacy of this drug.

Reboxetine is an experimental drug, that is, it has not been approved for marketing in the United States. Reboxetine has been extensively tested throughout the world for depression and has been marketed in England since July, 1997, under the trademark EDRONAX. It has since been approved in ten other European countries and an application to market this drug has been filed with the U.S. Food and Drug Administration. The European approvals have led to over 35,000 prescriptions being filled.

STUDY PROCEDURES

This is what will happen if you agree to participate in the study.

Before you start the study, the study doctor will talk with you for approximately an hour about your symptoms, record your medical and psychiatric history, and give you a physical examination, including determination of your weight and vital signs. At the same visit, you will provide a urine sample, have blood drawn, and have an electrocardiogram (a tracing of the electrical signals from your heart using sensors placed on your chest, arms, and/or legs). As part of this study, the electrocardiogram will be repeated **up to** three times during the study, and blood and urine samples will be collected **up to** four additional times during the study. The amount of blood drawn at each of these time periods will be about 20 milliliters (1½ tablespoons). At the beginning of the study, your urine will be tested to see if you have taken any drugs other than those provided in the study. Your vital signs (including blood pressure, pulse and respirations) and weight will be monitored at each visit.

To participate in this study, subjects must meet eligibility criteria, primarily to ensure that it is safe for them to participate in this study.

Once you qualify as above, you will begin taking reboxetine twice a day, one tablet in the morning and 1 to 1½ tablets in the evening. Throughout the study you will be asked to keep a diary to record your doses of study drug. You will need to bring this diary and your medication bottle(s) with you at each clinic visit.

You will be seen in the clinic before the start of this study, during weeks 1, 2, 4 and then about every 4 weeks for the last 20 weeks of the study. If your participation in this study is for less than 6 months, then your visit schedule may differ from this. If you end the study early, we ask that you make every effort to come back for a final visit. This is important because your doctor will perform final assessments and discuss treatment options with you.

At each of these clinic visits, you will complete forms that ask questions about your symptoms, about any problems you may be having, and about your lifestyle. All of these forms will take a total of approximately 50 minutes to complete.

You cannot participate in this study for more than six months. In addition, your physician or psychiatrist may remove you from the study, if he or she thinks this is in your best interest. If you become or plan to be pregnant (or suspect that you are pregant), you may not participate in this study. You may also be withdrawn from the protocol if you do not agree to follow its procedures, since continuing under these circumstances would put you at risk.

Other reasons you may be withdrawn from the protocol include: Your physician or psychiatrist no longer participates in it; the study is discontinued by Pharmacia and Upjohn; or three months have elapsed after U.S. Food and Drug Administration's

approval of reboxetine. If you are withdrawn from this study, other treatment options will be discussed with you, although these may not be free of charge.

RISKS OR DISCOMFORTS

Blood samples will be drawn from a vein in your arm. The risks of having blood drawn may include fainting or pain. There could be bruising or infection at the site where the blood was drawn.

The following side effects have been commonly reported with reboxetine: dry mouth, constipation, headache, nausea, increased sweating, sleeplessness, sleepiness, light-headedness, rapid heartbeat, dizzy sensation, burning or prickling sensations, sexual problems, and urinary hesitancy. It is possible that you may experience one or more of these effects. In studies conducted to date, these side effects have gone away, in general, when the drug was stopped. If you experience sleepiness, dizziness, or light-headedness please refrain from (or use your best judgment while) driving or engaging in potentially hazardous activity. Other side effects may also occur, but most of these are less common or rare.

Use of illicit drugs and consumption of alcohol during the study may increase the risk of adverse events and may cause harmful interactions with the study medication. This effect could make driving or operating machinery dangerous.

All medications taken (including over the counter) should be reported to your physician, so that appropriate advice about their safety can be given.

RESTRICTIONS

If you are a woman, you should not become pregnant while participating in this study, because the drug might affect your unborn child. If you are nursing a child you should not participate in this study. Women patients will have a pregnancy test before they start the study, and periodically during the study. If there is any chance you could become pregnant, you must agree to use a reliable birth control method during the study and for at least a month after stopping the study drug. Examples of acceptable birth control methods include birth control pills, IUD, diaphragm, long-acting progestin contraceptives, or use of condoms and spermicide. If this applies to you, you and your doctor should discuss this before your participate in this study.

If you plan to become pregnant in the next 9 months, do not participate in this study.

If you become or are found to be pregnant while you are taking study medication or within 30 days after stopping study medication, you must inform the study doctor. The study doctor must then report your pregnancy and its outcome to Pharmacia & Upjohn.

You must not use any other sedative or tranquilizer (like Halcion®, Xanax®, Valium, or Librium) while you are participating in this study. You must not use any type of street

drug. Before the study begins, your urine will be tested to make sure you have taken no other drugs.

UNFORESEEABLE RISKS

In addition to the risks described above, there may be other discomforts or risks to you from this study drug that we do not yet know about.

BENEFITS

Your benefits for participating in this study include a free psychiatric examination and up to six months of free treatment that might relieve your symptoms. Also you will have free laboratory tests and a medical examination including an electrocardiogram. You may give the results of these tests to your regular doctor.

An indirect benefit is the opportunity to possibly help yourself and other patients with depression by contributing to the knowledge of this new drug.

ALTERNATE TREATMENT

If you choose not to participate in the study, alternate treatment for your medical condition is available. That treatment could consist of psychotherapy or drugs or both and could be provided within a psychiatric clinic or by a private psychiatrist or other medical doctor.

CONFIDENTIALITY

If you volunteer to participate, your study information will be recorded on case report forms and sent to the study sponsor, which is Pharmacia & Upjohn. Pharmacia & Upjohn representatives, members of the local review committee which has approved this study, and governmental regulatory agencies may need to look at your medical records to verify the study records. Your signature on this form indicates you have authorized this access to your records in the event it is warranted.

Records which identify you will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Your name will not appear in any research report or publication.

COMPENSATION FOR INJURY

Pharmacia & Upjohn will pay for required medical treatment for any study-related physical injury. An injury is considered study related if it is caused by study activities that are different from the treatment you would have received if you were not in the study. Pharmacia & Upjohn assumes no obligation to pay for the medical treatment of other injuries or illnesses, nor to pay any other type of compensation.

NEW INFORMATION ON STUDY DRUG

If any significant new information about the study drug becomes available during your participation in the study, and that information might affect your willingness to continue the study, the doctor in charge of the study will tell you about it.

QUITTING THE STUDY EARLY

You may decide to quit the study at any time and the study physician may remove you from the study at any time for medical reasons or if you fail to follow instructions during the study. There is also a possibility the study could be stopped by Pharmacia & Upjohn before your participation is complete.

If you leave the study early for any reason:

- you will not lose any benefits that you would otherwise have;
- it will not affect your present or future medical care;
- you will be asked to undergo a final examination, lab tests, ECG and relevant assessments concerning your symptoms; and
- you must return any unused study drug and empty bottles to the study doctor.

VOLUNTEER'S STATEMENT

I voluntarily consent to participate in this study.

I have read and understand this statement of informed consent and the risks described.

I understand that I will receive a copy of this signed and dated consent form.

I understand that I may withdraw my consent at any time.

_____	_____	_____
Signature of Study Volunteer	Date	Time
_____	_____	_____
Signature of Witness	Date	Time

IF YOU HAVE QUESTIONS about this study, call one of the following people:

_____ at ( ) _____
[Investigator]

_____ at ( ) _____
[Subinvestigator]

IF YOU HAVE QUESTIONS about your rights as a research volunteer, call:

_____ at ( ) _____
[Patient Advocate/IRB Member]

IF YOU THINK YOU HAVE EXPERIENCED a study-related injury, call:

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Protocol: 950ECNS0005-071

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Product: REBOXETINE

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Product: REBOXETINE

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Product: REBOXETINE

Protocol: 950ECNS0005-071

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Product: REBOXETINE

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Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071

DATAFAX VISIT MAP

Schedule of CRF Pages to be Completed at Each Patient Assessment

Plate No.	Form Title	Study Period	Screen / Day 1	End of Week							Final Visit	End of Week					Final Visit	End of Week		Final Visit
			1	2	4	8	12	16	20	24	32	40	48	56	64	72	80	88	96
		Seq. #	0	1	2	4	8	12	16	20	24	32	40	48	56	64	72	80	88	96
1	Subject Identification Page		SUBJID																	
2	Eligibility Checklist		1																	
3	Medical History		2																	
4	Physical Examination		3								60*						95**			114
5	Demographics / Pregnancy Test / ECG		4																	
6	Social / Occupational Status		5																	
7	Psychiatric History		6																	
8-9	History of Other Psychoactive Drugs - *2 pages*		7-8																	
10-13	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *4 pages*		9-12	16-19	22-25	29-32	35-38	42-45	48-51	55-58	63-66	70-73	75-78	81-84	86-89	91-94	98-101	105-108	110-113	117-120
14	Vital Signs / AE & Concomitant Medication / Study Medication Record (Screen/Day 1)		13																	
15	Vital Signs / AE & Concomitant Medication / Study Medication Record			15	21	27	34	40	47	53	61	69	74	79	85	90	96	104	109	115
16	Clinical Global Impressions (CGI)		14	20	26	33	39	46	52	59	67						102**			121
17	Pregnancy Test / Electrocardiogram (ECG)					28		41		54 *Preg. Test Only*	62*			80			97**			116
18	Study Termination Report										68*						103**			122
28	Continuation Assessment Case Report Form										CONT						CONT			
19	Adverse Event Form																			
20-21	Concomitant Medication Form																			
22-24	Serious Adverse Event Form - *3 pages*																			
25	Serious Adverse Event Form - *Page 3 of 3 (Extra Form)*																			
26	Adverse Event Follow-up Report																			
27	Exposure in Utero																			

AS NEEDED

* *Please SKIP End of Week 24 "Physical Examination", "Pregnancy Test" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 24 (Please complete header information, leave rest of form blank and fax to DataFax)*

** *Please SKIP End of Week 72 "Physical Examination", "Pregnancy Test/ECG" , "CGI" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 72 (Please complete header information, leave rest of form blank and fax to DataFax)*

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Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071

DATAFAX SCHEDULE OF ACTIVITIES

(CHECK BOXES AS FORMS/ACTIVITIES ARE COMPLETED)

Study Period / Study Activities	Screen/ Day 1	End of Week							Final Visit	End of Week					Final Visit	End of Week		Final Visit
		1	2	4	8	12	16	20	24	32	40	48	56	64	72	80	88	96
Informed Consent	☐																	
Subject Identification Page	☐																	
Eligibility Checklist	☐																	
Medical History	☐																	
Physical Examination	☐								☐*						☐**			☐
Demographic	☐																	
Pregnancy Test	☐			☐		☐		☐	☐*			☐			☐**			☐
Electrocardiogram (ECG)	☐			☐		☐			☐			☐			☐**			☐
Lab. Assessment Test (Serum Chemistry, Hematology, Urinalysis)	☐			☐		☐			☐			☐			☐**			☐
Urine Drug Screen	☐																	
Social / Occupational Status	☐																	
Psychiatric History	☐																	
History of Other Psychoactive Drugs	☐																	
Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vital Signs	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Study Medication Record (Dispensing (D) / Returning (R))	☐$_{D}^{+}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$^{D}/_{R}$	☐$_{R}$
Clinical Global Impressions (CGI)	☐	☐	☐	☐	☐	☐	☐	☐	☐						☐**			☐
Continuation Assessment Case Report Form									☐						☐			
Study Termination Report									☐*						☐**			☐
Adverse Event Form	**AS NEEDED**																	
Concomitant Medication Form																		
Serious Adverse Event Form - *3 pages*																		
Serious Adverse Event Form - *Page 3 of 3 (Extra Form)*																		
Adverse Event Follow-up Report																		
Exposure in Utero																		

* *Please SKIP End of Week 24 "Physical Examination", "Pregnancy Test" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 24 (Please complete header information, leave rest of form blank and fax to DataFax)*

\+ *Verify eligibility criteria before dispensing study drug.*

** *Please SKIP End of Week 72 "Physical Examination", "Pregnancy Test/ECG", "CGI" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 72 (Please complete header information, leave rest of form blank and fax to DataFax)*

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Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071

(New Tab)

NOTE: Complete the NEW "Continuation Assessment case report form" (CONT CRF) prior to completing any other assessments.

Original END OF WEEK 72 Activities

(Complete if subject is NOT continuing on further Reboxetine Treatment)

- Complete the following CRFs:

Page #	Form
95	Physical Examination
96	Vital Signs / AE & Concomitant Medication / Study Medication Record
97	Pregnancy Test / Electrocardiogram (ECG)
	Note: Mail duplicate original ECG to Premier.
98-101	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)
102	Clinical Global Impressions (CGI)
103	Study Termination Report

- Draw End of Week 72/Final Visit safety laboratory assessment tests *(Serum Chemistry, Hematology, Urinalysis, Pregnancy Test)*

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 96)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Collect and check subject's Dosing Diary and study medication compliance. Record on CRF page 96.

New END OF WEEK 72 Activities

(Complete if subject IS continuing on further Reboxetine Treatment)

- Complete the following CRFs:

Page #	Form
96	Vital Signs / AE & Concomitant Medication / Study Medication Record
98-101	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 96)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 96.

- Dispense Week 73-80's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.

- Schedule subject for End of Week 80 visit.

Pharmacia & Upjohn

Protocol 950ECNS0005-071
Principal Monitor: Saeeduddin Ahmed, M.D.

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #072**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

Original END OF WEEK 72 / FINAL VISIT

All **End of Week 72** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	CONT	Continuation Assessment Case Report Form
☐	95	Physical Examination
☐	96	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	97	Pregnancy Test / Electrocardiogram (ECG)
☐	98	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	99	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	100	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	101	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*
☐	102	Clinical Global Impressions (CGI)
☐	103	Study Termination Report

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form

Pharmacia & Upjohn **Protocol 950ECNS0005-071**
Principal Monitor: Saeeduddin Ahmed, M.D.

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #072**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

New END OF WEEK 72

All **End of Week 72** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	CONT	Continuation Assessment Case Report Form
☐	96	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	98	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	99	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	100	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	101	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form

Pharmacia & Upjohn

Protocol 950ECNS0005-071
Principal Monitor: Saeeduddin Ahmed, M.D.

CONTINUATION ASSESSMENT
CASE REPORT FORM

DataFax #153 **Plate #028** **Seq. #072**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

1. I interviewed the subject today, reviewed the subject's history, current mental and physical symptoms and am of the opinion that continuation of Reboxetine treatment is indicated at this time:

   ☐ *Yes* *(go to item 2)*

   ☐ *No* *(perform the ORIGINAL End of Week 72 Final Visit activities and Study Termination Report)*

2. I discussed the possible benefits, risks and alternatives of continuing Reboxetine treatment with the subject, and the subject concurs with my decision:

   ☐ *Yes* *(go to item 3)*

   ☐ *No* *(perform the ORIGINAL End of Week 72 Final Visit activities and Study Termination Report)*

3. If the responses to items 1 and 2 are "Yes", has the amendment #A informed consent been presented to and signed by the subject?

   ☐ *Yes* *(perform the NEW End of Week 72 Visit activities listed on NEW End of Week 72 tab)*

   ☐ *No* *(perform the ORIGINAL End of Week 72 Final Visit activities and Study Termination Report)*

Signature of person who performed this evaluation *(must be licensed physician who is noted on 1572)*:

Signature: _____ **Date:** ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Signature of primary investigator if assessment was performed by designee: ☐ ***N/A***
(NOTE: If same as above, please check "N/A")

Signature: _____ **Date:** ☐☐☐☐☐☐☐☐ *y y y y m m d d*

PROTOCOL 950ECNS0005-071

END OF WEEK 80

- Complete the following CRFs:

Page #	Form
104	Vital Signs / AE & Concomitant Medication / Study Medication Record
105-108	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 104)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 104.
- Dispense Week 81-88's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.
- Schedule subject for End of Week 88 visit.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**
Principal Monitor: Saeeduddin Ahmed, M.D.

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #080**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

END OF WEEK 80

All **End of Week 80** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	104	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	105	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	106	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	107	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	108	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form
☐	122	Study Termination Report

DataFax #153 **Plate #015** **Seq. #080**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*

Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min*

Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐

Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

Pharmacia & Upjohn

Protocol 950ECNS0005-071
Principal Monitor: Saeeduddin Ahmed, M.D.

HAMILTON PSYCHIATRIC RATING SCALE FOR DEPRESSION (25-ITEM HAMD) - ***Page 1 of 4***

End of Week 80

DataFax #153 **Plate #010** **Seq. #080**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*)

Subject's Initials ☐☐☐ (*F M L*)

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

1. Depressed mood

- ☐ 0 *Absent*
- ☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*
- ☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*
- ☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*
- ☐ 4 *Extreme symptoms - complete withdrawal*
- ☐ *Can't rate*

2. Distinct quality of mood

- ☐ 0 *No distinct qualities*
- ☐ 1 *Mild or moderate (slightly different)*
- ☐ 2 *Severe (definitely different)*
- ☐ *Can't rate*

3. Lack of reactivity

- ☐ 0 *Reactive mood (mood varies according to situation)*
- ☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*
- ☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*
- ☐ *Can't rate*

4. Diurnal variation

- ☐ 0 *No variation in mood*
- ☐ 1 *Mild variation between a.m. and p.m.*
- ☐ 2 *Definite variation between a.m. and p.m.*
- ☐ *Can't rate*

5. Worthlessness

- ☐ 0 *Not present*
- ☐ 1 *Mild feelings of low self-esteem evident only from questioning*
- ☐ 2 *Feelings of worthlessness*
- ☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*
- ☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*
- ☐ *Can't rate*

6. Guilt

- ☐ 0 *Absent*
- ☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*
- ☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*
- ☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*
- ☐ 4 *Delusional guilt, with hallucinations*
- ☐ *Can't rate*

DataFax #153 **Plate #011** **Seq. #080**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*
Subject's Initials ☐☐☐ *F M L*
Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*
Principal Investigator _____ ☐☐☐☐☐
Country US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ 0 *Not present*
- ☐ 1 *Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ 2 *Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ 3 *Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ 4 *Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ 0 *Not present*
- ☐ 1 *Intermittently doubts that things will improve but can be reassured*
- ☐ 2 *Consistently feels hopeless but accepts reassurances*
- ☐ 3 *Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ 4 *Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ 0 *Absent*
- ☐ 1 *Feels life is not worth living*
- ☐ 2 *Wishes he were dead or any thoughts of possible death to himself*
- ☐ 3 *Suicidal ideas, gestures, or plans*
- ☐ 4 *Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ 0 *Absent*
- ☐ 1 *Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ 2 *Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ 0 *Absent*
- ☐ 1 *Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ 2 *Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ 0 *Absent*
- ☐ 1 *Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ 2 *Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #080**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

---

16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

---

20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #080**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD - Continued

21. Somatic anxiety - *(**Note:** Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

PROTOCOL 950ECNS0005-071

END OF WEEK 88

- Complete the following CRFs:

Page #	Form
109	Vital Signs / AE & Concomitant Medication / Study Medication Record
110-113	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 109)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 109.
- Dispense Week 89-96's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.
- Schedule subject for End of Week 96 visit.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**
Principal Monitor: Saeeduddin Ahmed, M.D.

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #088**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

END OF WEEK 88

All **End of Week 88** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	109	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	110	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	111	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	112	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	113	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form
☐	122	Study Termination Report

DataFax #153 **Plate #015** **Seq. #088**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*

Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min*

Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐

Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

HAMILTON PSYCHIATRIC RATING SCALE FOR DEPRESSION (25-ITEM HAMD) - ***Page 1 of 4***

DataFax #153 **Plate #010** **Seq. #088**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

1. Depressed mood

☐ 0 *Absent*

☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*

☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*

☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*

☐ 4 *Extreme symptoms - complete withdrawal*

☐ *Can't rate*

2. Distinct quality of mood

☐ 0 *No distinct qualities*

☐ 1 *Mild or moderate (slightly different)*

☐ 2 *Severe (definitely different)*

☐ *Can't rate*

3. Lack of reactivity

☐ 0 *Reactive mood (mood varies according to situation)*

☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*

☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*

☐ *Can't rate*

4. Diurnal variation

☐ 0 *No variation in mood*

☐ 1 *Mild variation between a.m. and p.m.*

☐ 2 *Definite variation between a.m. and p.m.*

☐ *Can't rate*

5. Worthlessness

☐ 0 *Not present*

☐ 1 *Mild feelings of low self-esteem evident only from questioning*

☐ 2 *Feelings of worthlessness*

☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*

☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*

☐ *Can't rate*

6. Guilt

☐ 0 *Absent*

☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*

☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*

☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*

☐ 4 *Delusional guilt, with hallucinations*

☐ *Can't rate*

DataFax #153 **Plate #011** **Seq. #088**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ *0 Not present*
- ☐ *1 Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ *2 Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ *3 Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ *4 Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ *0 Not present*
- ☐ *1 Intermittently doubts that things will improve but can be reassured*
- ☐ *2 Consistently feels hopeless but accepts reassurances*
- ☐ *3 Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ *4 Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ *0 Absent*
- ☐ *1 Feels life is not worth living*
- ☐ *2 Wishes he were dead or any thoughts of possible death to himself*
- ☐ *3 Suicidal ideas, gestures, or plans*
- ☐ *4 Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ *2 Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ *2 Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ *2 Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #088**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

---

16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

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20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #088**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

21. Somatic anxiety - *(**Note:** Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

PROTOCOL 950ECNS0005-071

END OF WEEK 96 / FINAL VISIT

- Complete the following CRFs:

Page #	Form
114	Physical Examination
115	Vital Signs / AE & Concomitant Medication / Study Medication Record
116	Pregnancy Test / Electrocardiogram (ECG)
	Note: Mail duplicate original ECG to Premier.
117-120	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)
121	Clinical Global Impressions (CGI)
122	Study Termination Report

- Draw End of Week 96/Final Visit safety laboratory assessment tests *(Serum Chemistry, Hematology, Urinalysis, Pregnancy test)*

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 114)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Collect and check subject's Dosing Diary and study medication compliance. Record on CRF page 114.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**
Principal Monitor: Saeeduddin Ahmed, M.D.

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

END OF WEEK 96 / FINAL VISIT

All **End of Week 96** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	114	Physical Examination
☐	115	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	116	Pregnancy Test / Electrocardiogram (ECG)
☐	117	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	118	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	119	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	120	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*
☐	121	Clinical Global Impressions (CGI)
☐	122	Study Termination Report

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form

DataFax #153 **Plate #004** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

INSTRUCTIONS: Check appropriate box to indicate current physical findings. Describe any abnormalities, indicating left or right where applicable. If evaluation of the category is not performed, write "Not Done".

PHYSICAL FINDINGS	HEAD AND NECK ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	EENT / MOUTH ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	CHEST / LUNGS ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	HEART ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	BREASTS *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	BACK / SPINE *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	ABDOMEN ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	EXTREMITIES ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	SKIN ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	LYMPH NODES *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	NERVOUS SYSTEM ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	MENTATION ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	ENDOCRINE ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	OTHER ABNORMAL PHYSICAL FINDINGS? ☐ *No* ☐ *Yes*	IF YES, BRIEFLY DESCRIBE

COMMENTS:

Initials or Signature: _____

DataFax #153 **Plate #015** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*
Subject's Initials ☐☐☐ *F M L*
Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐
Country US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*
Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)
Sitting Pulse: ☐☐☐ */min*
Temperature: ☐☐☐.☐ °*F*
Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐
Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

DataFax #153 **Plate #017** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

PREGNANCY TEST *(Serum)*

NOT DONE, Reason: ☐ *Male* ☐ *Surgically sterile* ☐ *Postmenopausal (>2 years)*

DONE, Result: ☐ *Negative* ☐ *Positive* ☐ *Inconclusive*

Note: If test is positive or inconclusive, subject should be removed from the study.

ELECTROCARDIOGRAM *(ECG)*

Date ECG Performed ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*) Time ☐☐ : ☐☐ *hours* (*00:01 - 24:00*)

Date of last dose of study medication ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*) Time ☐☐ : ☐☐ *hours* (*00:01 - 24:00*)

Are there any clinically significant changes noted from Screen ECG? ☐ *No* ☐ *Yes*

Note: Please mail a duplicate original Electrocardiogram (ECG) to PREMIER.

Initials or Signature: _____

Pharmacia & Upjohn **Protocol 950ECNS0005-071**
Principal Monitor: Saeeduddin Ahmed, M.D.

HAMILTON PSYCHIATRIC RATING SCALE FOR DEPRESSION (25-ITEM HAMD) - ***Page 1 of 4***

End of Week 96/ Final Visit

DataFax #153 **Plate #010** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

25-ITEM HAMD - *Page 1 of 4*

1. Depressed mood

- ☐ 0 *Absent*
- ☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*
- ☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*
- ☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*
- ☐ 4 *Extreme symptoms - complete withdrawal*
- ☐ *Can't rate*

2. Distinct quality of mood

- ☐ 0 *No distinct qualities*
- ☐ 1 *Mild or moderate (slightly different)*
- ☐ 2 *Severe (definitely different)*
- ☐ *Can't rate*

3. Lack of reactivity

- ☐ 0 *Reactive mood (mood varies according to situation)*
- ☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*
- ☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*
- ☐ *Can't rate*

4. Diurnal variation

- ☐ 0 *No variation in mood*
- ☐ 1 *Mild variation between a.m. and p.m.*
- ☐ 2 *Definite variation between a.m. and p.m.*
- ☐ *Can't rate*

5. Worthlessness

- ☐ 0 *Not present*
- ☐ 1 *Mild feelings of low self-esteem evident only from questioning*
- ☐ 2 *Feelings of worthlessness*
- ☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*
- ☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*
- ☐ *Can't rate*

6. Guilt

- ☐ 0 *Absent*
- ☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*
- ☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*
- ☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*
- ☐ 4 *Delusional guilt, with hallucinations*
- ☐ *Can't rate*

Protocol 950ECNS0005-071 FINAL 05JUL99 (amended 30MAY01)

DataFax #153 **Plate #011** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ *0 Not present*
- ☐ *1 Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ *2 Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ *3 Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ *4 Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ *0 Not present*
- ☐ *1 Intermittently doubts that things will improve but can be reassured*
- ☐ *2 Consistently feels hopeless but accepts reassurances*
- ☐ *3 Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ *4 Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ *0 Absent*
- ☐ *1 Feels life is not worth living*
- ☐ *2 Wishes he were dead or any thoughts of possible death to himself*
- ☐ *3 Suicidal ideas, gestures, or plans*
- ☐ *4 Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ *2 Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ *2 Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ *2 Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

---

16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

---

20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

21. Somatic anxiety - *(**Note:** Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

DataFax #153 **Plate #016** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

Pharmacia
& Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071

STUDY TERMINATION REPORT
(End of Week 96)

Pharmacia
& Upjohn

STUDY TERMINATION REPORT - Instructions

DEFINITION OF STUDY TERMINATION REPORT

Study Termination Report refers to the end of study medication period. It is not meant for temporary withdrawal or for the end of follow-up or observation period.

- Always refer back to the ***Subject's Dosing Diary*** and double check the day of last study medication.
  This date must be in accordance with other visit dates (i.e., not be before the first visit or after the last visit).

- If the subject did NOT complete the treatment period as defined in the study protocol, choose one primary reason for withdrawal. Try to find out what lies behind the withdrawal, e.g., why a consent was withdrawn or a protocol violation happened. Do not enter that cause on this form, but keep it ready for review. Do not be too quick to enter "Lost to follow-up", subjects sometimes return.

- Always choose the most severe reason. Example: If the subject withdrew the informed consent and had side effects that caused problems, check "Adverse event".

- Termination: The *Study Termination Report* page must be completed and submitted for all subjects who were assigned study medication.

DataFax #153 **Plate #018** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** **US**

Date of last dose of study medication: ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Did patient complete 96 weeks of treatment? ☐ *Yes* ☐ *No*

*If **No**, choose **one** primary reason for withdrawal:*

☐ 1 *Adverse event* → ***Fill in / update Adverse Event page***

☐ 2 *Protocol violation* → ***Explain in Comments section below***

☐ 3 *Consent withdrawn* → ***Explain in Comments section if necessary***

☐ 4 *Lost to follow-up*

☐ 5 *Protocol specific withdrawal criteria* → ***Explain in Comments section below***

☐ 6 *Lack of efficacy*

☐ 7 *Progression of disease*

☐ 8 *Improvement*

☐ 9 *Other, specify:* _____

COMMENTS

Investigator's Signature: _____

Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071 (Amendment B)

DATAFAX VISIT MAP

Schedule of CRF Pages to be Completed at Each Patient Assessment

Plate No.	Form Title	Study Period	End of Week					Final Visit	End of Week		Final Visit	End of Week		Final Visit
			32	40	48	56	64	72	80	88	96	104	112	120
		Seq. #	32	40	48	56	64	72	80	88	96	104	112	120
3	Medical History													135
4	Physical Examination							95 *			114 **			136
10-13	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *4 pages*		70-73	75-78	81-84	86-89	91-94	98-101	105-108	110-113	117-120	125-128	131-134	140-143
15	Vital Signs / AE & Concomitant Medication / Study Medication Record		69	74	79	85	90	96	104	109	115	123	129	137
16	Clinical Global Impressions (CGI)		CGI.W32	CGI.W40	CGI.W48	CGI.W56	CGI.W64	102	CGI.W80	CGI.W88	121	124	130	139
17	Pregnancy Test / Electrocardiogram (ECG)				80			97			116			138
18	Study Termination Report							103 *			122 **			144
28	Continuation Assessment Case Report Form							CONT			CONT			
19	Adverse Event Form		**AS NEEDED**											
20-21	Concomitant Medication Form													
22-24	Serious Adverse Event Form - *3 pages*													
25	Serious Adverse Event Form - *Page 3 of 3 (Extra Form)*													
26	Adverse Event Follow-up Report													
27	Exposure in Utero													

* *Please SKIP End of Week 72 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 72 (Please complete header information, leave rest of form blank and fax to DataFax)*

** *Please SKIP End of Week 96 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 96 (Please complete header information, leave rest of form blank and fax to DataFax)*

Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071 (Amendment B)

DATAFAX SCHEDULE OF ACTIVITIES

(CHECK BOXES AS FORMS/ACTIVITIES ARE COMPLETED)

Study Period / Study Activities	End of Week					Final Visit	End of Week		Final Visit	End of Week		Final Visit
	32	40	48	56	64	72	80	88	96	104	112	120
Informed Consent						☐			☐			☐
Medical History												☐
Physical Examination						☐*			☐**			☐
Pregnancy Test			☐			☐			☐			☐
Electrocardiogram (ECG)			☐			☐			☐			☐
Lab. Assessment Test (Serum Chemistry, Hematology, Urinalysis)			☐			☐			☐			☐
Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vital Signs	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Study Medication Record (Dispensing (D) / Returning (R))	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ R
Clinical Global Impressions (CGI) +	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Continuation Assessment Case Report Form						☐			☐			☐
Study Termination Report						☐*			☐**			☐
Adverse Event Form	AS NEEDED											
Concomitant Medication Form												
Serious Adverse Event Form - *3 pages*												
Serious Adverse Event Form - *Page 3 of 3 (Extra Form)*												
Adverse Event Follow-up Report												
Exposure in Utero												

* *Please SKIP End of Week 72 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 72 (Please complete header information, leave rest of form blank and fax to DataFax)*

** *Please SKIP End of Week 96 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 96 (Please complete header information, leave rest of form blank and fax to DataFax)*

\+ *CGI assessments will now be completed at all visits. If the patient has already completed visits that now require the CGI, the corresponding CGI case report form should be marked NOT DONE and faxed to DataFax.*

Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071

Clinical Global Impressions (CGI)
(End of Week 32 to 88)

NOTE: Please insert the CGI case report form in the appropriate visits.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CLINICAL GLOBAL IMPRESSIONS (CGI)

End of Week 32

DataFax #153 **Plate #016** **Seq. #032**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CLINICAL GLOBAL IMPRESSIONS (CGI)

End of Week 40

DataFax #153 **Plate #016** **Seq. #040**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

CGI.W40

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CLINICAL GLOBAL IMPRESSIONS (CGI)

End of Week 48

DataFax #153 **Plate #016** **Seq. #048**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CLINICAL GLOBAL IMPRESSIONS (CGI)

End of Week 56

DataFax #153 **Plate #016** **Seq. #056**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

CGI.W56

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CLINICAL GLOBAL IMPRESSIONS (CGI)

End of Week 64

DataFax #153 **Plate #016** **Seq. #064**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

CGI.W64

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CLINICAL GLOBAL IMPRESSIONS (CGI)

End of Week 80

DataFax #153 **Plate #016** **Seq. #080**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

CGI.W80

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CLINICAL GLOBAL IMPRESSIONS (CGI)

End of Week 88

DataFax #153 **Plate #016** **Seq. #088**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071 (Amendment B)

NOTE: Complete the NEW "Continuation Assessment case report form" (CONT CRF) prior to completing any other assessments.

Original END OF WEEK 96 Activities

(Complete if subject is NOT continuing on further Reboxetine Treatment)

- Complete the following CRFs:

Page #	Form
114	Physical Examination
115	Vital Signs / AE & Concomitant Medication / Study Medication Record
116	Pregnancy Test / Electrocardiogram (ECG)
	Note: Mail duplicate original ECG to Premier.
117-120	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)
121	Clinical Global Impressions (CGI)
122	Study Termination Report

- Draw End of Week 96/Final Visit safety laboratory assessment tests *(Serum Chemistry, Hematology, Urinalysis, Pregnancy Test)*

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 115)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Collect and check subject's Dosing Diary and study medication compliance. Record on CRF page 115.

New END OF WEEK 96 Activities

(Complete if subject IS continuing on further Reboxetine Treatment)

- Complete the following CRFs:

Page #	Form
	Informed Consent - *(Not included in this set of Case Report Forms, also do not fax to DataFax)*
CONT	Continuation Assessment Case Report Form
115	Vital Signs / AE & Concomitant Medication / Study Medication Record
116	Pregnancy Test / Electrocardiogram (ECG)
	Note: Mail duplicate original ECG to Premier.
117-120	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)
121	Clinical Global Impressions (CGI)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 115)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 115.

- Dispense Week 97-104's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.

- Schedule subject for End of Week 104 visit.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

Original END OF WEEK 96 / FINAL VISIT

All **End of Week 96** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	CONT	Continuation Assessment Case Report Form
☐	114	Physical Examination
☐	115	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	116	Pregnancy Test / Electrocardiogram (ECG)
☐	117	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	118	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	119	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	120	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*
☐	121	Clinical Global Impressions (CGI)
☐	122	Study Termination Report

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

New END OF WEEK 96

All **End of Week 96** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
		Informed Consent - *(Not included in this set of Case Report Forms, also do not fax to DataFax)*
☐	CONT	Continuation Assessment Case Report Form
☐	115	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	116	Pregnancy Test / Electrocardiogram (ECG)
☐	117	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	118	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	119	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	120	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*
☐	121	Clinical Global Impressions (CGI)

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CONTINUATION ASSESSMENT CASE REPORT FORM

DataFax #153 **Plate #028** **Seq. #096**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

1. I interviewed the subject today, reviewed the subject's history, current mental and physical symptoms and am of the opinion that continuation of Reboxetine treatment is indicated at this time:

   ☐ *Yes* *(go to item 2)*

   ☐ *No* *(perform the ORIGINAL End of Week 96 Final Visit activities and Study Termination Report)*

2. I discussed the possible benefits, risks and alternatives of continuing Reboxetine treatment with the subject, and the subject concurs with my decision:

   ☐ *Yes* *(go to item 3)*

   ☐ *No* *(perform the ORIGINAL End of Week 96 Final Visit activities and Study Termination Report)*

3. If the responses to items 1 and 2 are "Yes", has the amendment #A informed consent been presented to and signed by the subject?

   ☐ *Yes* *(perform the NEW End of Week 96 Visit activities listed on NEW End of Week 96 tab)*

   ☐ *No* *(perform the ORIGINAL End of Week 96 Final Visit activities and Study Termination Report)*

Signature of person who performed this evaluation *(must be licensed physician who is noted on 1572)*:

Signature: _____ **Date:** ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Signature of primary investigator if assessment was performed by designee: ☐ ***N/A***
(NOTE: If same as above, please check "N/A")

Signature: _____ **Date:** ☐☐☐☐☐☐☐☐ *y y y y m m d d*

PROTOCOL 950ECNS0005-071

END OF WEEK 104

- Complete the following CRFs:

Page #	Form
123	Vital Signs / AE & Concomitant Medication / Study Medication Record
124	Clinical Global Impressions (CGI)
125-128	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 123)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 123.
- Dispense Week 105-112's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.
- Schedule subject for End of Week 112 visit.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #104**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

END OF WEEK 104

All **End of Week 104** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	123	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	124	Clinical Global Impressions (CGI)
☐	125	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	126	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	127	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	128	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form
☐	144	Study Termination Report

DataFax #153 **Plate #015** **Seq. #104**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*

Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min*

Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐

Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

DataFax #153 **Plate #016** **Seq. #104**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

DataFax #153 **Plate #010** **Seq. #104**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*)

Subject's Initials ☐☐☐ (*F M L*)

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

1. Depressed mood

- ☐ 0 *Absent*
- ☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*
- ☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*
- ☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*
- ☐ 4 *Extreme symptoms - complete withdrawal*
- ☐ *Can't rate*

2. Distinct quality of mood

- ☐ 0 *No distinct qualities*
- ☐ 1 *Mild or moderate (slightly different)*
- ☐ 2 *Severe (definitely different)*
- ☐ *Can't rate*

3. Lack of reactivity

- ☐ 0 *Reactive mood (mood varies according to situation)*
- ☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*
- ☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*
- ☐ *Can't rate*

4. Diurnal variation

- ☐ 0 *No variation in mood*
- ☐ 1 *Mild variation between a.m. and p.m.*
- ☐ 2 *Definite variation between a.m. and p.m.*
- ☐ *Can't rate*

5. Worthlessness

- ☐ 0 *Not present*
- ☐ 1 *Mild feelings of low self-esteem evident only from questioning*
- ☐ 2 *Feelings of worthlessness*
- ☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*
- ☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*
- ☐ *Can't rate*

6. Guilt

- ☐ 0 *Absent*
- ☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*
- ☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*
- ☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*
- ☐ 4 *Delusional guilt, with hallucinations*
- ☐ *Can't rate*

DataFax #153 **Plate #011** **Seq. #104**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ *0 Not present*
- ☐ *1 Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ *2 Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ *3 Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ *4 Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ *0 Not present*
- ☐ *1 Intermittently doubts that things will improve but can be reassured*
- ☐ *2 Consistently feels hopeless but accepts reassurances*
- ☐ *3 Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ *4 Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ *0 Absent*
- ☐ *1 Feels life is not worth living*
- ☐ *2 Wishes he were dead or any thoughts of possible death to himself*
- ☐ *3 Suicidal ideas, gestures, or plans*
- ☐ *4 Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ *2 Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ *2 Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ *2 Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #104**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

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16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

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20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #104**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD - Continued

21. Somatic anxiety - *(**Note:** Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

PROTOCOL 950ECNS0005-071

END OF WEEK 112

- Complete the following CRFs:

Page #	Form
129	Vital Signs / AE & Concomitant Medication / Study Medication Record
130	Clinical Global Impressions (CGI)
131-134	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 129)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 129.
- Dispense Week 113-120's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.
- Schedule subject for End of Week 120 visit.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #112**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

END OF WEEK 112

All **End of Week 112** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	129	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	130	Clinical Global Impressions (CGI)
☐	131	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	132	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	133	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	134	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form
☐	144	Study Termination Report

DataFax #153 **Plate #015** **Seq. #112**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs* Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min* Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐ Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

DataFax #153 **Plate #016** **Seq. #112**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

DataFax #153 **Plate #010** **Seq. #112**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

1. Depressed mood

- ☐ 0 *Absent*
- ☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*
- ☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*
- ☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*
- ☐ 4 *Extreme symptoms - complete withdrawal*
- ☐ *Can't rate*

2. Distinct quality of mood

- ☐ 0 *No distinct qualities*
- ☐ 1 *Mild or moderate (slightly different)*
- ☐ 2 *Severe (definitely different)*
- ☐ *Can't rate*

3. Lack of reactivity

- ☐ 0 *Reactive mood (mood varies according to situation)*
- ☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*
- ☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*
- ☐ *Can't rate*

4. Diurnal variation

- ☐ 0 *No variation in mood*
- ☐ 1 *Mild variation between a.m. and p.m.*
- ☐ 2 *Definite variation between a.m. and p.m.*
- ☐ *Can't rate*

5. Worthlessness

- ☐ 0 *Not present*
- ☐ 1 *Mild feelings of low self-esteem evident only from questioning*
- ☐ 2 *Feelings of worthlessness*
- ☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*
- ☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*
- ☐ *Can't rate*

6. Guilt

- ☐ 0 *Absent*
- ☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*
- ☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*
- ☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*
- ☐ 4 *Delusional guilt, with hallucinations*
- ☐ *Can't rate*

DataFax #153 **Plate #011** **Seq. #112**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ *0 Not present*
- ☐ *1 Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ *2 Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ *3 Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ *4 Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ *0 Not present*
- ☐ *1 Intermittently doubts that things will improve but can be reassured*
- ☐ *2 Consistently feels hopeless but accepts reassurances*
- ☐ *3 Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ *4 Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ *0 Absent*
- ☐ *1 Feels life is not worth living*
- ☐ *2 Wishes he were dead or any thoughts of possible death to himself*
- ☐ *3 Suicidal ideas, gestures, or plans*
- ☐ *4 Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ *2 Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ *2 Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ *2 Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #112**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

---

16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

---

20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #112**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD - Continued

21. Somatic anxiety - *(**Note:** Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

PROTOCOL 950ECNS0005-071

END OF WEEK 120 / FINAL VISIT

- Complete the following CRFs:

Page #	Form
135	Medical History
136	Physical Examination
137	Vital Signs / AE & Concomitant Medication / Study Medication Record
138	Pregnancy Test / Electrocardiogram (ECG)
	Note: Mail duplicate original ECG to Premier.
139	Clinical Global Impressions (CGI)
140-143	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)
144	Study Termination Report

- Draw End of Week 120/Final Visit safety laboratory assessment tests *(Serum Chemistry, Hematology, Urinalysis, Pregnancy test)*

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 137)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Collect and check subject's Dosing Diary and study medication compliance. Record on CRF page 137.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM

DataFax #153 **Plate #500** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

END OF WEEK 120 / FINAL VISIT

All **End of Week 120** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	135	Medical History
☐	136	Physical Examination
☐	137	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	138	Pregnancy Test / Electrocardiogram (ECG)
☐	139	Clinical Global Impressions (CGI)
☐	140	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	141	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	142	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	143	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*
☐	144	Study Termination Report

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form

MEDICAL HISTORY

DataFax #153 **Plate #003** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

INSTRUCTIONS: Check appropriate box to indicate medical history of disorders in the areas listed below.

Include any surgeries or hospitalizations under the appropriate category. Describe or comment if "*History*" box is checked.

DO NOT INCLUDE PSYCHIATRIC HISTORY

MEDICAL HISTORY

	DESCRIBE / COMMENT
HEENT / MOUTH ☐ *None* ☐ *History*	DESCRIBE / COMMENT
CARDIOVASCULAR ☐ *None* ☐ *History*	DESCRIBE / COMMENT
PULMONARY ☐ *None* ☐ *History*	DESCRIBE / COMMENT
GASTROINTESTINAL ☐ *None* ☐ *History*	DESCRIBE / COMMENT
RENAL / URINARY TRACT ☐ *None* ☐ *History*	DESCRIBE / COMMENT
MUSCULOSKELETAL ☐ *None* ☐ *History*	DESCRIBE / COMMENT
NEUROLOGIC *(including convulsive disorders)* ☐ *None* ☐ *History*	DESCRIBE / COMMENT
DERMATOLOGIC ☐ *None* ☐ *History*	DESCRIBE / COMMENT
METABOLIC / ENDOCRINE ☐ *None* ☐ *History*	DESCRIBE / COMMENT
HEMATOLOGIC ☐ *None* ☐ *History*	DESCRIBE / COMMENT
ALLERGIC ☐ *None* ☐ *History*	DESCRIBE / COMMENT
OTHER *(Specify)* _____	DESCRIBE / COMMENT

Initials or Signature: _____

PHYSICAL EXAMINATION

DataFax #153 **Plate #004** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

INSTRUCTIONS: Check appropriate box to indicate current physical findings. Describe any abnormalities, indicating left or right where applicable. If evaluation of the category is not performed, write "Not Done".

PHYSICAL FINDINGS	HEAD AND NECK ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	EENT / MOUTH ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	CHEST / LUNGS ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	HEART ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	BREASTS *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	BACK / SPINE *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	ABDOMEN ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	EXTREMITIES ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	SKIN ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	LYMPH NODES *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	NERVOUS SYSTEM ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	MENTATION ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	ENDOCRINE ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	OTHER ABNORMAL PHYSICAL FINDINGS? ☐ *No* ☐ *Yes*	IF YES, BRIEFLY DESCRIBE

COMMENTS:

Initials or Signature: _____

DataFax #153 **Plate #015** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*

Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min*

Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐

Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

PREGNANCY TEST/ELECTROCARDIOGRAM (ECG)

DataFax #153 **Plate #017** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

PREGNANCY TEST *(Serum)*

NOT DONE, Reason: ☐ *Male* ☐ *Surgically sterile* ☐ *Postmenopausal (>2 years)*

DONE, Result: ☐ *Negative* ☐ *Positive* ☐ *Inconclusive*

Note: If test is positive or inconclusive, subject should be removed from the study.

ELECTROCARDIOGRAM *(ECG)*

Date ECG Performed ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Time ☐☐ : ☐☐ *hours* *(00:01 - 24:00)*

Date of last dose of study medication ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Time ☐☐ : ☐☐ *hours* *(00:01 - 24:00)*

Are there any clinically significant changes noted from Screen ECG? ☐ *No* ☐ *Yes*

Note: Please mail a duplicate original Electrocardiogram (ECG) to PREMIER.

Initials or Signature: _____

CLINICAL GLOBAL IMPRESSIONS (CGI)

DataFax #153 **Plate #016** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

HAMILTON PSYCHIATRIC RATING SCALE FOR DEPRESSION (25-ITEM HAMD) - ***Page 1 of 4***

End of Week 120/ Final Visit

DataFax #153 **Plate #010** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

1. Depressed mood

☐ 0 *Absent*

☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*

☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*

☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*

☐ 4 *Extreme symptoms - complete withdrawal*

☐ *Can't rate*

2. Distinct quality of mood

☐ 0 *No distinct qualities*

☐ 1 *Mild or moderate (slightly different)*

☐ 2 *Severe (definitely different)*

☐ *Can't rate*

3. Lack of reactivity

☐ 0 *Reactive mood (mood varies according to situation)*

☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*

☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*

☐ *Can't rate*

4. Diurnal variation

☐ 0 *No variation in mood*

☐ 1 *Mild variation between a.m. and p.m.*

☐ 2 *Definite variation between a.m. and p.m.*

☐ *Can't rate*

5. Worthlessness

☐ 0 *Not present*

☐ 1 *Mild feelings of low self-esteem evident only from questioning*

☐ 2 *Feelings of worthlessness*

☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*

☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*

☐ *Can't rate*

6. Guilt

☐ 0 *Absent*

☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*

☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*

☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*

☐ 4 *Delusional guilt, with hallucinations*

☐ *Can't rate*

DataFax #153 **Plate #011** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐☐☐☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ *0 Not present*
- ☐ *1 Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ *2 Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ *3 Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ *4 Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ *0 Not present*
- ☐ *1 Intermittently doubts that things will improve but can be reassured*
- ☐ *2 Consistently feels hopeless but accepts reassurances*
- ☐ *3 Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ *4 Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ *0 Absent*
- ☐ *1 Feels life is not worth living*
- ☐ *2 Wishes he were dead or any thoughts of possible death to himself*
- ☐ *3 Suicidal ideas, gestures, or plans*
- ☐ *4 Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ *2 Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ *2 Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ *2 Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

21. Somatic anxiety - *(**Note:** Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071

STUDY TERMINATION REPORT
(End of Week 120)

Pharmacia & Upjohn

STUDY TERMINATION REPORT - Instructions

DEFINITION OF STUDY TERMINATION REPORT

Study Termination Report refers to the end of study medication period. It is not meant for temporary withdrawal or for the end of follow-up or observation period.

- Always refer back to the ***Subject's Dosing Diary*** and double check the day of last study medication.
  This date must be in accordance with other visit dates (i.e., not be before the first visit or after the last visit).

- If the subject did NOT complete the treatment period as defined in the study protocol, choose one primary reason for withdrawal. Try to find out what lies behind the withdrawal, e.g., why a consent was withdrawn or a protocol violation happened. Do not enter that cause on this form, but keep it ready for review. Do not be too quick to enter "Lost to follow-up", subjects sometimes return.

- Always choose the most severe reason. Example: If the subject withdrew the informed consent and had side effects that caused problems, check "Adverse event".

- Termination: The *Study Termination Report* page must be completed and submitted for all subjects who were assigned study medication.

STUDY TERMINATION REPORT

DataFax #153 **Plate #018** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

Date of last dose of study medication: ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Did patient complete 120 weeks of treatment? ☐ *Yes* ☐ *No*

*If **No**, choose **one** primary reason for withdrawal:*

☐ 1 *Adverse event* → ***Fill in / update Adverse Event page***

☐ 2 *Protocol violation* → ***Explain in Comments section below***

☐ 3 *Consent withdrawn* → ***Explain in Comments section if necessary***

☐ 4 *Lost to follow-up*

☐ 5 *Protocol specific withdrawal criteria* → ***Explain in Comments section below***

☐ 6 *Lack of efficacy*

☐ 7 *Progression of disease*

☐ 8 *Improvement*

☐ 9 *Other, specify:* _____

COMMENTS

Investigator's Signature: _____

Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071 (Amendment C)

DATAFAX VISIT MAP

Schedule of CRF Pages to be Completed at Each Patient Assessment

Plate No.	Form Title	Study Period	End of Week										End of Study
			72 [I]	80	88	96 [II]	104	112	120 [III]	128	136	144	
		Seq. #	72	80	88	96	104	112	120	128	136	144	501
4	Physical Examination		95 [I]			114 [II]			136 [III]				PE
10-13	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *4 pages*		98-101	105-108	110-113	117-120	125-128	131-134	140-143	147-150	153-156	159-162	
15	Vital Signs / AE & Concomitant Medication / Study Medication Record		96	104	109	115	123	129	137	145	151	157	
16	Clinical Global Impressions (CGI)		102	CGI.W80	CGI.W88	121	124	130	139	146	152	158	
17	Pregnancy Test / Electrocardiogram (ECG)		97			116			138				PGECG
18	Study Termination Report		103 [I]			122 [II]			144 [III]				STDYTERM
28	Continuation Assessment Case Report Form		CONT			CONT			CONT				
19	Adverse Event Form		**AS NEEDED**										
20-21	Concomitant Medication Form												
22-24	Serious Adverse Event Form - *3 pages*												
25	Serious Adverse Event Form - *Page 3 of 3 (Extra Form)*												
26	Adverse Event Follow-up Report												
27	Exposure in Utero												

[I] *Please SKIP End of Week 72 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 72 (Please complete header information, leave rest of form blank and fax to DataFax)*

[II] *Please SKIP End of Week 96 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 96 (Please complete header information, leave rest of form blank and fax to DataFax)*

[III] *Please SKIP End of Week 120 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 120 (Please complete header information, leave rest of form blank and fax to DataFax)*

Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071 (Amendment C)

DATAFAX SCHEDULE OF ACTIVITIES

(CHECK BOXES AS FORMS/ACTIVITIES ARE COMPLETED)

Study Period / Study Activities	End of Week										End of Study
	72 [I]	80	88	96 [II]	104	112	120 [III]	128	136	144	
Informed Consent	☐			☐			☐				
Physical Examination	☐ [I]			☐ [II]			☐ [III]				☐
Pregnancy Test	☐			☐			☐				☐
Electrocardiogram (ECG)	☐			☐			☐				☐
Lab. Assessment Test (Serum Chemistry, Hematology, Urinalysis)	☐			☐			☐				
Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vital Signs	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Study Medication Record (Dispensing (D) / Returning (R))	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ D/R	☐ R	
Clinical Global Impressions (CGI) [+]	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Continuation Assessment Case Report Form	☐			☐			☐				
Study Termination Report	☐ [I]			☐ [II]			☐ [III]				☐
Adverse Event Form	**AS NEEDED**										
Concomitant Medication Form											
Serious Adverse Event Form - *3 pages*											
Serious Adverse Event Form - *Page 3 of 3 (Extra Form)*											
Adverse Event Follow-up Report											
Exposure in Utero											

[I] *Please SKIP End of Week 72 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 72 (Please complete header information, leave rest of form blank and fax to DataFax)*

[II] *Please SKIP End of Week 96 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 96 (Please complete header information, leave rest of form blank and fax to DataFax)*

[III] *Please SKIP End of Week 120 "Physical Examination" and "Study Termination Report" if subject is continuing Reboxetine treatment past Week 120 (Please complete header information, leave rest of form blank and fax to DataFax)*

[+] *CGI assessments will now be completed at all visits. If the patient has already completed visits that now require the CGI, the corresponding CGI case report form should be marked NOT DONE and faxed to DataFax.*

Pharmacia & Upjohn

Open-label Reboxetine Rescue and Continuation Therapy

PROTOCOL 950ECNS0005-071 (Amendment C)

NOTE: Complete the "Continuation Assessment case report form" (CONT CRF) prior to completing any other assessments.

END OF WEEK 120 Activities

If subject is continuing Reboxetine Treatment past *Week 120*, complete the following activities. *Please refer to your previous binder for the CRFs pages.*

- Complete the following CRFs:

Page #	Form
	Informed Consent - *(Not included in this set of Case Report Forms, also do not fax to DataFax)*
CONT	Continuation Assessment Case Report Form - *(Included in this binder)*
137	Vital Signs / AE & Concomitant Medication / Study Medication Record
138	Pregnancy Test / Electrocardiogram (ECG)
	Note: Mail duplicate original ECG to eRT (eResearch Technology).
140-143	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)
139	Clinical Global Impressions (CGI)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 137)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 137.
- Dispense Week 121-128's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.
- Schedule subject for End of Week 128 visit.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

CONTINUATION ASSESSMENT CASE REPORT FORM

End of Week 120

DataFax #153 **Plate #028** **Seq. #120**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

1. I interviewed the subject today, reviewed the subject's history, current mental and physical symptoms and am of the opinion that continuation of Reboxetine treatment is indicated at this time:

   ☐ *Yes* *(go to item 2)*

   ☐ *No* *(perform the ORIGINAL End of Week 120 Final Visit activities and Study Termination Report)*

2. I discussed the possible benefits, risks and alternatives of continuing Reboxetine treatment with the subject, and the subject concurs with my decision:

   ☐ *Yes* *(go to item 3)*

   ☐ *No* *(perform the ORIGINAL End of Week 120 Final Visit activities and Study Termination Report)*

3. If the responses to items 1 and 2 are "Yes", has the amendment #C informed consent been presented to and signed by the subject?

   ☐ *Yes* *(perform the next visit)*

   ☐ *No* *(perform the ORIGINAL End of Week 120 Final Visit activities and Study Termination Report)*

Signature of person who performed this evaluation *(must be licensed physician who is noted on 1572)*:

Signature: _____ **Date:** ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Signature of primary investigator if assessment was performed by designee: ☐ ***N/A***
(NOTE: If same as above, please check "N/A")

Signature: _____ **Date:** ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

PROTOCOL 950ECNS0005-071

END OF WEEK 128

- Complete the following CRFs:

Page #	Form
145	Vital Signs / AE & Concomitant Medication / Study Medication Record
146	Clinical Global Impressions (CGI)
147-150	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 145)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 145.
- Dispense Week 129-136's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.
- Schedule subject for End of Week 136 visit.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM End of Week 128

DataFax #153 **Plate #500** **Seq. #128**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

END OF WEEK 128

All **End of Week 128** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	145	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	146	Clinical Global Impressions (CGI)
☐	147	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	148	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	149	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	150	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form
☐	PE	Physical Examination
☐	PGECG	Pregnancy Test / Electrocardiogram (ECG)
☐	STDYTERM	Study Termination Report

DataFax #153 **Plate #015** **Seq. #128**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*

Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min*

Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐

Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

DataFax #153 **Plate #016** **Seq. #128**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

DataFax #153 **Plate #010** **Seq. #128**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*)

Subject's Initials ☐☐☐ (*F M L*)

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

1. Depressed mood

- ☐ 0 *Absent*
- ☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*
- ☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*
- ☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*
- ☐ 4 *Extreme symptoms - complete withdrawal*
- ☐ *Can't rate*

2. Distinct quality of mood

- ☐ 0 *No distinct qualities*
- ☐ 1 *Mild or moderate (slightly different)*
- ☐ 2 *Severe (definitely different)*
- ☐ *Can't rate*

3. Lack of reactivity

- ☐ 0 *Reactive mood (mood varies according to situation)*
- ☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*
- ☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*
- ☐ *Can't rate*

4. Diurnal variation

- ☐ 0 *No variation in mood*
- ☐ 1 *Mild variation between a.m. and p.m.*
- ☐ 2 *Definite variation between a.m. and p.m.*
- ☐ *Can't rate*

5. Worthlessness

- ☐ 0 *Not present*
- ☐ 1 *Mild feelings of low self-esteem evident only from questioning*
- ☐ 2 *Feelings of worthlessness*
- ☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*
- ☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*
- ☐ *Can't rate*

6. Guilt

- ☐ 0 *Absent*
- ☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*
- ☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*
- ☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*
- ☐ 4 *Delusional guilt, with hallucinations*
- ☐ *Can't rate*

DataFax #153 **Plate #011** **Seq. #128**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ *0 Not present*
- ☐ *1 Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ *2 Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ *3 Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ *4 Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ *0 Not present*
- ☐ *1 Intermittently doubts that things will improve but can be reassured*
- ☐ *2 Consistently feels hopeless but accepts reassurances*
- ☐ *3 Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ *4 Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ *0 Absent*
- ☐ *1 Feels life is not worth living*
- ☐ *2 Wishes he were dead or any thoughts of possible death to himself*
- ☐ *3 Suicidal ideas, gestures, or plans*
- ☐ *4 Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ *2 Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ *2 Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ *2 Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #128**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

---

16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

---

20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #128**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

21. Somatic anxiety - (***Note:*** *Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

PROTOCOL 950ECNS0005-071

END OF WEEK 136

- Complete the following CRFs:

Page #	Form
151	Vital Signs / AE & Concomitant Medication / Study Medication Record
152	Clinical Global Impressions (CGI)
153-156	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 151)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Check subject's Dosing Diary and study medication compliance. Record on CRF page 151.
- Dispense Week 137-144's supply of study medication to the subject. Give Subject Dosing Diary, Dosing Diary instructions and AM/PM dosing instructions to subject.
- Schedule subject for End of Week 144 visit.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM End of Week 136

DataFax #153 **Plate #500** **Seq. #136**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

END OF WEEK 136

All **End of Week 136** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	151	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	152	Clinical Global Impressions (CGI)
☐	153	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	154	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	155	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	156	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form
☐	PE	Physical Examination
☐	PGECG	Pregnancy Test / Electrocardiogram (ECG)
☐	STDYTERM	Study Termination Report

DataFax #153 **Plate #015** **Seq. #136**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*

Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min*

Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐

Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

DataFax #153 **Plate #016** **Seq. #136**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

DataFax #153 **Plate #010** **Seq. #136**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

1. Depressed mood

- ☐ 0 *Absent*
- ☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*
- ☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*
- ☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*
- ☐ 4 *Extreme symptoms - complete withdrawal*
- ☐ *Can't rate*

2. Distinct quality of mood

- ☐ 0 *No distinct qualities*
- ☐ 1 *Mild or moderate (slightly different)*
- ☐ 2 *Severe (definitely different)*
- ☐ *Can't rate*

3. Lack of reactivity

- ☐ 0 *Reactive mood (mood varies according to situation)*
- ☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*
- ☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*
- ☐ *Can't rate*

4. Diurnal variation

- ☐ 0 *No variation in mood*
- ☐ 1 *Mild variation between a.m. and p.m.*
- ☐ 2 *Definite variation between a.m. and p.m.*
- ☐ *Can't rate*

5. Worthlessness

- ☐ 0 *Not present*
- ☐ 1 *Mild feelings of low self-esteem evident only from questioning*
- ☐ 2 *Feelings of worthlessness*
- ☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*
- ☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*
- ☐ *Can't rate*

6. Guilt

- ☐ 0 *Absent*
- ☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*
- ☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*
- ☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*
- ☐ 4 *Delusional guilt, with hallucinations*
- ☐ *Can't rate*

DataFax #153 **Plate #011** **Seq. #136**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ *0 Not present*
- ☐ *1 Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ *2 Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ *3 Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ *4 Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ *0 Not present*
- ☐ *1 Intermittently doubts that things will improve but can be reassured*
- ☐ *2 Consistently feels hopeless but accepts reassurances*
- ☐ *3 Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ *4 Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ *0 Absent*
- ☐ *1 Feels life is not worth living*
- ☐ *2 Wishes he were dead or any thoughts of possible death to himself*
- ☐ *3 Suicidal ideas, gestures, or plans*
- ☐ *4 Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ *2 Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ *2 Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ *2 Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #136**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

---

16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

---

20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #136**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

25 ITEM HAMD - Continued

21. Somatic anxiety - *(**Note:** Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

PROTOCOL 950ECNS0005-071

END OF WEEK 144

- Complete the following CRFs:

Page #	Form
157	Vital Signs / AE & Concomitant Medication / Study Medication Record
158	Clinical Global Impressions (CGI)
159-162	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD)

- Question subject regarding Adverse Events and Concomitant Medications *(CRF page 157)*. Complete the following if indicated.

AEF	Adverse Event Form
CM	Concomitant Medication Form

- Draw End of Week 144 safety laboratory assessment tests *(Serum Chemistry, Hematology, Urinalysis, Pregnancy test)*

- Collect and check subject's Dosing Diary and study medication compliance. Record on CRF page 157.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM End of Week 144

DataFax #153 **Plate #500** **Seq. #144**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

END OF WEEK 144

All **End of Week 144** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	157	Vital Signs / AE & Concomitant Medication / Study Medication Record
☐	158	Clinical Global Impressions (CGI)
☐	159	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 1 of 4*
☐	160	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 2 of 4*
☐	161	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 3 of 4*
☐	162	Hamilton Psychiatric Rating Scale for Depression (25-item HAMD) - *Page 4 of 4*

As Needed Form

☐	AEF	Adverse Event Form
☐	CM	Concomitant Medication Form
☐	PE	Physical Examination
☐	PGECG	Pregnancy Test / Electrocardiogram (ECG)
☐	STDYTERM	Study Termination Report

DataFax #153 **Plate #015** **Seq. #144**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

VITAL SIGNS

Weight *(without shoes)*: ☐☐☐ *lbs*

Sitting Blood Pressure: ☐☐☐ / ☐☐☐ *mmHg* (*Systolic* / *Diastolic*)

Sitting Pulse: ☐☐☐ */min*

Temperature: ☐☐☐.☐ °*F*

Respiration Rate: ☐☐ */min*

Were any clinically significant changes in vital signs observed at this examination?

☐ *No* ☐ *Yes, specify*:* _____

**** If any changes are considered to be an Adverse Event, also complete an ADVERSE EVENT FORM (AEF).***

ADVERSE EVENTS AND CONCOMITANT MEDICATION

If there is any change in reported adverse event(s) from previous visits, please update ADVERSE EVENT FORM (AEF).

Has the subject had any **new** adverse events since the last visit?

☐ *No* ☐ *Yes* If *Yes*, record the event(s) on the ADVERSE EVENT forms.

Have there been any changes in concomitant medication since the last visit?

☐ *No* ☐ *Yes* If *Yes,* update the CONCOMITANT MEDICATION forms.

STUDY MEDICATION RECORD

Total number of tablets returned today: ☐☐☐.☐

Total number of tablets dispensed today: ☐☐☐.☐

Did the subject skip drug for more than 2 doses per week?

☐ *No* ☐ *Yes* *Comments, if any:* _____

Since the last visit, what has been the subject's usual total daily dose?

☐ *2 tabs* ☐ *2 1/2 tabs* ☐ *Other, specify:* _____

Initials or Signature: _____

DataFax #153 **Plate #016** **Seq. #144**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

A. Severity of Illness Considering your total clinical experience with this particular population, how mentally ill is this patient at this time? *(Please check only **ONE**)*

- ☐ 1 *Normal, not at all ill*
- ☐ 2 *Borderline ill*
- ☐ 3 *Mildly ill*
- ☐ 4 *Moderately ill*
- ☐ 5 *Markedly ill*
- ☐ 6 *Severely ill*
- ☐ 7 *Among the most extremely ill patients*

B. Global Improvement *RATE TOTAL IMPROVEMENT WHETHER OR NOT, IN YOUR JUDGEMENT, IT IS DUE ENTIRELY TO DRUG TREATMENT.*

Compared to the patient's condition at DAY 1 (Day 1), how much has the patient changed? *(Please check only **ONE**)*

- ☐ 1 *Very much improved*
- ☐ 2 *Much improved*
- ☐ 3 *Minimally improved*
- ☐ 4 *No change*
- ☐ 5 *Minimally worse*
- ☐ 6 *Much worse*
- ☐ 7 *Very much worse*

C. Efficacy Index *RATE THIS ITEM ON THE BASIS OF DRUG EFFECT ONLY. (Please check only **ONE**)*

ACTIVITY	Tolerability: side effects			
	None	Do not significantly interfere with patient's functioning	Significantly interfere with patient's functioning	Outweigh therapeutic effect
MARKED *Vast improvement, complete or nearly complete remission of all symptoms*	1 ☐	2 ☐	3 ☐	4 ☐
MODERATE *Decided improvement, partial remission of symptoms*	5 ☐	6 ☐	7 ☐	8 ☐
MINIMAL *Slight improvement which does not alter status of care of patient*	9 ☐	10 ☐	11 ☐	12 ☐
UNCHANGED OR WORSE	13 ☐	14 ☐	15 ☐	16 ☐

Initials or Signature: _____

DataFax #153 **Plate #010** **Seq. #144**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD

INSTRUCTIONS: The time frame for this scale is the past week, except where otherwise indicated on specific items.

1. Depressed mood

☐ 0 *Absent*

☐ 1 *Mild - gloomy attitude, may be accompanied by infrequent weeping spells, sad, blue, waning of interests*

☐ 2 *Moderate - may be accompanied by feelings of inadequacy, self-pity, worrying, decrease in social interests and activity level, pessimism, "Locked in", occasional weeping, apathy, decrease in experience of pleasure*

☐ 3 *Severe - may be characterized by hopelessness, greater tendency to withdraw socially, near absence of interest or participation in other than essential activities, hardly anything produces pleasure, weeping may be frequent (or beyond tears)*

☐ 4 *Extreme symptoms - complete withdrawal*

☐ *Can't rate*

2. Distinct quality of mood

☐ 0 *No distinct qualities*

☐ 1 *Mild or moderate (slightly different)*

☐ 2 *Severe (definitely different)*

☐ *Can't rate*

3. Lack of reactivity

☐ 0 *Reactive mood (mood varies according to situation)*

☐ 1 *Mild to moderate lack of reactivity (patient's mood is somewhat reactive but also has a constant depressive overtone)*

☐ 2 *Severe lack of reactivity (patient's mood lacks any reactivity to situational factors)*

☐ *Can't rate*

4. Diurnal variation

☐ 0 *No variation in mood*

☐ 1 *Mild variation between a.m. and p.m.*

☐ 2 *Definite variation between a.m. and p.m.*

☐ *Can't rate*

5. Worthlessness

☐ 0 *Not present*

☐ 1 *Mild feelings of low self-esteem evident only from questioning*

☐ 2 *Feelings of worthlessness*

☐ 3 *Strong feelings of worthlessness - differs from "2" by degree ("I am no good at all." "Inferior to all others.")*

☐ 4 *Delusions of worthlessness ("I am a heap of garbage." "I am a sinner." etc.)*

☐ *Can't rate*

6. Guilt

☐ 0 *Absent*

☐ 1 *Feelings of self-reproach, self-blame, specific instance of lapse*

☐ 2 *Thoughts that negative events or reactions were caused by oneself; general or many instances or lapses for which one feels guilty; stronger convictions of one's guilt*

☐ 3 *Belief that illness might be a punishment, possibly delusional guilt*

☐ 4 *Delusional guilt, with hallucinations*

☐ *Can't rate*

DataFax #153 **Plate #011** **Seq. #144**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

7. Helplessness

- ☐ *0 Not present*
- ☐ *1 Patient reports mild feelings of helplessness upon questioning ("There are some things that I can't change.")*
- ☐ *2 Moderate feelings of helplessness ("I can't seem to change most things in my life.")*
- ☐ *3 Strong feelings of helplessness ("I can't change anything in my life.")*
- ☐ *4 Strong feelings of helplessness and has given up routine activities of normal life (decreased personal hygiene, doesn't get out of bed, difficulty feeding self, etc.)*
- ☐ *Can't rate*

8. Hopelessness

- ☐ *0 Not present*
- ☐ *1 Intermittently doubts that things will improve but can be reassured*
- ☐ *2 Consistently feels hopeless but accepts reassurances*
- ☐ *3 Expresses feelings of discouragement, despair, pessimism about the future, which cannot be dispelled*
- ☐ *4 Spontaneously and inappropriately perseverates, "I'll never get well" or equivalent*
- ☐ *Can't rate*

9. Suicide

- ☐ *0 Absent*
- ☐ *1 Feels life is not worth living*
- ☐ *2 Wishes he were dead or any thoughts of possible death to himself*
- ☐ *3 Suicidal ideas, gestures, or plans*
- ☐ *4 Attempted suicide (any serious attempt rated 4)*
- ☐ *Can't rate*

Insomnia

10. Early

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild, trivial (less than 1-hour delay)*
- ☐ *2 Frequent (3 or more times per week) and severe (1 hour or more delay)*
- ☐ *Can't rate*

11. Middle

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1-hour delay in returning to sleep)*
- ☐ *2 Frequent (several times per night with difficulty returning to sleep, 3 or more times per week) and severe (1 hour or more to return to sleep)*
- ☐ *Can't rate*

12. Late

- ☐ *0 Absent*
- ☐ *1 Occasional (fewer than 3 days a week), mild (less than 1 hour early)*
- ☐ *2 Frequent (3 or more days per week) and severe (1 hour or more early)*
- ☐ *Can't rate*

DataFax #153 **Plate #012** **Seq. #144**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

13. Loss of appetite

- ☐ *0 Absent*
- ☐ *1 Loss of appetite, mild or occasional*
- ☐ *2 Loss of appetite, severe or constant: constipation*
- ☐ *Can't rate*

14. Loss of weight

- ☐ *0 Absent*
- ☐ *1 One or 2 pounds over the past month*
- ☐ *2 Three pounds or more over the past month*
- ☐ *Can't rate*

15. Weight gain

- ☐ *0 Absent*
- ☐ *1 Gained 1 or 2 pounds over the past month*
- ☐ *2 Gained 3 or more pounds over the last month*
- ☐ *Can't rate*

---

16. Loss of energy

- ☐ *0 No loss of energy*
- ☐ *1 Subjective loss of energy or feelings of tiredness*
- ☐ *2 Marked interferences with functioning (decrease in work and activities), feelings of heaviness or achiness*
- ☐ *Can't rate*

17. Loss of interest

- ☐ *0 No loss of interest*
- ☐ *1 Mild loss of interest*
- ☐ *2 Severe loss of interest in most activities, including clothes, food, and appearance*
- ☐ *Can't rate*

18. Work and activities

- ☐ *0 Absent*
- ☐ *1 Somewhat decreased efficiency, effortfulness; and/or decreased interest in or gets less pleasure from hobbies, interest, social contacts*
- ☐ *2 Decreased performance, neglects or delays some things; withdraws from unnecessary activity, decreased participation in hobbies, social events*
- ☐ *3 Considerably diminished performances of work or routine activities, more things are neglected or postponed indefinitely, virtually unproductive; avoids social contacts, nothing seems pleasurable, no interests*
- ☐ *4 Unable to work, nonproductive, completely immobilized*
- ☐ *Can't rate*

19. Loss of libido

- ☐ *0 No change*
- ☐ *1 Some loss of interest and performance*
- ☐ *2 Almost total loss of interest and sexual activity*
- ☐ *Can't rate*

---

20. Psychic anxiety *- anxious, tense, jittery, nervous, restless, "up tight," apprehensive, frightened, scared, irritable, worrying*

- ☐ *0 Absent*
- ☐ *1 Transient tension, occasional irritability, mild exaggeration of worrying*
- ☐ *2 Fairly constant tension, more frequent irritability, somewhat "hyper" or jittery.*
- ☐ *3 Pervasive apprehension, tension, irritability, constant ruminative worrying*
- ☐ *4 Panic attacks: phobias restrict activity*
- ☐ *Can't rate*

DataFax #153 **Plate #013** **Seq. #144**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

25 ITEM HAMD - Continued

21. Somatic anxiety - (***Note:*** *Symptoms are rated on the basis of the report of symptoms in the following systems (a) respiratory: labored breathing, shortness of breath, smothering or choking feelings, etc.; (b) cardiovascular: flushing, accelerated heart rate, palpitations, faintness, chest pain or discomfort, etc.; (c) gastrointestinal: indigestion, stomach upset, heartburn, stomach cramps, diarrhea, etc.; (d) genito-urinary frequency; (e) sweating; (f) giddiness, blurred vision, tinnitus; (g) neuromuscular, trembling or shaking, headaches, muscle tension, dizziness, tingling, etc.)*

- ☐ *0 Absent*
- ☐ *1 Mild - one or more symptoms, complains of some discomfort but continues to participate in daily activities*
- ☐ *2 Moderate - e.g., symptoms from more than one system, occasionally patient can't take part in activities because of bodily discomfort*
- ☐ *3 Severe - symptoms so uncomfortable that patient frequently has trouble taking part in activities*
- ☐ *4 Extreme - multiple systems that are incapacitating, i.e., bodily discomfort precludes taking part in any activities*
- ☐ *Can't rate*

22. Hypochondriasis

- ☐ *0 Absent*
- ☐ *1 Preoccupation with health, bodily function, trivial or doubtful symptoms*
- ☐ *2 Much preoccupation with physical symptoms, thoughts of organic disease*
- ☐ *3 Strong conviction of presence of physical disease, querulous attitude*
- ☐ *4 Hypochondriacal delusions and hallucinations, e.g., rotting, blockages, etc.*
- ☐ *Can't rate*

23. Insight

- ☐ *0 Acknowledges being depressed or ill*
- ☐ *1 Acknowledges illness but attributes cause to unlikely factors, e.g., bad food, climate, overwork, etc.*
- ☐ *2 Denies being ill*
- ☐ *Can't rate*

24. Retardation

- ☐ *0 Absent*
- ☐ *1 Slight retardation at interview; flattening of affect and fixity of expression*
- ☐ *2 Obvious retardation at interview; monotonous voice; delay in answering, motionless*
- ☐ *3 Interview difficult, prolonged*
- ☐ *4 Complete stupor*
- ☐ *Can't rate*

25. Agitation

- ☐ *0 Absent*
- ☐ *1 Low level of agitation, fidgeting, obvious restlessness (e.g., picking at hands or clothing, leg movements) for large proportion of interview*
- ☐ *2 High level of agitation, includes fidgeting, obvious restlessness as well as the patient getting up during the interview, pacing, etc.*
- ☐ *Can't rate*

TOTAL SCORE: ☐☐☐

Initials or Signature: _____

PROTOCOL 950ECNS0005-071

END OF STUDY

If subject completed the study or terminated the study early, complete the following activities.

Page #	Form
PE	Physical Examination
PGECG	Pregnancy Test / Electrocardiogram (ECG) ***Note: Mail duplicate original ECG to eRT (eResearch Technology).***
STDYTERM	Study Termination Report

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

TRANSMITTAL FORM End of Study

DataFax #153 **Plate #500** **Seq. #501**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

End of Study

All **End of Study** case report forms should be faxed to the DataFax system (1-888-272-7778).

Check box if faxed	Page #	Form
☐	PE	Physical Examination
☐	PGECG	Pregnancy Test / Electrocardiogram (ECG) ***Note: Mail duplicate original ECG to eRT (eResearch Technology).***
☐	STDYTERM	Study Termination Report

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

PHYSICAL EXAMINATION End of Study

DataFax #153 **Plate #004** **Seq. #501**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐ ☐☐ ☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

INSTRUCTIONS: Check appropriate box to indicate current physical findings. Describe any abnormalities, indicating left or right where applicable. If evaluation of the category is not performed, write "Not Done".

PHYSICAL FINDINGS	HEAD AND NECK ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	EENT / MOUTH ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	CHEST / LUNGS ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	HEART ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	BREASTS *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	BACK / SPINE *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	ABDOMEN ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	EXTREMITIES ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	SKIN ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	LYMPH NODES *(Optional)* ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	NERVOUS SYSTEM ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	MENTATION ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	ENDOCRINE ☐ *Normal* ☐ *Abnormal*	IF ABNORMAL, BRIEFLY DESCRIBE
	OTHER ABNORMAL PHYSICAL FINDINGS? ☐ *No* ☐ *Yes*	IF YES, BRIEFLY DESCRIBE

COMMENTS:

Initials or Signature: _____

PE

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

PREGNANCY TEST/ELECTROCARDIOGRAM (ECG) End of Study

DataFax #153 **Plate #017** **Seq. #501**

Subject Number ☐☐ - ☐☐☐☐ *Site No.*

Subject's Initials ☐☐☐ *F M L*

Date of Evaluation ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Principal Investigator _____ ☐☐☐☐☐

Country US

PREGNANCY TEST *(Serum)*

NOT DONE, Reason: ☐ *Male* ☐ *Surgically sterile* ☐ *Postmenopausal (>2 years)*

DONE, Result: ☐ *Negative* ☐ *Positive* ☐ *Inconclusive*

Note: If test is positive or inconclusive, subject should be removed from the study.

ELECTROCARDIOGRAM *(ECG)*

Date ECG Performed ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Time ☐☐ : ☐☐ *hours* *(00:01 - 24:00)*

Date of last dose of study medication ☐☐☐☐ ☐☐ ☐☐ *y y y y m m d d*

Time ☐☐ : ☐☐ *hours* *(00:01 - 24:00)*

Are there any clinically significant changes noted from Screen ECG? ☐ *No* ☐ *Yes*

Note: Please mail a duplicate original Electrocardiogram (ECG) to eRT (eResearch Technology).

Initials or Signature: _____

PGECG

PREGNANCT TEST/ECG

Protocol 950ECNS0005-071 FINAL 05JUL99 (amended 05MAR2002)

Pharmacia
& Upjohn

STUDY TERMINATION REPORT - Instructions

DEFINITION OF STUDY TERMINATION REPORT

Study Termination Report refers to the end of study medication period. It is not meant for temporary withdrawal or for the end of follow-up or observation period.

- Always refer back to the ***Subject's Dosing Diary*** and double check the day of last study medication.
  This date must be in accordance with other visit dates (i.e., not be before the first visit or after the last visit).

- If the subject did NOT complete the treatment period as defined in the study protocol, choose one primary reason for withdrawal. Try to find out what lies behind the withdrawal, e.g., why a consent was withdrawn or a protocol violation happened. Do not enter that cause on this form, but keep it ready for review. Do not be too quick to enter "Lost to follow-up", subjects sometimes return.

- Always choose the most severe reason. Example: If the subject withdrew the informed consent and had side effects that caused problems, check "Adverse event".

- Termination: The *Study Termination Report* page must be completed and submitted for all subjects who were assigned study medication.

Pharmacia & Upjohn **Protocol 950ECNS0005-071**

STUDY TERMINATION REPORT End of Study

DataFax #153 **Plate #018** **Seq. #501**

Subject Number ☐☐ - ☐☐☐☐ (*Site No.*) **Subject's Initials** ☐☐☐ (*F M L*) **Date of Evaluation** ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Principal Investigator _____ ☐☐☐☐☐ **Country** US

Date of last dose of study medication: ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

Did patient completed the treatment as per protocol? ☐ *Yes* ☐ *No*

*If **No**, choose **one** primary reason for withdrawal:*

☐ 1 *Adverse event* → ***Fill in / update Adverse Event page***

☐ 2 *Protocol violation* → ***Explain in Comments section below***

☐ 3 *Consent withdrawn* → ***Explain in Comments section if necessary***

☐ 4 *Lost to follow-up*

☐ 5 *Protocol specific withdrawal criteria* → ***Explain in Comments section below***

☐ 6 *Lack of efficacy*

☐ 7 *Progression of disease*

☐ 8 *Improvement*

☐ 9 *Other, specify:* _____

Last Visit the patient attended: **WEEK** ☐☐☐ ☐☐☐☐☐☐☐☐ (*y y y y m m d d*)

COMMENTS

Investigator's Signature: _____

STDYTERM

STUDY TERMINATION REPORT

Protocol 950ECNS0005-071 FINAL 05JUL99 (amended 05MAR2002)

Appendix 4. Individual Patient Data Listings

These data listings are available electronically upon request.

LISTING 3.1.1
Reason for Early Discontinuation - Subject Listing
All Enrolled Subjects
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Reason for Discontinuation	Comment
Amsterdam	11052	56	Male	Lack of efficacy	
	11053	49	Male	Lack of efficacy	
	11054	61	Male	Consent withdrawn	PT. WISHES TO WITHDRAWAL CONSENT & MOVE TO W. HE SAID HE'D "TAKE HIS CHANCES"
	11060	54	Female	Consent withdrawn	PT. NO LONGER WISHES TO CONTINUE IN RESEARCH TRIAL. SYMPTOMS OF DEPRESSION FLUCTUATE IN SEVERITY. CM#'S 303 & 304 WERE INADVERTENTLY SKIPPED.
Clayton	31058	44	Female	Protocol violation	PT. TOOK KLONOPIN FOR ANXIETY ATTACKS AND DID NOT NOTIFY THE INVESTIGATOR UNTIL SHE HAD BEEN TAKING THE KLONOPIN FOR SEVERAL DAYS.
Croft	231024	57	Female	Other	SITUATIONAL FACTORS CAUSING ANXIETY THAT IS REQUIRING DAILY ATIVAN USE. SITUATIONAL FACTORS WILL NOT BE IMPROVING OR ENDING ANY TIME SOON AND SUBJECT NEEDS DAILY ATIVAN TO COPE.
	231025	54	Female	Consent withdrawn	HAMD SCORE SHOWS INCREASE IN DEPRESSION (RELAPSE) BUT DR. CROFT FEELS INCREASE IS LIKELY DUE TO RELATIONSHIP ISSUES THAT MAY IMPROVE IN FEW DAYS, RECOMMENDED THAT SHE CONTINUE STUDY DRUG AND RETURN IN A WEEK FOR REASSESSMENT, SUBJECT CHOSE TO DISCONTINUE STUDY INSTEAD.

LISTING 3.1.1
Reason for Early Discontinuation - Subject Listing
All Enrolled Subjects
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Reason for Discontinuation	Comment
Croft	231039	36	Female	Protocol violation	NON-COMPLIANCE WITH VISIT SCHEDULE AND STUDY DRUG DOSING.
	231042	66	Male	Protocol violation	SUBJECT WAS NON COMPLIANT WITH OFFICE VISITS
Delgado	41009	41	Female	Lost to follow-up	PT DID NOT KEEP APPT FOR WK 80. DID NOT RESPOND TO PHONE CALLS OR LETTER.
	41019	57	Female	Other	LAST VISIT THE SUBJECT ATTENDED: WEEK 128 2002/10/03; STUDY TERMINATED BY COMPANY
	41021	64	Female	Adverse event	
Dunner	211020	43	Male	Other	SUBJECT ELECTED TO DISCONTINUE FROM THE STUDY BECAUSE HE SUBJECTIVELY DOES NOT EXPERIENCE ENOUGH BENEFIT TO MERIT THE EFFORT INVOLVED FOR HIM TO PARTICIPATE IN THE STUDY.
	211037	55	Female	Lack of efficacy	INCREASE DEP X 6 WEEKS PRIOR TO 11/14/00 VISIT
Fava	51028	54	Female	Consent withdrawn	STUDY DRUG NO LONGER EFFICACIOUS FOR SUBJECT
	51041	30	Female	Lack of efficacy	
Helfing	81001	66	Female	Lack of efficacy	

LISTING 3.1.1
Reason for Early Discontinuation - Subject Listing
All Enrolled Subjects
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Reason for Discontinuation	Comment
Helfing	81005	43	Female	Consent withdrawn	SUBJECT UPSET WITH LAB PROCEDURES AFTER HAVING A POSITIVE URINE DRUG SCREEN, AND REFUSING TO GIVE A SECOND UDS. SEE END OF WEEK 4 CRFS FOR FINAL SCALES.
	81016	48	Female	Adverse event	
	81045	23	Female	Lost to follow-up	SUBJECT LOST TO FOLLOW UP LAST KNOWN DOSE DATE IS 2/15/01
Hoopes	271007	42	Female	Other	SUBJECT FELT HER DEPRESSION HAD NOT IMPROVED ENOUGH TO CONTINUE TAKING REBOXETINE. PER CRA, PRIMARY REASON NOT CONSENT WITHDRAWN BUT SUBJECT REQUEST.
Julie	321044	55	Male	Progression of disease	SUBJECT'S PSYCHIATRIST RE-STARTED HIM ON PROZAC ON 12/27/2000, PRIOR TO EARLY TERMINATION VISIT, DUE TO PROGRESSION OF HIS DEPRESSION
Leuchter	361014	40	Female	Lack of efficacy	PT. STATES LACK OF EFFICACY AT THIS TIME, BUT WAS GREATLY IMPROVED 1 MONTH AGO WITH A HAM SCORE OF 6. HAM IS NOW 9.
	361015	44	Female	Protocol violation	PT. STOPPED MEDICATION ON 9-24-00 & RESUMED TAKING 1 PILL DAILY ON 10-13-00 WITHOUT NOTIFYING US.
	361027	55	Female	Lack of efficacy	

LISTING 3.1.1
Reason for Early Discontinuation - Subject Listing
All Enrolled Subjects
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Reason for Discontinuation	Comment
Leuchter	361029	35	Female	Lack of efficacy	ENERGY & WAKEFULNESS IMPROVED - MOOD DEPRESSED
	361046	20	Female	Protocol violation	PT. WENT TO EUROPE & DID NOT RETURN UNTIL MID SEPT. SHE MISSED WK 12,16 & 20 VISIT SHE ALSO REDUCED HER REBOXETINE DOSE TO 4MG /DAY. PT. IS EUTHYMIC.
	361056	50	Female	Adverse event	ALTHOUGH PT DISCONTINUED MED ABRUPTLY DUE TO SHORTNESS OF BREATH SHE WAS CONSIDERING DISCONTINUING BECAUSE OF DRAMATIC IMPROVEMENT IN MOOD.
	361057	35	Female	Protocol violation	PT. MISSED 14 DOSES THIS MONTH
	361059	35	Female	Adverse event	PT. IS NO LONGER DEPRESSED, BUT FEELS DRY MOUTH & RECENT WT. LOSS & LACK OF APPETITE WARRANT GOING OFF DRUG NOW. SHE IS WAITRESS & DRY MOUTH BOTHERS HE WHILE WORKING
	361061	38	Male	Lack of efficacy	
	361062	40	Female	Improvement	
	361063	45	Female	Lack of efficacy	
	361064	46	Female	Adverse event	PT. CHOOCES TO TERMINATE DUE TO HEADACHES, BUT HAS BEEN EUTHYMIC FOR SEVERAL MONTHS. FEELS REBOXETINE HAS BEEN VERY EFFECTIVE.

LISTING 3.1.1
Reason for Early Discontinuation - Subject Listing
All Enrolled Subjects
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Reason for Discontinuation	Comment
Leuchter	361066	57	Female	Adverse event	PT. DROPPED DUE TO PROBLEM WITH SEVERE CONSTIPATION
	361067	55	Female	Lost to follow-up	PT. CAME IN 7-25-01 & MOVED TO CANADA AFTER. STATED SHE WOULD NOT RETURN FOR FOLLOW-UP.
	361068	51	Male	Adverse event	
	361069	55	Male	Adverse event	PT. WITHDREW FROM STUDY BECAUSE OF INTERRUPTED SLEEP, COLD FLASHES, SOB ON EXTREME EXERTION & NAUSEA. SIGNIFICANT MOOD IMPROVEMENT OCCURED.
Londborg	101002	31	Female	Protocol specific withdrawal c	SUBJECT REQUIRED TREATMENT WITH ANOTHER PSYCHOTROPIC MEDICATION, NEURONTIN 300MG TID FOR A BACK PROBLEM SECONDARY TO A MOTOR VEHICLE ACCIDENT ON 10/6/99.
Lydiard	221055	45	Male	Lack of efficacy	
Munjack	131032	34	Female	Adverse event	
	131033	45	Male	Other	
	131043	40	Female	Other	
Rapaport	151018	60	Male	Other	
	151023	62	Female	Adverse event	

LISTING 3.1.1
Reason for Early Discontinuation - Subject Listing
All Enrolled Subjects
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Reason for Discontinuation	Comment
Rapaport	151038	49	Male	Lost to follow-up	SUBJECT WAS LOST TO FOLLOW-UP WEEK24/EARLY TERMINATION PROCEDURES NOT COMPLETED.
	151048	47	Male	Lack of efficacy	
Smith	281011	40	Female	Protocol specific withdrawal c	PT.HAD TWO POSITIVE URINE DRUG SCREEN
	281013	44	Female	Other	LAST VISIT THE SUBJECT ATTENDED: WEEK 120 2002/09/04
	281022	54	Female	Consent withdrawn	PT. DISCONTINUED MEDICATION ON HER OWN ACCORD APPROXIMATELY TWO WEEKS AGO.
Thase	181026	32	Male	Other	LAST VISIT THE SUBJECT ATTENDED: WEEK 128 2002/09/12
	181031	58	Male	Other	LAST VISIT THE SUBJECT ATTENDED: WEEK 128 2002/09/17; PT WAS GIVEN 30 DAYS OF STUDY MED AT LAST VISIT BUT WAS DISPENSED AN ADDITIONAL 30 DAYS BY DR. THASE AS THE MEDS HE ORDERED THROUGH THE INTERNET HAD NOT ARRIVED
	181050	55	Female	Adverse event	
Walsh	171006	45	Female	Protocol violation	PT MISSED 4.5 DOSES OF STUDY MEDICATION AND WAS TERMINATED
	171012	27	Male	Other	LOOKING FOR PERMANENT FIX TO PROBLEM, DOES NOT WISH TO PARTICIPATE FURTHER.

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Eosinophils	41009	41	Female	SCREEN	0	7	0	8.4	%	13.1	H
				WEEK 24	0	7	0	8.4	%	8.9	H
	41019	57	Female	SCREEN	0	7	0	8.4	%	3.9	N
				WEEK 24	0	7	0	8.4	%	6.4	N
				WEEK 72	0	7	0	8.4	%	9.6	H
				WEEK 96	0	7	0	8.4	%	6.2	N
				WEEK 120	0	7	0	8.4	%	4.7	N
	131049	33	Female	WEEK 24	0	7	0	8.4	%	8.6	H
					0	7	0	8.4	%	4	N
	361046	20	Female	SCREEN	0	7	0	8.4	%	5.5	N
				WEEK 24	0	7	0	8.4	%	8.1	H
	361057	35	Female	SCREEN	0	7	0	8.4	%	8.1	H
				WEEK 24	0	7	0	8.4	%	5.1	N
Erythrocytes (RBC)	31058	44	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.8	L
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	4	N
	51028	54	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.6	L
	131032	34	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	5	N
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	5.3	H
					3.9	5.2	3.12	6.24	mill/mcL	4.8	N
	181031	58	Male	SCREEN	4.4	5.8	3.52	6.96	mill/mcL	4.4	N
				WEEK 24	4.4	5.8	3.52	6.96	mill/mcL	4.1	L
					4.4	5.8	3.52	6.96	mill/mcL	4.4	N
				WEEK 72	4.4	5.8	3.52	6.96	mill/mcL	4.5	N
				WEEK 96	4.4	5.8	3.52	6.96	mill/mcL	4.4	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Erythrocytes (RBC)	361046	20	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.9	N
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	3.8	L
	361051	47	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.7	L
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	3.8	L
					3.9	5.2	3.12	6.24	mill/mcL	4	N
	361056	50	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	4.7	N
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	3.8	L
					3.9	5.2	3.12	6.24	mill/mcL	4.8	N
	361064	46	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.7	L
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	3.7	L
					3.9	5.2	3.12	6.24	mill/mcL	3.9	N
Hematocrit	31004	45	Male	SCREEN	41	50	32.8	60	%	43	N
				WEEK 24	41	50	32.8	60	%	40.9	L
					41	50	32.8	60	%	42.1	N
				WEEK 72	41	50	32.8	60	%	43	N
	51028	54	Female	SCREEN	35	46	28	55.2	%	32.3	L
	51047	44	Female	WEEK 24	35	46	28	55.2	%	35.4	N
				WEEK 72	35	46	28	55.2	%	34.3	L
				WEEK 96	35	46	28	55.2	%	34.7	L
				WEEK 120	35	46	28	55.2	%	35.6	N
	131033	45	Male	SCREEN	41	50	32.8	60	%	50.3	H
				WEEK 24	41	50	32.8	60	%	52.2	H
					41	50	32.8	60	%	48.9	N
	151038	49	Male	SCREEN	41	50	32.8	60	%	50.7	H

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Hematocrit	151038	49	Male	WEEK 24	41	50	32.8	60	%	50.6	H
	181031	58	Male	SCREEN	41	50	32.8	60	%	41.5	N
				WEEK 24	41	50	32.8	60	%	36.1	L
					41	50	32.8	60	%	42.4	N
				WEEK 72	41	50	32.8	60	%	38.7	L
				WEEK 96	41	50	32.8	60	%	38.8	L
	211010	53	Female	SCREEN	35	46	28	55.2	%	44.8	N
				WEEK 24	35	46	28	55.2	%	47	H
					35	46	28	55.2	%	41.3	N
				WEEK 72	35	46	28	55.2	%	45.9	N
				WEEK 96	35	46	28	55.2	%	42.5	N
				WEEK 120	35	46	28	55.2	%	41.2	N
	361015	44	Female	SCREEN	35	46	28	55.2	%	40.5	N
				WEEK 24	35	46	28	55.2	%	46.1	H
					35	46	28	55.2	%	41.8	N
	361035	42	Female	SCREEN	35	46	28	55.2	%	34.8	L
				WEEK 24	35	46	28	55.2	%	35.9	N
	361051	47	Female	SCREEN	35	46	28	55.2	%	31.8	L
				WEEK 24	35	46	28	55.2	%	32.9	L
					35	46	28	55.2	%	35.2	N
	361056	50	Female	SCREEN	35	46	28	55.2	%	39.7	N
				WEEK 24	35	46	28	55.2	%	34	L
					35	46	28	55.2	%	41.8	N
	361065	50	Male	SCREEN	41	50	32.8	60	%	42.8	N
				WEEK 24	41	50	32.8	60	%	40.6	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Hematocrit	361065	50	Male	WEEK 24	41	50	32.8	60	%	44.3	N
Hemoglobin	31058	44	Female	SCREEN	12	15.6	9.6	18.72	g/dL	11.2	L
				WEEK 24	12	15.6	9.6	18.72	g/dL	11.8	L
					12	15.6	9.6	18.72	g/dL	12.4	N
	51028	54	Female	SCREEN	12	15.6	9.6	18.72	g/dL	10.9	L
	51047	44	Female	WEEK 24	12	15.6	9.6	18.72	g/dL	11.3	L
					12	15.6	9.6	18.72	g/dL	12.4	N
				WEEK 72	12	15.6	9.6	18.72	g/dL	11.3	L
				WEEK 96	12	15.6	9.6	18.72	g/dL	11.4	L
				WEEK 120	12	15.6	9.6	18.72	g/dL	11.8	L
	131033	45	Male	SCREEN	13.8	17.2	11.04	20.64	g/dL	17.3	H
				WEEK 24	13.8	17.2	11.04	20.64	g/dL	17.2	N
	181031	58	Male	SCREEN	13.8	17.2	11.04	20.64	g/dL	13.8	N
				WEEK 24	13.8	17.2	11.04	20.64	g/dL	12	L
					13.8	17.2	11.04	20.64	g/dL	13.9	N
				WEEK 72	13.8	17.2	11.04	20.64	g/dL	13	L
				WEEK 96	13.8	17.2	11.04	20.64	g/dL	12.8	L
	361015	44	Female	SCREEN	12	15.6	9.6	18.72	g/dL	14.3	N
				WEEK 24	12	15.6	9.6	18.72	g/dL	16	H
					12	15.6	9.6	18.72	g/dL	14.6	N
	361035	42	Female	SCREEN	12	15.6	9.6	18.72	g/dL	11.6	L
				WEEK 24	12	15.6	9.6	18.72	g/dL	11.6	L
	361051	47	Female	SCREEN	12	15.6	9.6	18.72	g/dL	10.9	L
				WEEK 24	12	15.6	9.6	18.72	g/dL	11	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Hemoglobin	361056	50	Female	SCREEN	12	15.6	9.6	18.72	g/dL	13	N
				WEEK 24	12	15.6	9.6	18.72	g/dL	11.1	L
					12	15.6	9.6	18.72	g/dL	13.9	N
	361068	51	Male	SCREEN	13.8	17.2	11.04	20.64	g/dL	14.3	N
				WEEK 24	13.8	17.2	11.04	20.64	g/dL	13.6	L
					13.8	17.2	11.04	20.64	g/dL	14.4	N
				WEEK 72	13.8	17.2	11.04	20.64	g/dL	14.6	N
Lymphocytes	31030	55	Male	SCREEN	16	46	12.8	55.2	%	50.6	H
				WEEK 24	16	46	12.8	55.2	%	49.3	H
				WEEK 72	16	46	12.8	55.2	%	46.6	H
				WEEK 96	16	46	12.8	55.2	%	46.4	H
	41009	41	Female	SCREEN	16	46	12.8	55.2	%	32.9	N
				WEEK 24	16	46	12.8	55.2	%	49.4	H
					16	46	12.8	55.2	%	33.3	N
	41021	64	Female	SCREEN	16	46	12.8	55.2	%	23.9	N
				WEEK 24	16	46	12.8	55.2	%	37.5	N
				WEEK 72	16	46	12.8	55.2	%	25	N
				WEEK 96	16	46	12.8	55.2	%	13.8	L
	51047	44	Female	WEEK 24	16	46	12.8	55.2	%	14	L
					16	46	12.8	55.2	%	23.7	N
				WEEK 72	16	46	12.8	55.2	%	20.3	N
				WEEK 96	16	46	12.8	55.2	%	21.7	N
				WEEK 120	16	46	12.8	55.2	%	16.1	N
	151038	49	Male	SCREEN	16	46	12.8	55.2	%	12	L
				WEEK 24	16	46	12.8	55.2	%	17.1	N

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Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Lymphocytes	181031	58	Male	SCREEN	16	46	12.8	55.2	%	26.1	N
				WEEK 24	16	46	12.8	55.2	%	14.4	L
					16	46	12.8	55.2	%	19.6	N
				WEEK 72	16	46	12.8	55.2	%	31	N
				WEEK 96	16	46	12.8	55.2	%	16.6	N
	281022	54	Female	SCREEN	16	46	12.8	55.2	%	24.6	N
				WEEK 24	16	46	12.8	55.2	%	15.1	L
					16	46	12.8	55.2	%	16	N
	361056	50	Female	SCREEN	16	46	12.8	55.2	%	12	L
				WEEK 24	16	46	12.8	55.2	%	24.7	N
MCV	131043	40	Female	SCREEN	80	100	64	120	fL	78	L
				WEEK 24	80	100	64	120	fL	76	L
	281011	40	Female	SCREEN	80	100	64	120	fL	102	H
Neutrophils	31030	55	Male	SCREEN	40	75	32	90	%	38.1	L
				WEEK 24	40	75	32	90	%	39.1	L
				WEEK 72	40	75	32	90	%	42.6	N
				WEEK 96	40	75	32	90	%	44.1	N
	41009	41	Female	SCREEN	40	75	32	90	%	44.4	N
				WEEK 24	40	75	32	90	%	35.9	L
					40	75	32	90	%	50.5	N
	41021	64	Female	SCREEN	40	75	32	90	%	66.8	N
				WEEK 24	40	75	32	90	%	54.1	N
				WEEK 72	40	75	32	90	%	65	N
				WEEK 96	40	75	32	90	%	79	H

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LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Neutrophils	51047	44	Female	WEEK 24	40	75	32	90	%	77	H
					40	75	32	90	%	71.2	N
				WEEK 72	40	75	32	90	%	72.1	N
				WEEK 96	40	75	32	90	%	70.8	N
				WEEK 120	40	75	32	90	%	77.1	H
	131032	34	Female	SCREEN	40	75	32	90	%	76.3	H
				WEEK 24	40	75	32	90	%	76.6	H
					40	75	32	90	%	74.6	N
	151038	49	Male	SCREEN	40	75	32	90	%	80	H
				WEEK 24	40	75	32	90	%	72.1	N
	181031	58	Male	SCREEN	40	75	32	90	%	65.5	N
				WEEK 24	40	75	32	90	%	82.4	H
					40	75	32	90	%	72.3	N
				WEEK 72	40	75	32	90	%	60.8	N
				WEEK 96	40	75	32	90	%	77.1	H
	281022	54	Female	SCREEN	40	75	32	90	%	67.4	N
				WEEK 24	40	75	32	90	%	76.4	H
					40	75	32	90	%	72.7	N
	361056	50	Female	SCREEN	40	75	32	90	%	80.6	H
				WEEK 24	40	75	32	90	%	68.8	N
Platelet Count	31058	44	Female	SCREEN	130000	400000	104000	480000	per/cumm	422000	H
				WEEK 24	130000	400000	104000	480000	per/cumm	309000	N
	41019	57	Female	SCREEN	130000	400000	104000	480000	per/cumm	396000	N
				WEEK 24	130000	400000	104000	480000	per/cumm	445000	H
				WEEK 72	130000	400000	104000	480000	per/cumm	414000	H

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Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Platelet Count	41019	57	Female	WEEK 96	130000	400000	104000	480000	per/cumm	485000	H
				WEEK 120	130000	400000	104000	480000	per/cumm	423000	H
	151034	49	Female	SCREEN	130000	400000	104000	480000	per/cumm	416000	H
				WEEK 24	130000	400000	104000	480000	per/cumm	413000	H
					130000	400000	104000	480000	per/cumm	380000	N
	211010	53	Female	SCREEN	130000	400000	104000	480000	per/cumm	427000	H
				WEEK 24	130000	400000	104000	480000	per/cumm	475000	H
				WEEK 72	130000	400000	104000	480000	per/cumm	383000	N
				WEEK 96	130000	400000	104000	480000	per/cumm	405000	H
				WEEK 120	130000	400000	104000	480000	per/cumm	416000	H
	211020	43	Male	SCREEN	130000	400000	104000	480000	per/cumm	320000	N
				WEEK 24	130000	400000	104000	480000	per/cumm	439000	H
					130000	400000	104000	480000	per/cumm	349000	N
	231039	36	Female	SCREEN	130000	400000	104000	480000	per/cumm	405000	H
				WEEK 24	130000	400000	104000	480000	per/cumm	437000	H
					130000	400000	104000	480000	per/cumm	389000	N
	361057	35	Female	SCREEN	130000	400000	104000	480000	per/cumm	394000	N
				WEEK 24	130000	400000	104000	480000	per/cumm	403000	H
Reticulocytes, Count	41009	41	Female	SCREEN	0.8	3.5	0.64	4.2	%	0.9	N
				WEEK 24	0.8	3.5	0.64	4.2	%	0.5	L
					0.8	3.5	0.64	4.2	%	1.2	N
	41021	64	Female	SCREEN	0.8	3.5	0.64	4.2	%	1.1	N
				WEEK 24	0.8	3.5	0.64	4.2	%	1.2	N
				WEEK 72	0.8	3.5	0.64	4.2	%	1.3	N
				WEEK 96	0.8	3.5	0.64	4.2	%	0.6	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Reticulocytes, Count	181026	32	Male	SCREEN	0.8	3.5	0.64	4.2	%	2.8	N
				WEEK 24	0.8	3.5	0.64	4.2	%	3.6	H
					0.8	3.5	0.64	4.2	%	3.3	N
				WEEK 72	0.8	3.5	0.64	4.2	%	3.9	H
				WEEK 96	0.8	3.5	0.64	4.2	%	4.9	H
	181050	55	Female	SCREEN	0.8	3.5	0.64	4.2	%	4.1	H
				WEEK 24	0.8	3.5	0.64	4.2	%	5.2	H
					0.8	3.5	0.64	4.2	%	3.4	N
	281022	54	Female	SCREEN	0.8	3.5	0.64	4.2	%	4.3	H
				WEEK 24	0.8	3.5	0.64	4.2	%	4.1	H
					0.8	3.5	0.64	4.2	%	3.5	N
	361014	40	Female	SCREEN	0.8	3.5	0.64	4.2	%	1.1	N
				WEEK 24	0.8	3.5	0.64	4.2	%	0.7	L
					0.8	3.5	0.64	4.2	%	1	N
	361065	50	Male	SCREEN	0.8	3.5	0.64	4.2	%	3.7	H
				WEEK 24	0.8	3.5	0.64	4.2	%	4	H
					0.8	3.5	0.64	4.2	%	2.9	N
WBC	31030	55	Male	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	3.7	L
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	3.4	L
					3.8	10.8	3.04	12.96	thou/mcL	4.2	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	3.8	N
				WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	3.5	L
	41019	57	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	11	H
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	12	H
					3.8	10.8	3.04	12.96	thou/mcL	10.6	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	9.7	N

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Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
WBC	41019	57	Female	WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	10.3	N
				WEEK 120	3.8	10.8	3.04	12.96	thou/mcL	11.4	H
	41021	64	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	5.6	N
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	5.2	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	3.7	L
				WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	5.7	N
	81005	43	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	4.8	N
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	3.2	L
	151038	49	Male	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	11.9	H
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	8.5	N
	211010	53	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	11.6	H
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	10.7	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	11.7	H
				WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	10.1	N
				WEEK 120	3.8	10.8	3.04	12.96	thou/mcL	9.8	N
	281011	40	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	3.6	L
	281013	44	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	5.8	N
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	3.7	L
					3.8	10.8	3.04	12.96	thou/mcL	4.9	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	4.4	N
				WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	4.9	N
				WEEK 120	3.8	10.8	3.04	12.96	thou/mcL	4.4	N
	361014	40	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	3.9	N
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	3.5	L

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LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Eosinophils	41009	41	Female	SCREEN	0	7	0	8.4	%	13.1	H
				WEEK 24	0	7	0	8.4	%	8.9	H
	41019	57	Female	SCREEN	0	7	0	8.4	%	3.9	N
				WEEK 24	0	7	0	8.4	%	6.4	N
				WEEK 72	0	7	0	8.4	%	9.6	H
				WEEK 96	0	7	0	8.4	%	6.2	N
				WEEK 120	0	7	0	8.4	%	4.7	N
	131049	33	Female	WEEK 24	0	7	0	8.4	%	8.6	H
					0	7	0	8.4	%	4	N
	361046	20	Female	SCREEN	0	7	0	8.4	%	5.5	N
				WEEK 24	0	7	0	8.4	%	8.1	H
	361057	35	Female	SCREEN	0	7	0	8.4	%	8.1	H
				WEEK 24	0	7	0	8.4	%	5.1	N
Erythrocytes (RBC)	31058	44	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.8	L
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	4	N
	51028	54	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.6	L
	131032	34	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	5	N
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	5.3	H
					3.9	5.2	3.12	6.24	mill/mcL	4.8	N
	181031	58	Male	SCREEN	4.4	5.8	3.52	6.96	mill/mcL	4.4	N
				WEEK 24	4.4	5.8	3.52	6.96	mill/mcL	4.1	L
					4.4	5.8	3.52	6.96	mill/mcL	4.4	N
				WEEK 72	4.4	5.8	3.52	6.96	mill/mcL	4.5	N
				WEEK 96	4.4	5.8	3.52	6.96	mill/mcL	4.4	N

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Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Erythrocytes (RBC)	361046	20	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.9	N
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	3.8	L
	361051	47	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.7	L
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	3.8	L
					3.9	5.2	3.12	6.24	mill/mcL	4	N
	361056	50	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	4.7	N
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	3.8	L
					3.9	5.2	3.12	6.24	mill/mcL	4.8	N
	361064	46	Female	SCREEN	3.9	5.2	3.12	6.24	mill/mcL	3.7	L
				WEEK 24	3.9	5.2	3.12	6.24	mill/mcL	3.7	L
					3.9	5.2	3.12	6.24	mill/mcL	3.9	N
Hematocrit	31004	45	Male	SCREEN	41	50	32.8	60	%	43	N
				WEEK 24	41	50	32.8	60	%	40.9	L
					41	50	32.8	60	%	42.1	N
				WEEK 72	41	50	32.8	60	%	43	N
	51028	54	Female	SCREEN	35	46	28	55.2	%	32.3	L
	51047	44	Female	WEEK 24	35	46	28	55.2	%	35.4	N
				WEEK 72	35	46	28	55.2	%	34.3	L
				WEEK 96	35	46	28	55.2	%	34.7	L
				WEEK 120	35	46	28	55.2	%	35.6	N
	131033	45	Male	SCREEN	41	50	32.8	60	%	50.3	H
				WEEK 24	41	50	32.8	60	%	52.2	H
					41	50	32.8	60	%	48.9	N
	151038	49	Male	SCREEN	41	50	32.8	60	%	50.7	H

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Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Hematocrit	151038	49	Male	WEEK 24	41	50	32.8	60	%	50.6	H
	181031	58	Male	SCREEN	41	50	32.8	60	%	41.5	N
				WEEK 24	41	50	32.8	60	%	36.1	L
					41	50	32.8	60	%	42.4	N
				WEEK 72	41	50	32.8	60	%	38.7	L
				WEEK 96	41	50	32.8	60	%	38.8	L
	211010	53	Female	SCREEN	35	46	28	55.2	%	44.8	N
				WEEK 24	35	46	28	55.2	%	47	H
					35	46	28	55.2	%	41.3	N
				WEEK 72	35	46	28	55.2	%	45.9	N
				WEEK 96	35	46	28	55.2	%	42.5	N
				WEEK 120	35	46	28	55.2	%	41.2	N
	361015	44	Female	SCREEN	35	46	28	55.2	%	40.5	N
				WEEK 24	35	46	28	55.2	%	46.1	H
					35	46	28	55.2	%	41.8	N
	361035	42	Female	SCREEN	35	46	28	55.2	%	34.8	L
				WEEK 24	35	46	28	55.2	%	35.9	N
	361051	47	Female	SCREEN	35	46	28	55.2	%	31.8	L
				WEEK 24	35	46	28	55.2	%	32.9	L
					35	46	28	55.2	%	35.2	N
	361056	50	Female	SCREEN	35	46	28	55.2	%	39.7	N
				WEEK 24	35	46	28	55.2	%	34	L
					35	46	28	55.2	%	41.8	N
	361065	50	Male	SCREEN	41	50	32.8	60	%	42.8	N
				WEEK 24	41	50	32.8	60	%	40.6	L

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LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Hematocrit	361065	50	Male	WEEK 24	41	50	32.8	60	%	44.3	N
Hemoglobin	31058	44	Female	SCREEN	12	15.6	9.6	18.72	g/dL	11.2	L
				WEEK 24	12	15.6	9.6	18.72	g/dL	11.8	L
					12	15.6	9.6	18.72	g/dL	12.4	N
	51028	54	Female	SCREEN	12	15.6	9.6	18.72	g/dL	10.9	L
	51047	44	Female	WEEK 24	12	15.6	9.6	18.72	g/dL	11.3	L
					12	15.6	9.6	18.72	g/dL	12.4	N
				WEEK 72	12	15.6	9.6	18.72	g/dL	11.3	L
				WEEK 96	12	15.6	9.6	18.72	g/dL	11.4	L
				WEEK 120	12	15.6	9.6	18.72	g/dL	11.8	L
	131033	45	Male	SCREEN	13.8	17.2	11.04	20.64	g/dL	17.3	H
				WEEK 24	13.8	17.2	11.04	20.64	g/dL	17.2	N
	181031	58	Male	SCREEN	13.8	17.2	11.04	20.64	g/dL	13.8	N
				WEEK 24	13.8	17.2	11.04	20.64	g/dL	12	L
					13.8	17.2	11.04	20.64	g/dL	13.9	N
				WEEK 72	13.8	17.2	11.04	20.64	g/dL	13	L
				WEEK 96	13.8	17.2	11.04	20.64	g/dL	12.8	L
	361015	44	Female	SCREEN	12	15.6	9.6	18.72	g/dL	14.3	N
				WEEK 24	12	15.6	9.6	18.72	g/dL	16	H
					12	15.6	9.6	18.72	g/dL	14.6	N
	361035	42	Female	SCREEN	12	15.6	9.6	18.72	g/dL	11.6	L
				WEEK 24	12	15.6	9.6	18.72	g/dL	11.6	L
	361051	47	Female	SCREEN	12	15.6	9.6	18.72	g/dL	10.9	L
				WEEK 24	12	15.6	9.6	18.72	g/dL	11	L

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Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Hemoglobin	361056	50	Female	SCREEN	12	15.6	9.6	18.72	g/dL	13	N
				WEEK 24	12	15.6	9.6	18.72	g/dL	11.1	L
					12	15.6	9.6	18.72	g/dL	13.9	N
	361068	51	Male	SCREEN	13.8	17.2	11.04	20.64	g/dL	14.3	N
				WEEK 24	13.8	17.2	11.04	20.64	g/dL	13.6	L
					13.8	17.2	11.04	20.64	g/dL	14.4	N
				WEEK 72	13.8	17.2	11.04	20.64	g/dL	14.6	N
Lymphocytes	31030	55	Male	SCREEN	16	46	12.8	55.2	%	50.6	H
				WEEK 24	16	46	12.8	55.2	%	49.3	H
				WEEK 72	16	46	12.8	55.2	%	46.6	H
				WEEK 96	16	46	12.8	55.2	%	46.4	H
	41009	41	Female	SCREEN	16	46	12.8	55.2	%	32.9	N
				WEEK 24	16	46	12.8	55.2	%	49.4	H
					16	46	12.8	55.2	%	33.3	N
	41021	64	Female	SCREEN	16	46	12.8	55.2	%	23.9	N
				WEEK 24	16	46	12.8	55.2	%	37.5	N
				WEEK 72	16	46	12.8	55.2	%	25	N
				WEEK 96	16	46	12.8	55.2	%	13.8	L
	51047	44	Female	WEEK 24	16	46	12.8	55.2	%	14	L
					16	46	12.8	55.2	%	23.7	N
				WEEK 72	16	46	12.8	55.2	%	20.3	N
				WEEK 96	16	46	12.8	55.2	%	21.7	N
				WEEK 120	16	46	12.8	55.2	%	16.1	N
	151038	49	Male	SCREEN	16	46	12.8	55.2	%	12	L
				WEEK 24	16	46	12.8	55.2	%	17.1	N

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Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Lymphocytes	181031	58	Male	SCREEN	16	46	12.8	55.2	%	26.1	N
				WEEK 24	16	46	12.8	55.2	%	14.4	L
					16	46	12.8	55.2	%	19.6	N
				WEEK 72	16	46	12.8	55.2	%	31	N
				WEEK 96	16	46	12.8	55.2	%	16.6	N
	281022	54	Female	SCREEN	16	46	12.8	55.2	%	24.6	N
				WEEK 24	16	46	12.8	55.2	%	15.1	L
					16	46	12.8	55.2	%	16	N
	361056	50	Female	SCREEN	16	46	12.8	55.2	%	12	L
				WEEK 24	16	46	12.8	55.2	%	24.7	N
MCV	131043	40	Female	SCREEN	80	100	64	120	fL	78	L
				WEEK 24	80	100	64	120	fL	76	L
	281011	40	Female	SCREEN	80	100	64	120	fL	102	H
Neutrophils	31030	55	Male	SCREEN	40	75	32	90	%	38.1	L
				WEEK 24	40	75	32	90	%	39.1	L
				WEEK 72	40	75	32	90	%	42.6	N
				WEEK 96	40	75	32	90	%	44.1	N
	41009	41	Female	SCREEN	40	75	32	90	%	44.4	N
				WEEK 24	40	75	32	90	%	35.9	L
					40	75	32	90	%	50.5	N
	41021	64	Female	SCREEN	40	75	32	90	%	66.8	N
				WEEK 24	40	75	32	90	%	54.1	N
				WEEK 72	40	75	32	90	%	65	N
				WEEK 96	40	75	32	90	%	79	H

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LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
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Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Neutrophils	51047	44	Female	WEEK 24	40	75	32	90	%	77	H
					40	75	32	90	%	71.2	N
				WEEK 72	40	75	32	90	%	72.1	N
				WEEK 96	40	75	32	90	%	70.8	N
				WEEK 120	40	75	32	90	%	77.1	H
	131032	34	Female	SCREEN	40	75	32	90	%	76.3	H
				WEEK 24	40	75	32	90	%	76.6	H
					40	75	32	90	%	74.6	N
	151038	49	Male	SCREEN	40	75	32	90	%	80	H
				WEEK 24	40	75	32	90	%	72.1	N
	181031	58	Male	SCREEN	40	75	32	90	%	65.5	N
				WEEK 24	40	75	32	90	%	82.4	H
					40	75	32	90	%	72.3	N
				WEEK 72	40	75	32	90	%	60.8	N
				WEEK 96	40	75	32	90	%	77.1	H
	281022	54	Female	SCREEN	40	75	32	90	%	67.4	N
				WEEK 24	40	75	32	90	%	76.4	H
					40	75	32	90	%	72.7	N
	361056	50	Female	SCREEN	40	75	32	90	%	80.6	H
				WEEK 24	40	75	32	90	%	68.8	N
Platelet Count	31058	44	Female	SCREEN	130000	400000	104000	480000	per/cumm	422000	H
				WEEK 24	130000	400000	104000	480000	per/cumm	309000	N
	41019	57	Female	SCREEN	130000	400000	104000	480000	per/cumm	396000	N
				WEEK 24	130000	400000	104000	480000	per/cumm	445000	H
				WEEK 72	130000	400000	104000	480000	per/cumm	414000	H

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Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
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Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Platelet Count	41019	57	Female	WEEK 96	130000	400000	104000	480000	per/cumm	485000	H
				WEEK 120	130000	400000	104000	480000	per/cumm	423000	H
	151034	49	Female	SCREEN	130000	400000	104000	480000	per/cumm	416000	H
				WEEK 24	130000	400000	104000	480000	per/cumm	413000	H
					130000	400000	104000	480000	per/cumm	380000	N
	211010	53	Female	SCREEN	130000	400000	104000	480000	per/cumm	427000	H
				WEEK 24	130000	400000	104000	480000	per/cumm	475000	H
				WEEK 72	130000	400000	104000	480000	per/cumm	383000	N
				WEEK 96	130000	400000	104000	480000	per/cumm	405000	H
				WEEK 120	130000	400000	104000	480000	per/cumm	416000	H
	211020	43	Male	SCREEN	130000	400000	104000	480000	per/cumm	320000	N
				WEEK 24	130000	400000	104000	480000	per/cumm	439000	H
					130000	400000	104000	480000	per/cumm	349000	N
	231039	36	Female	SCREEN	130000	400000	104000	480000	per/cumm	405000	H
				WEEK 24	130000	400000	104000	480000	per/cumm	437000	H
					130000	400000	104000	480000	per/cumm	389000	N
	361057	35	Female	SCREEN	130000	400000	104000	480000	per/cumm	394000	N
				WEEK 24	130000	400000	104000	480000	per/cumm	403000	H
Reticulocytes, Count	41009	41	Female	SCREEN	0.8	3.5	0.64	4.2	%	0.9	N
				WEEK 24	0.8	3.5	0.64	4.2	%	0.5	L
					0.8	3.5	0.64	4.2	%	1.2	N
	41021	64	Female	SCREEN	0.8	3.5	0.64	4.2	%	1.1	N
				WEEK 24	0.8	3.5	0.64	4.2	%	1.2	N
				WEEK 72	0.8	3.5	0.64	4.2	%	1.3	N
				WEEK 96	0.8	3.5	0.64	4.2	%	0.6	L

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LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
Reticulocytes, Count	181026	32	Male	SCREEN	0.8	3.5	0.64	4.2	%	2.8	N
				WEEK 24	0.8	3.5	0.64	4.2	%	3.6	H
					0.8	3.5	0.64	4.2	%	3.3	N
				WEEK 72	0.8	3.5	0.64	4.2	%	3.9	H
				WEEK 96	0.8	3.5	0.64	4.2	%	4.9	H
	181050	55	Female	SCREEN	0.8	3.5	0.64	4.2	%	4.1	H
				WEEK 24	0.8	3.5	0.64	4.2	%	5.2	H
					0.8	3.5	0.64	4.2	%	3.4	N
	281022	54	Female	SCREEN	0.8	3.5	0.64	4.2	%	4.3	H
				WEEK 24	0.8	3.5	0.64	4.2	%	4.1	H
					0.8	3.5	0.64	4.2	%	3.5	N
	361014	40	Female	SCREEN	0.8	3.5	0.64	4.2	%	1.1	N
				WEEK 24	0.8	3.5	0.64	4.2	%	0.7	L
					0.8	3.5	0.64	4.2	%	1	N
	361065	50	Male	SCREEN	0.8	3.5	0.64	4.2	%	3.7	H
				WEEK 24	0.8	3.5	0.64	4.2	%	4	H
					0.8	3.5	0.64	4.2	%	2.9	N
WBC	31030	55	Male	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	3.7	L
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	3.4	L
					3.8	10.8	3.04	12.96	thou/mcL	4.2	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	3.8	N
				WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	3.5	L
	41019	57	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	11	H
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	12	H
					3.8	10.8	3.04	12.96	thou/mcL	10.6	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	9.7	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: hema_out.sas

LISTING 3.2.1
Hematology Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Units	Assay Value	Assay Flag
WBC	41019	57	Female	WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	10.3	N
				WEEK 120	3.8	10.8	3.04	12.96	thou/mcL	11.4	H
	41021	64	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	5.6	N
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	5.2	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	3.7	L
				WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	5.7	N
	81005	43	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	4.8	N
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	3.2	L
	151038	49	Male	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	11.9	H
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	8.5	N
	211010	53	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	11.6	H
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	10.7	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	11.7	H
				WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	10.1	N
				WEEK 120	3.8	10.8	3.04	12.96	thou/mcL	9.8	N
	281011	40	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	3.6	L
	281013	44	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	5.8	N
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	3.7	L
					3.8	10.8	3.04	12.96	thou/mcL	4.9	N
				WEEK 72	3.8	10.8	3.04	12.96	thou/mcL	4.4	N
				WEEK 96	3.8	10.8	3.04	12.96	thou/mcL	4.9	N
				WEEK 120	3.8	10.8	3.04	12.96	thou/mcL	4.4	N
	361014	40	Female	SCREEN	3.8	10.8	3.04	12.96	thou/mcL	3.9	N
				WEEK 24	3.8	10.8	3.04	12.96	thou/mcL	3.5	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
ALT/SGPT	131033	45	Male	SCREEN	0	48	0	57.6	U/L	71	H
				WEEK 24	0	48	0	57.6	U/L	47	N
				WEEK 72	0	48	0	57.6	U/L	37	N
				WEEK FINAL	0	48	0	57.6	U/L	48	N
	151018	60	Male	WEEK 24	0	48	0	57.6	U/L	28	N
				WEEK 72	0	48	0	57.6	U/L	67	H
				WEEK FINAL	0	48	0	57.6	U/L	49	H
	231039	36	Female	SCREEN	0	48	0	57.6	U/L	19	N
				WEEK 24	0	48	0	57.6	U/L	39	N
				WEEK FINAL	0	48	0	57.6	U/L	69	H
	361017	60	Male	SCREEN	0	48	0	57.6	U/L	65	H
				WEEK 24	0	48	0	57.6	U/L	46	N
				WEEK 72	0	48	0	57.6	U/L	31	N
				WEEK 96	0	48	0	57.6	U/L	30	N
				WEEK 120	0	48	0	57.6	U/L	30	N
				WEEK FINAL	0	48	0	57.6	U/L	31	N
AST/SGOT	361017	60	Male	SCREEN	0	42	0	50.4	U/L	45	H
				WEEK 24	0	42	0	50.4	U/L	34	N
				WEEK 72	0	42	0	50.4	U/L	30	N
				WEEK 96	0	42	0	50.4	U/L	26	N
				WEEK 120	0	42	0	50.4	U/L	27	N
				WEEK FINAL	0	42	0	50.4	U/L	31	N
Alkaline Phosphatase (ALP)	131032	34	Female	SCREEN	20	125	16	150	U/L	105	N
				WEEK 24	20	125	16	150	U/L	108	N
				WEEK 72	20	125	16	150	U/L	112	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Alkaline Phosphatase (ALP)	131032	34	Female	WEEK FINAL	20	125	16	150	U/L	126	H
	211010	53	Female	SCREEN	20	125	16	150	U/L	150	H
				WEEK 24	20	125	16	150	U/L	138	H
				WEEK 72	20	125	16	150	U/L	142	H
				WEEK 96	20	125	16	150	U/L	150	H
				WEEK 120	20	125	16	150	U/L	138	H
	361017	60	Male	SCREEN	20	125	16	150	U/L	127	H
				WEEK 24	20	125	16	150	U/L	129	H
					20	125	16	150	U/L	122	N
				WEEK 72	20	125	16	150	U/L	130	H
				WEEK 96	20	125	16	150	U/L	132	H
				WEEK 120	20	125	16	150	U/L	129	H
				WEEK FINAL	20	125	16	150	U/L	140	H
Bilirubin, Total	281013	44	Female	SCREEN	0	1.3	0	1.56	mg/dL	0.6	N
				WEEK 24	0	1.3	0	1.56	mg/dL	1	N
				WEEK 72	0	1.3	0	1.56	mg/dL	1.4	H
				WEEK 96	0	1.3	0	1.56	mg/dL	0.5	N
				WEEK 120	0	1.3	0	1.56	mg/dL	0.9	N
				WEEK FINAL	0	1.3	0	1.56	mg/dL	0.4	N
	361068	51	Male	SCREEN	0	1.3	0	1.56	mg/dL	1.7	H
				WEEK 24	0	1.3	0	1.56	mg/dL	1.2	N
				WEEK 72	0	1.3	0	1.56	mg/dL	1.1	N
	361069	55	Male	SCREEN	0	1.3	0	1.56	mg/dL	1.5	H
				WEEK FINAL	0	1.3	0	1.56	mg/dL	1.4	H

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
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Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Blood Urea Nitrogen (BUN)	181026	32	Male	SCREEN	7	25	5.6	30	mg/dL	18	N
				WEEK 24	7	25	5.6	30	mg/dL	24	N
				WEEK 72	7	25	5.6	30	mg/dL	29	H
				WEEK 96	7	25	5.6	30	mg/dL	28	H
				WEEK FINAL	7	25	5.6	30	mg/dL	17	N
Carbon Dioxide (CO2)	281013	44	Female	SCREEN	20	32	16	38.4	mEq/L	25	N
				WEEK 24	20	32	16	38.4	mEq/L	23	N
				WEEK 72	20	32	16	38.4	mEq/L	23	N
				WEEK 96	20	32	16	38.4	mEq/L	27	N
				WEEK 120	20	32	16	38.4	mEq/L	17	L
				WEEK FINAL	20	32	16	38.4	mEq/L	23	N
	361051	47	Female	SCREEN	20	32	16	38.4	mEq/L	21	N
				WEEK 24	20	32	16	38.4	mEq/L	24	N
				WEEK FINAL	20	32	16	38.4	mEq/L	19	L
	361069	55	Male	SCREEN	20	32	16	38.4	mEq/L	27	N
				WEEK FINAL	20	32	16	38.4	mEq/L	33	H
Chloride	31004	45	Male	SCREEN	95	108	76	129.6	mEq/L	106	N
				WEEK 24	95	108	76	129.6	mEq/L	107	N
				WEEK 72	95	108	76	129.6	mEq/L	109	H
					95	108	76	129.6	mEq/L	107	N
	31058	44	Female	SCREEN	95	108	76	129.6	mEq/L	104	N
				WEEK 24	95	108	76	129.6	mEq/L	109	H
					95	108	76	129.6	mEq/L	107	N
				WEEK FINAL	95	108	76	129.6	mEq/L	107	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Chloride	131033	45	Male	SCREEN	95	108	76	129.6	mEq/L	108	N
				WEEK 24	95	108	76	129.6	mEq/L	111	H
					95	108	76	129.6	mEq/L	106	N
				WEEK 72	95	108	76	129.6	mEq/L	106	N
				WEEK FINAL	95	108	76	129.6	mEq/L	107	N
	151018	60	Male	WEEK 24	95	108	76	129.6	mEq/L	105	N
				WEEK 72	95	108	76	129.6	mEq/L	108	N
				WEEK FINAL	95	108	76	129.6	mEq/L	109	H
	181031	58	Male	SCREEN	95	108	76	129.6	mEq/L	111	H
				WEEK 24	95	108	76	129.6	mEq/L	102	N
				WEEK 72	95	108	76	129.6	mEq/L	102	N
				WEEK 96	95	108	76	129.6	mEq/L	103	N
				WEEK FINAL	95	108	76	129.6	mEq/L	101	N
	281011	40	Female	SCREEN	95	108	76	129.6	mEq/L	109	H
				WEEK FINAL	95	108	76	129.6	mEq/L	106	N
	361035	42	Female	SCREEN	95	108	76	129.6	mEq/L	107	N
				WEEK 24	95	108	76	129.6	mEq/L	109	H
					95	108	76	129.6	mEq/L	107	N
	361056	50	Female	SCREEN	95	108	76	129.6	mEq/L	105	N
				WEEK 24	95	108	76	129.6	mEq/L	106	N
				WEEK 72	95	108	76	129.6	mEq/L	107	N
				WEEK FINAL	95	108	76	129.6	mEq/L	109	H
Creatinine	31058	44	Female	SCREEN	0.5	1.4	0.4	1.68	mg/dL	0.6	N
				WEEK 24	0.5	1.4	0.4	1.68	mg/dL	0.6	N
				WEEK FINAL	0.5	1.4	0.4	1.68	mg/dL	0.4	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Creatinine	281011	40	Female	SCREEN	0.5	1.4	0.4	1.68	mg/dL	0.4	L
				WEEK FINAL	0.5	1.4	0.4	1.68	mg/dL	0.5	N
	281022	54	Female	SCREEN	0.5	1.4	0.4	1.68	mg/dL	0.4	L
				WEEK 24	0.5	1.4	0.4	1.68	mg/dL	0.4	L
					0.5	1.4	0.4	1.68	mg/dL	0.5	N
				WEEK 72	0.5	1.4	0.4	1.68	mg/dL	0.5	N
				WEEK FINAL	0.5	1.4	0.4	1.68	mg/dL	0.5	N
Glucose	31004	45	Male	SCREEN	70	115	56	138	mg/dL	113	N
				WEEK 24	70	115	56	138	mg/dL	102	N
				WEEK 72	70	115	56	138	mg/dL	126	H
					70	115	56	138	mg/dL	63	L
	31030	55	Male	SCREEN	70	125	56	150	mg/dL	89	N
				WEEK 24	70	125	56	150	mg/dL	64	L
					70	125	56	150	mg/dL	87	N
				WEEK 72	70	125	56	150	mg/dL	67	L
					70	125	56	150	mg/dL	91	N
				WEEK 96	70	125	56	150	mg/dL	85	N
	41009	41	Female	SCREEN	70	115	56	138	mg/dL	81	N
				WEEK 24	70	115	56	138	mg/dL	122	H
					70	115	56	138	mg/dL	87	N
				WEEK 72	70	115	56	138	mg/dL	85	N
	41019	57	Female	SCREEN	70	125	56	150	mg/dL	94	N
				WEEK 24	70	125	56	150	mg/dL	89	N
				WEEK 72	70	125	56	150	mg/dL	78	N
				WEEK 96	70	125	56	150	mg/dL	131	H
				WEEK 120	70	125	56	150	mg/dL	98	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Glucose	81040	37	Female	SCREEN	70	115	56	138	mg/dL	123	H
				WEEK 24	70	115	56	138	mg/dL	93	N
				WEEK 72	70	115	56	138	mg/dL	105	N
	81045	23	Female	SCREEN	70	115	56	138	mg/dL	147	H
				WEEK 24	70	115	56	138	mg/dL	129	H
					70	115	56	138	mg/dL	93	N
	101002	31	Female	WEEK 24	70	115	56	138	mg/dL	116	H
					70	115	56	138	mg/dL	92	N
				WEEK FINAL	70	115	56	138	mg/dL	52	L
	121003	33	Female	SCREEN	70	115	56	138	mg/dL	88	N
				WEEK 24	70	115	56	138	mg/dL	137	H
					70	115	56	138	mg/dL	85	N
				WEEK FINAL	70	115	56	138	mg/dL	79	N
	131033	45	Male	SCREEN	70	115	56	138	mg/dL	90	N
				WEEK 24	70	115	56	138	mg/dL	141	H
					70	115	56	138	mg/dL	89	N
				WEEK 72	70	115	56	138	mg/dL	103	N
				WEEK FINAL	70	115	56	138	mg/dL	91	N
	151034	49	Female	SCREEN	70	115	56	138	mg/dL	123	H
				WEEK 24	70	115	56	138	mg/dL	100	N
				WEEK 72	70	125	56	150	mg/dL	101	N
				WEEK FINAL	70	125	56	150	mg/dL	89	N
	151038	49	Male	SCREEN	70	115	56	138	mg/dL	111	N
				WEEK 24	70	115	56	138	mg/dL	116	H

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Glucose	181031	58	Male	SCREEN	70	125	56	150	mg/dL	86	N
				WEEK 24	70	125	56	150	mg/dL	108	N
				WEEK 72	70	125	56	150	mg/dL	103	N
				WEEK 96	70	125	56	150	mg/dL	50	L
				WEEK FINAL	70	125	56	150	mg/dL	84	N
	181050	55	Female	SCREEN	70	125	56	150	mg/dL	112	N
				WEEK 24	70	125	56	150	mg/dL	137	H
					70	125	56	150	mg/dL	114	N
	211020	43	Male	SCREEN	70	115	56	138	mg/dL	95	N
				WEEK 24	70	115	56	138	mg/dL	120	H
					70	115	56	138	mg/dL	95	N
				WEEK FINAL	70	115	56	138	mg/dL	76	N
	221055	45	Male	WEEK 24	70	115	56	138	mg/dL	59	L
					70	115	56	138	mg/dL	83	N
	231024	57	Female	SCREEN	70	125	56	150	mg/dL	91	N
				WEEK 24	70	125	56	150	mg/dL	80	N
				WEEK 72	70	125	56	150	mg/dL	102	N
				WEEK FINAL	70	125	56	150	mg/dL	150	H
	281011	40	Female	SCREEN	70	115	56	138	mg/dL	68	L
				WEEK FINAL	70	115	56	138	mg/dL	68	L
	281013	44	Female	SCREEN	70	115	56	138	mg/dL	87	N
				WEEK 24	70	115	56	138	mg/dL	88	N
				WEEK 72	70	115	56	138	mg/dL	78	N
				WEEK 96	70	115	56	138	mg/dL	72	N
				WEEK 120	70	115	56	138	mg/dL	58	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Glucose	281013	44	Female	WEEK FINAL	70	115	56	138	mg/dL	118	H
	321044	55	Male	SCREEN	70	125	56	150	mg/dL	103	N
				WEEK FINAL	70	125	56	150	mg/dL	138	H
	361017	60	Male	SCREEN	70	125	56	150	mg/dL	98	N
				WEEK 24	70	125	56	150	mg/dL	134	H
					70	125	56	150	mg/dL	100	N
				WEEK 72	70	125	56	150	mg/dL	77	N
				WEEK 96	70	125	56	150	mg/dL	105	N
				WEEK 120	70	125	56	150	mg/dL	59	L
				WEEK FINAL	70	125	56	150	mg/dL	94	N
	361027	55	Female	SCREEN	70	125	56	150	mg/dL	97	N
				WEEK 24	70	125	56	150	mg/dL	166	H
	361059	35	Female	SCREEN	70	115	56	138	mg/dL	68	L
				WEEK 24	70	115	56	138	mg/dL	73	N
				WEEK 72	70	115	56	138	mg/dL	69	L
	361061	38	Male	SCREEN	70	115	56	138	mg/dL	143	H
				WEEK FINAL	70	115	56	138	mg/dL	80	N
	361062	40	Female	SCREEN	70	115	56	138	mg/dL	84	N
				WEEK 24	70	115	56	138	mg/dL	81	N
				WEEK 72	70	115	56	138	mg/dL	48	L
					70	115	56	138	mg/dL	79	N
				WEEK FINAL	70	115	56	138	mg/dL	94	N
	361064	46	Female	SCREEN	70	115	56	138	mg/dL	92	N
				WEEK 24	70	115	56	138	mg/dL	63	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Glucose	361064	46	Female	WEEK 24	70	115	56	138	mg/dL	88	N
				WEEK FINAL	70	115	56	138	mg/dL	76	N
	361065	50	Male	SCREEN	70	125	56	150	mg/dL	86	N
				WEEK 24	70	125	56	150	mg/dL	67	L
					70	125	56	150	mg/dL	76	N
	361066	57	Female	SCREEN	70	125	56	150	mg/dL	80	N
				WEEK 24	70	125	56	150	mg/dL	75	N
				WEEK FINAL	70	125	56	150	mg/dL	50	L
	361068	51	Male	SCREEN	70	125	56	150	mg/dL	79	N
				WEEK 24	70	125	56	150	mg/dL	64	L
					70	125	56	150	mg/dL	87	N
				WEEK 72	70	125	56	150	mg/dL	47	L
Potassium	41021	64	Female	SCREEN	3.5	5.3	2.8	6.36	mEq/L	4.2	N
				WEEK 24	3.5	5.3	2.8	6.36	mEq/L	5.7	H
					3.5	5.3	2.8	6.36	mEq/L	4.4	N
				WEEK 72	3.5	5.3	2.8	6.36	mEq/L	4.1	N
				WEEK 96	3.5	5.3	2.8	6.36	mEq/L	4.6	N
	151018	60	Male	WEEK 24	3.5	5.3	2.8	6.36	mEq/L	4.5	N
				WEEK 72	3.5	5.3	2.8	6.36	mEq/L	3.4	L
				WEEK FINAL	3.5	5.3	2.8	6.36	mEq/L	4.4	N
	181026	32	Male	SCREEN	3.5	5.3	2.8	6.36	mEq/L	4.4	N
				WEEK 24	3.5	5.3	2.8	6.36	mEq/L	5.4	H
					3.5	5.3	2.8	6.36	mEq/L	4.9	N
				WEEK 72	3.5	5.3	2.8	6.36	mEq/L	4.9	N
				WEEK 96	3.5	5.3	2.8	6.36	mEq/L	4.3	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Potassium	181026	32	Male	WEEK FINAL	3.5	5.3	2.8	6.36	mEq/L	4.5	N
	231024	57	Female	SCREEN	3.5	5.3	2.8	6.36	mEq/L	4.3	N
				WEEK 24	3.5	5.3	2.8	6.36	mEq/L	5.4	H
					3.5	5.3	2.8	6.36	mEq/L	4.3	N
				WEEK 72	3.5	5.3	2.8	6.36	mEq/L	4.3	N
				WEEK FINAL	3.5	5.3	2.8	6.36	mEq/L	4.6	N
	281022	54	Female	SCREEN	3.5	5.3	2.8	6.36	mEq/L	3.6	N
				WEEK 24	3.5	5.3	2.8	6.36	mEq/L	2.9	L
					3.5	5.3	2.8	6.36	mEq/L	3.5	N
				WEEK 72	3.5	5.3	2.8	6.36	mEq/L	3.5	N
				WEEK FINAL	3.5	5.3	2.8	6.36	mEq/L	3.5	N
	361035	42	Female	SCREEN	3.5	5.3	2.8	6.36	mEq/L	3.7	N
				WEEK 24	3.5	5.3	2.8	6.36	mEq/L	3.4	L
					3.5	5.3	2.8	6.36	mEq/L	3.9	N
Sodium (Na)	81001	66	Female	SCREEN	135	146	108	175.2	mEq/L	137	N
				WEEK 24	135	146	108	175.2	mEq/L	134	L
				WEEK FINAL	135	146	108	175.2	mEq/L	135	N
	131043	40	Female	SCREEN	135	146	108	175.2	mEq/L	140	N
				WEEK 24	135	146	108	175.2	mEq/L	139	N
				WEEK FINAL	135	146	108	175.2	mEq/L	132	L
	151018	60	Male	WEEK 24	135	146	108	175.2	mEq/L	142	N
				WEEK 72	135	146	108	175.2	mEq/L	143	N
				WEEK FINAL	135	146	108	175.2	mEq/L	147	H
	181026	32	Male	SCREEN	135	146	108	175.2	mEq/L	143	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Sodium (Na)	181026	32	Male	WEEK 24	135	146	108	175.2	mEq/L	140	N
				WEEK 72	135	146	108	175.2	mEq/L	137	N
				WEEK 96	135	146	108	175.2	mEq/L	140	N
				WEEK FINAL	135	146	108	175.2	mEq/L	134	L
	361035	42	Female	SCREEN	135	146	108	175.2	mEq/L	143	N
				WEEK 24	135	146	108	175.2	mEq/L	147	H
					135	146	108	175.2	mEq/L	144	N
T4	361017	60	Male	SCREEN	4.5	12.5	3.6	15	mcg/dL	4.4	L
TSH	361066	57	Female	SCREEN	0.4	5.5	0.32	6.6	mcIU/mL	0.1	L
Uric Acid	31030	55	Male	SCREEN	4	8.5	3.2	10.2	mg/dL	4.1	N
				WEEK 24	4	8.5	3.2	10.2	mg/dL	3.9	L
					4	8.5	3.2	10.2	mg/dL	4	N
				WEEK 72	4	8.5	3.2	10.2	mg/dL	3.8	L
					4	8.5	3.2	10.2	mg/dL	4	N
				WEEK 96	4	8.5	3.2	10.2	mg/dL	4.2	N
	81001	66	Female	SCREEN	2.5	7.5	2	9	mg/dL	2.3	L
				WEEK 24	2.5	7.5	2	9	mg/dL	2.7	N
				WEEK FINAL	2.5	7.5	2	9	mg/dL	5.4	N
	81005	43	Female	SCREEN	2.5	7.5	2	9	mg/dL	2.3	L
				WEEK 24	2.5	7.5	2	9	mg/dL	2.9	N
	81016	48	Female	SCREEN	2.5	7.5	2	9	mg/dL	1.7	L
				WEEK FINAL	2.5	7.5	2	9	mg/dL	2.2	L
	151018	60	Male	WEEK 24	4	8.5	3.2	10.2	mg/dL	4.7	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Uric Acid	151018	60	Male	WEEK 72	4	8.5	3.2	10.2	mg/dL	4.2	N
				WEEK FINAL	4	8.5	3.2	10.2	mg/dL	3.9	L
	151048	47	Male	SCREEN	4	8.5	3.2	10.2	mg/dL	4.4	N
				WEEK FINAL	4	8.5	3.2	10.2	mg/dL	3.9	L
	171008	52	Female	WEEK 24	2.5	7.5	2	9	mg/dL	3.7	N
				WEEK 72	2.5	7.5	2	9	mg/dL	2.2	L
					2.5	7.5	2	9	mg/dL	2.6	N
	181031	58	Male	SCREEN	4	8.5	3.2	10.2	mg/dL	5.2	N
				WEEK 24	4	8.5	3.2	10.2	mg/dL	3.8	L
					4	8.5	3.2	10.2	mg/dL	5.5	N
				WEEK 72	4	8.5	3.2	10.2	mg/dL	4.8	N
				WEEK 96	4	8.5	3.2	10.2	mg/dL	4.2	N
				WEEK FINAL	4	8.5	3.2	10.2	mg/dL	4.7	N
	211036	58	Male	SCREEN	4	8.5	3.2	10.2	mg/dL	4.9	N
				WEEK 24	4	8.5	3.2	10.2	mg/dL	3.8	L
				WEEK FINAL	4	8.5	3.2	10.2	mg/dL	3.3	L
	221055	45	Male	WEEK 24	4	8.5	3.2	10.2	mg/dL	3.6	L
					4	8.5	3.2	10.2	mg/dL	4.7	N
	271007	42	Female	SCREEN	2.5	7.5	2	9	mg/dL	3.5	N
				WEEK 24	2.5	7.5	2	9	mg/dL	3.4	N
				WEEK FINAL	2.5	7.5	2	9	mg/dL	2.2	L
	361029	35	Female	SCREEN	2.5	7.5	2	9	mg/dL	2.2	L
				WEEK 24	2.5	7.5	2	9	mg/dL	2.4	L
				WEEK FINAL	2.5	7.5	2	9	mg/dL	2.1	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

Program: seru_out.sas

LISTING 3.2.2
Serum Chemistry Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Conventional Unit	Assay Value	Assay Flag
Uric Acid	361051	47	Female	SCREEN	2.5	7.5	2	9	mg/dL	2.9	N
				WEEK 24	2.5	7.5	2	9	mg/dL	1.8	L
					2.5	7.5	2	9	mg/dL	3	N
				WEEK FINAL	2.5	7.5	2	9	mg/dL	1.9	L
	361059	35	Female	SCREEN	2.5	7.5	2	9	mg/dL	1.7	L
				WEEK 24	2.5	7.5	2	9	mg/dL	2.4	L
				WEEK 72	2.5	7.5	2	9	mg/dL	3	N
	361061	38	Male	SCREEN	4	8.5	3.2	10.2	mg/dL	3.1	L
				WEEK FINAL	4	8.5	3.2	10.2	mg/dL	4	N
	361062	40	Female	SCREEN	2.5	7.5	2	9	mg/dL	2.2	L
				WEEK 24	2.5	7.5	2	9	mg/dL	2.3	L
					2.5	7.5	2	9	mg/dL	2.5	N
				WEEK 72	2.5	7.5	2	9	mg/dL	2.8	N
				WEEK FINAL	2.5	7.5	2	9	mg/dL	2.5	N
	361063	45	Female	SCREEN	2.5	7.5	2	9	mg/dL	3.6	N
				WEEK 24	2.5	7.5	2	9	mg/dL	2.4	L
				WEEK FINAL	2.5	7.5	2	9	mg/dL	3.2	N
	361064	46	Female	SCREEN	2.5	7.5	2	9	mg/dL	2.7	N
				WEEK 24	2.5	7.5	2	9	mg/dL	2.2	L
					2.5	7.5	2	9	mg/dL	2.9	N
				WEEK FINAL	2.5	7.5	2	9	mg/dL	3.1	N
	361068	51	Male	SCREEN	4	8.5	3.2	10.2	mg/dL	3.4	L
				WEEK 24	4	8.5	3.2	10.2	mg/dL	3.8	L
				WEEK 72	4	8.5	3.2	10.2	mg/dL	3.5	L

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
'N' = Normal, 'H' = High, 'L' = Low

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Appearance	41019	57	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Clear	N
				WEEK 72	.	.	.	.	.	Clear	N
				WEEK 96	.	.	.	.	.	Clear	N
				WEEK 120	.	.	.	.	.	Hazy	A
	51047	44	Female	WEEK 24	.	.	.	.	.	Turbid	A
					.	.	.	.	.	Clear	N
				WEEK 72	.	.	.	.	.	Clear	N
				WEEK 96	.	.	.	.	.	Clear	N
				WEEK 120	.	.	.	.	.	Clear	N
	81040	37	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Hazy	A
					.	.	.	.	.	Clear	N
				WEEK 72	.	.	.	.	.	Clear	N
	131032	34	Female	SCREEN	.	.	.	.	.	Hazy	A
				WEEK 24	.	.	.	.	.	Hazy	A
					.	.	.	.	.	Clear	N
	131033	45	Male	SCREEN	.	.	.	.	.	Hazy	A
				WEEK 24	.	.	.	.	.	Clear	N
	211010	53	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Clear	N
				WEEK 72	.	.	.	.	.	Cloudy	A
				WEEK 96	.	.	.	.	.	Hazy	A
				WEEK 120	.	.	.	.	.	Clear	N
	281011	40	Female	SCREEN	.	.	.	.	.	Hazy	A

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Appearance	281013	44	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Cloudy	A
					.	.	.	.	.	Clear	N
				WEEK 72	.	.	.	.	.	Cloudy	A
				WEEK 96	.	.	.	.	.	Clear	N
				WEEK 120	.	.	.	.	.	Clear	N
	281022	54	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Cloudy	A
					.	.	.	.	.	Clear	N
	361014	40	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Hazy	A
					.	.	.	.	.	Clear	N
	361015	44	Female	SCREEN	.	.	.	.	.	Hazy	A
				WEEK 24	.	.	.	.	.	Cloudy	A
					.	.	.	.	.	Clear	N
	361017	60	Male	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Hazy	A
					.	.	.	.	.	Clear	N
				WEEK 72	.	.	.	.	.	Clear	N
				WEEK 96	.	.	.	.	.	Clear	N
				WEEK 120	.	.	.	.	.	Turbid	A
	361027	55	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Cloudy	A
	361029	35	Female	SCREEN	.	.	.	.	.	Hazy	A
				WEEK 24	.	.	.	.	.	Cloudy	A

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Appearance	361035	42	Female	SCREEN	.	.	.	.	.	Cloudy	A
				WEEK 24	.	.	.	.	.	Clear	N
	361056	50	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Turbid	A
					.	.	.	.	.	Clear	N
	361057	35	Female	SCREEN	.	.	.	.	.	Cloudy	A
				WEEK 24	.	.	.	.	.	Clear	N
	361059	35	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Cloudy	A
				WEEK 72	.	.	.	.	.	Clear	N
	361064	46	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Cloudy	A
					.	.	.	.	.	Clear	N
	361066	57	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Cloudy	A
	361067	55	Female	SCREEN	.	.	.	.	.	Clear	N
				WEEK 24	.	.	.	.	.	Cloudy	A
Bilirubin, Qual	131032	34	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	1+	A
					.	.	.	.	.	Negative	N
Blood	31030	55	Male	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.
Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Blood	31030	55	Male	WEEK 96	.	.	.	.	.	1+	A
	41009	41	Female	SCREEN	.	.	.	.	.	Trace	A
				WEEK 24	.	.	.	.	.	2+	A
					.	.	.	.	.	Negative	N
	121003	33	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
	131032	34	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	1+	A
					.	.	.	.	.	Negative	N
	151034	49	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
	281011	40	Female	SCREEN	.	.	.	.	.	3+	A
	281013	44	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
				WEEK 96	.	.	.	.	.	Negative	N
				WEEK 120	.	.	.	.	.	Negative	N
	361035	42	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	3+	A
					.	.	.	.	.	Negative	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Blood	361056	50	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	3+	A
					.	.	.	.	.	Negative	N
Color	31004	45	Male	SCREEN	.	.	.	.	.	Yellow	N
				WEEK 24	.	.	.	.	.	Yellow	N
				WEEK 72	.	.	.	.	.	Dark yellow	A
	181026	32	Male	SCREEN	.	.	.	.	.	Yellow	N
				WEEK 24	.	.	.	.	.	Yellow	N
				WEEK 72	.	.	.	.	.	Yellow	N
				WEEK 96	.	.	.	.	.	Dark yellow	A
	281022	54	Female	SCREEN	.	.	.	.	.	Yellow	N
				WEEK 24	.	.	.	.	.	Dark yellow	A
					.	.	.	.	.	Yellow	N
	361056	50	Female	SCREEN	.	.	.	.	.	Yellow	N
				WEEK 24	.	.	.	.	.	Red	A
					.	.	.	.	.	Yellow	N
	361064	46	Female	SCREEN	.	.	.	.	.	Yellow	N
				WEEK 24	.	.	.	.	.	Dark yellow	A
					.	.	.	.	.	Yellow	N
	361065	50	Male	SCREEN	.	.	.	.	.	Dark yellow	A
				WEEK 24	.	.	.	.	.	Yellow	N
	361068	51	Male	SCREEN	.	.	.	.	.	Yellow	N
				WEEK 24	.	.	.	.	.	Dark yellow	A
					.	.	.	.	.	Yellow	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Color	361068	51	Male	WEEK 72	.	.	.	.	.	Yellow	N
Glucose, Qual	41009	41	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace or 1/10 g/dl (	A
					.	.	.	.	.	Negative	N
	81045	23	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	1+ or 1/4 g/dl (%)	A
					.	.	.	.	.	Negative	N
Ketones	31004	45	Male	SCREEN	.	.	.	.	.	Trace	A
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
	81040	37	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	2+	A
					.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
	131032	34	Female	SCREEN	.	.	.	.	.	Trace	A
				WEEK 24	.	.	.	.	.	2+	A
					.	.	.	.	.	Negative	N
	211036	58	Male	SCREEN	.	.	.	.	.	1+	A
				WEEK 24	.	.	.	.	.	Negative	N
	361017	60	Male	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
				WEEK 96	.	.	.	.	.	Negative	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Ketones	361017	60	Male	WEEK 120	.	.	.	.	.	Trace	A
	361035	42	Female	SCREEN	.	.	.	.	.	2+	A
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
	361066	57	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
Leukocyte Esterase Strip	31004	45	Male	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
	31058	44	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
	41019	57	Female	SCREEN	.	.	.	.	.	1+	A
				WEEK 24	.	.	.	.	.	2+	A
					.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
				WEEK 96	.	.	.	.	.	Negative	N
				WEEK 120	.	.	.	.	.	1+	A
	41021	64	Female	SCREEN	.	.	.	.	.	1+	A
				WEEK 24	.	.	.	.	.	2+	A
				WEEK 72	.	.	.	.	.	1+	A
				WEEK 96	.	.	.	.	.	1+	A

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Leukocyte Esterase Strip	81045	23	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	1+	A
					.	.	.	.	.	Negative	N
	211010	53	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Trace	A
				WEEK 96	.	.	.	.	.	Negative	N
				WEEK 120	.	.	.	.	.	Negative	N
	231025	54	Female	WEEK 24	.	.	.	.	.	1+	A
	281013	44	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	3+	A
				WEEK 72	.	.	.	.	.	2+	A
				WEEK 96	.	.	.	.	.	Trace	A
				WEEK 120	.	.	.	.	.	2+	A
	361029	35	Female	SCREEN	.	.	.	.	.	2+	A
				WEEK 24	.	.	.	.	.	1+	A
	361035	42	Female	SCREEN	.	.	.	.	.	2+	A
				WEEK 24	.	.	.	.	.	Negative	N
	361056	50	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	1+	A
					.	.	.	.	.	Negative	N
	361059	35	Female	SCREEN	.	.	.	.	.	Negative	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Leukocyte Esterase Strip	361059	35	Female	WEEK 24	.	.	.	.	.	1+	A
				WEEK 72	.	.	.	.	.	1+	A
	361066	57	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
Protein, Qual	11054	61	Male	WEEK 24	.	.	.	.	.	Trace	A
	31030	55	Male	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
				WEEK 96	.	.	.	.	.	Trace	A
	41009	41	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
	81005	43	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
	181026	32	Male	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
				WEEK 96	.	.	.	.	.	Trace	A
	281013	44	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
					.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
				WEEK 96	.	.	.	.	.	Negative	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Protein, Qual	281013	44	Female	WEEK 120	.	.	.	.	.	Negative	N
	361017	60	Male	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
				WEEK 96	.	.	.	.	.	Negative	N
				WEEK 120	.	.	.	.	.	Trace	A
	361046	20	Female	SCREEN	.	.	.	.	.	Trace	A
				WEEK 24	.	.	.	.	.		
	361056	50	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	2+	A
					.	.	.	.	.	Negative	N
	361066	57	Female	SCREEN	.	.	.	.	.	Negative	N
				WEEK 24	.	.	.	.	.	Trace	A
Specific Gravity	181026	32	Male	SCREEN	1.001	1.035	0.8008	1.242	1.025		N
				WEEK 24	1.001	1.035	0.8008	1.242	1.025		N
				WEEK 72	1.001	1.035	0.8008	1.242	1.02		N
				WEEK 96	1.001	1.035	0.8008	1.242	1.036		H
	361017	60	Male	SCREEN	1.001	1.035	0.8008	1.242	1.015		N
				WEEK 24	1.001	1.035	0.8008	1.242	1.02		N
				WEEK 72	1.001	1.035	0.8008	1.242	1.03		N
				WEEK 96	1.001	1.035	0.8008	1.242	1.011		N
				WEEK 120	1.001	1.035	0.8008	1.242	1.036		H
Urinary Nitrite, Character	281013	44	Female	SCREEN	.	.	.	.	.	Negative	N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
Urinary Nitrite, Character	281013	44	Female	WEEK 24	.	.	.	.	.	Negative	N
				WEEK 72	.	.	.	.	.	Negative	N
				WEEK 96	.	.	.	.	.	Negative	N
				WEEK 120	.	.	.	.	.	Positive	A
pH, Urine	11060	54	Female	WEEK 24	4.6	8	3.68	9.6	8.5		H
	41009	41	Female	SCREEN	4.6	8	3.68	9.6	8		N
				WEEK 24	4.6	8	3.68	9.6	8.5		H
					4.6	8	3.68	9.6	7.5		N
	41021	64	Female	SCREEN	4.6	8	3.68	9.6	8.5		H
				WEEK 24	4.6	8	3.68	9.6	8.5		H
					4.6	8	3.68	9.6	8		N
				WEEK 72	4.6	8	3.68	9.6	6.5		N
				WEEK 96	4.6	8	3.68	9.6	6		N
	51047	44	Female	WEEK 24	4.6	8	3.68	9.6	8.5		H
					4.6	8	3.68	9.6	7		N
				WEEK 72	4.6	8	3.68	9.6	6.5		N
				WEEK 96	4.6	8	3.68	9.6	5.5		N
				WEEK 120	4.6	8	3.68	9.6	6		N
	81001	66	Female	SCREEN	4.6	8	3.68	9.6	8.5		H
	151034	49	Female	SCREEN	4.6	8	3.68	9.6	7.5		N
				WEEK 24	4.6	8	3.68	9.6	8.5		H
					4.6	8	3.68	9.6	7		N
	181031	58	Male	SCREEN	4.6	8	3.68	9.6	6.5		N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.2.3
Urinalysis Assays: Listing of Subjects with Values Outside Normal Range
Safety Population
Date Produced: August 25, 2003

Lab Test	Subject No.	Age (yrs)	Sex	Study Period	Normal Range Low	Normal Range High	Reference Range Low	Reference Range High	Assay Value Quantitative	Assay Value Qualitative	Assay Flag
pH, Urine	181031	58	Male	WEEK 24	4.6	8	3.68	9.6	8.5		H
					4.6	8	3.68	9.6	7		N
				WEEK 72	4.6	8	3.68	9.6	5.5		N
				WEEK 96	4.6	8	3.68	9.6	5.5		N
	231024	57	Female	SCREEN	4.6	8	3.68	9.6	7.5		N
				WEEK 24	4.6	8	3.68	9.6	8.5		H
					4.6	8	3.68	9.6	8		N
	361051	47	Female	SCREEN	4.6	8	3.68	9.6	8.5		H
				WEEK 24	4.6	8	3.68	9.6	7.5		N
	361059	35	Female	SCREEN	4.6	8	3.68	9.6	8.5		H
				WEEK 24	4.6	8	3.68	9.6	6.5		N
				WEEK 72	4.6	8	3.68	9.6	7		N

NOTE: Reference range was defined as the lower limit of Normal minus 20% to the upper limit of Normal plus 20%.

Program: urin_out.sas

LISTING 3.3.1
Subjects with Abnormal ECG Results
Safety Population
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Visit	ECG Result	Heart Rate	PR Interval	QRS Interval	QTC Mean, Bazett	QTC Mean, Fridericia	QT Interval	RR Interval
Clayton	31004	45	Male	Screen	Normal	81	145	87	399	380	345	746
				Week 4	Normal	85	140	95	403	380	338	701
				Week 12	Normal	86	137	90	397	373	331	696
				Week 24	Normal	89	145	90	407	382	335	674
				Week 48	Normal	84	137	101	419	396	353	712
				Week 72	Abnormal; not clinically relevant	91	137	95	417	389	338	658
Croft	231024	57	Female	Screen	Abnormal; not clinically relevant	75	180	77	381	367	340	797
				Week 4	Abnormal; not clinically relevant	70	170	81	350	341	324	857
				Week 12	Abnormal; not clinically relevant	88	162	78	389	365	321	682
				Week 24	Abnormal; not clinically relevant	85	161	85	418	395	351	706
				Week 48	Abnormal; not clinically relevant	85	167	84	397	375	335	709

Program: ECG3.sas

LISTING 3.3.1
Subjects with Abnormal ECG Results
Safety Population
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Visit	ECG Result	Heart Rate	PR Interval	QRS Interval	QTC Mean, Bazett	QTC Mean, Fridericia	QT Interval	RR Interval
Croft	231024	57	Female	Week 72	Abnormal; not clinically relevant	118	194	83	402	359	287	512
Delgado	41019	57	Female	Screen	Normal	97	129	83	418	386	328	616
				Week 4	Abnormal; not clinically relevant	109	112	83	433	392	322	553
				Week 12	Normal	91	115	90	426	398	346	657
				Week 24	Normal	101	109	73	435	398	335	593
				Week 48	Normal	89	126	80	425	398	349	673
				Week 72	Normal	91	127	77	430	401	350	663
				Week 96	Normal	89	121	77	428	401	353	681
				Week 120	Normal	82	120	82	383	363	327	732
				Week 144	Normal	98	122	82	419	386	328	613
	41021	64	Female	Screen	Abnormal; not clinically relevant	69	159	119	427	417	398	872
				Week 4	Abnormal; not clinically relevant	64	160	115	436	431	421	934
				Week 12	Abnormal; not clinically relevant	74	165	114	443	428	400	815

Program: ECG3.sas

LISTING 3.3.1
Subjects with Abnormal ECG Results
Safety Population
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Visit	ECG Result	Heart Rate	PR Interval	QRS Interval	QTC Mean, Bazett	QTC Mean, Fridericia	QT Interval	RR Interval
Delgado	41021	64	Female	Week 24	Abnormal; not clinically relevant	65	158	105	403	397	385	915
				Week 48	Abnormal; not clinically relevant	60	145	131	436	436	436	998
				Week 72	Abnormal; not clinically relevant	70	137	127	433	422	401	858
				Week 96	Abnormal; not clinically relevant	63	156	133	433	430	424	959
Helfing	81001	66	Female	Screen	Abnormal; not clinically relevant	87	155	82	388	365	322	688
				Week 4	Abnormal; not clinically relevant	92	135	78	409	380	330	654
				Week 12	Abnormal; not clinically relevant	89	152	80	411	386	339	678

Program: ECG3.sas

LISTING 3.3.1
Subjects with Abnormal ECG Results
Safety Population
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Visit	ECG Result	Heart Rate	PR Interval	QRS Interval	QTC Mean, Bazett	QTC Mean, Fridericia	QT Interval	RR Interval
Julie	321044	55	Male	Screen	Abnormal; clinically relevant	75	170	166	445	429	398	799
				Week 4	Abnormal; clinically relevant	83	184	151	448	424	380	722
				Week 12	Abnormal; clinically relevant	93	175	128	446	414	358	645
				Week 24	Abnormal; clinically relevant	71	169	162	428	416	394	849
				Week 72	Abnormal; clinically relevant	88	154	145	436	409	359	679
Leuchter	361065	50	Male	Screen	Normal	72	180	90	404	392	370	841
				Week 4	Normal	79	159	86	407	388	354	757
				Week 12	Normal	84	157	100	412	389	347	711
				Week 120	Abnormal; clinically relevant	137	.	74	426	371	282	437

LISTING 3.3.1
Subjects with Abnormal ECG Results
Safety Population
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Visit	ECG Result	Heart Rate	PR Interval	QRS Interval	QTC Mean, Bazett	QTC Mean, Fridericia	QT Interval	RR Interval
Leuchter	361068	51	Male	Screen	Abnormal; not clinically relevant	67	150	91	404	397	382	895
				Week 4	Normal	81	152	85	388	370	335	746
				Week 12	Abnormal; not clinically relevant	85	135	98	393	371	330	703
				Week 24	Normal	92	154	83	376	350	304	654
				Week 72	Normal	74	148	94	388	374	348	807
	361069	55	Male	Screen	Normal	63	176	87	389	386	381	958
				Week 72	Abnormal; not clinically relevant	55	206	88	391	398	410	1101
Munjack	131033	45	Male	Screen	Normal	91	152	92	466	435	378	658
				Week 4	Normal	91	133	95	443	414	360	659
				Week 12	Normal	108	141	85	445	404	332	557
				Week 24	Normal	98	142	93	418	386	328	616
				Week 48	Abnormal; not clinically relevant	109	138	91	460	416	342	552
				Week 120	Abnormal; not clinically relevant	97	130	85	441	407	347	621

Program: ECG3.sas

LISTING 3.3.1
Subjects with Abnormal ECG Results
Safety Population
Date Produced: August 25, 2003

Investigator	Subject No.	Age (yrs)	Sex	Visit	ECG Result	Heart Rate	PR Interval	QRS Interval	QTC Mean, Bazett	QTC Mean, Fridericia	QT Interval	RR Interval
Thase	181026	32	Male	Screen	Normal	80	162	88	405	386	350	747
				Week 4	Normal	97	159	81	421	389	332	622
				Week 12	Normal	106	152	92	418	381	315	568
				Week 24	Normal	97	150	91	439	405	346	621
				Week 48	Abnormal; not clinically relevant	95	162	92	441	408	351	635
				Week 72	Normal	99	159	86	410	378	320	609
				Week 96	Normal	91	142	92	416	388	337	656
				Week 120	Normal	99	153	88	436	401	339	605

Program: ECG3.sas

LISTING 3.4.1
Subjects with Significant Changes in Vital Signs
Safety Population
Date Produced: August 25, 2003

Subject Number	Sex	Age (yrs)	Week Number	Significant Changes in Vital Signs
41021	Female	64	32	7# WT. LOSS - PT. DIETING
81040	Female	37	8	INC. BP-PT. STATES DUE TO STRESSORS AT HOME & WORK
			16	BP DECREASED ON NEW BP MEDICATION
131032	Female	34	24	GAIN IN WEIGHT
181050	Female	55	24	ELEVATED BP NOTED. PT TO FOLLOW UP WITH PCP & MONITOR FOR PERSISTNECE PER DR. SPIKE.
			32	BORDERLINE HYPERTENSION
361017	Male	60	24	PULSE IRREGULAR/IRREGULAR
361035	Female	42	20	WEIGHT LOSS
361065	Male	50	24	TACHYCARDIA

Amendment

1 IDENTIFYING INFORMATION FOR AMENDMENT

Amendment Number: C

Amendment Date: 15 February 2002

Product: PNU-155950E (Reboxetine)

2 IDENTIFYING INFORMATION FOR ORIGINAL DOCUMENT

Document Number: 950ECNS0005-071

Document Type: Study Protocol

Title: Open-label Reboxetine Rescue and Continuation Therapy

Protocol Number: 950ECNS0005-071

Project / Product Identifier: 53,206

Author(s) / Study Director: Monica Froeschke, RN

Issue / Approval Date: 11 May 1999

3 PREVIOUS AMENDMENTS

Amendment Number:	1	2	3	A	B
Amendment Date:	7 July 1999	10 March 2000	7 February 2001	10 May 2001	13 September 2001

4 AMENDMENT SUMMARY

The original protocol, which was modified by Amendment 2, Amendment A, and Amendment B was written to allow subjects previously enrolled in another reboxetine trial to continue reboxetine treatment for an additional 72 weeks, 96 weeks, and 120 weeks respectively or until 3 months after reboxetine received FDA approval, whichever occurred first. This amendment would further extend of the protocol period from 120 weeks to 144 weeks. Site physicians will again assess the need for continued reboxetine therapy on a case-by-case basis. If both the physician and the subject agree that continued therapy with reboxetine is warranted, reboxetine treatment for an additional

24 weeks and continued routine safety assessments may be provided (up to 144 weeks total treatment per subject). The other stipulations for subject termination in section 5.1 of the protocol still apply. It is the responsibility of the Investigator to obtain signed and dated consent from subjects prior to inclusion in this fourth study extension (Amendment #C). After IRB approval of this amendment, all subjects who enter the study at the site should sign the most recent version of the informed consent form (allowing reboxetine treatment for up to 144 weeks).

5 SPECIFIC CHANGES

5.1 Change in Section 5.1, Duration/Schedule of Events, page 8

Reason for change: Extension of protocol an additional 24 weeks for subjects benefiting from reboxetine (per investigator's and subject's assessment).

a. Description of Change
From: Treatment will continue for 120 weeks or until (which ever is **sooner**):

To: Treatment will continue for 144 weeks or until (which ever is **sooner**): …

5.2 Change in Section 7.2, Treatment Schedule, page 11

Reason for change: An additional 24 weeks are added to the section added by Amendment #B. The total number of weeks a subject can be enrolled in this protocol will now be 144 weeks. *After IRB approval of this amendment, all subjects who enter the study at the site should sign the most recent version of the informed consent form (allowing reboxetine treatment for up to 144 weeks).*

a. Add to section **(portion in bold)**
At the end of 72 weeks of reboxetine treatment, the primary investigator or designee at each site shall interview the patient, review the subject's history, current mental and physical symptoms, and determine if further reboxetine treatment is warranted. If it is decided that the patient should continue on reboxetine treatment, the investigator, or designee, should complete the Continuation Assessment Case Report Form (for Week 72 extension). Subjects must sign and date a revised informed consent document prior to inclusion in this study extension.

At the end of 96 weeks of reboxetine treatment, the primary investigator or designee at each site shall interview the patient, review the subject's history, current mental and physical symptoms, and again determine if further reboxetine treatment is

warranted. If it is decided that the patient should continue on reboxetine treatment, the investigator, or designee, should complete the Continuation Assessment Case Report Form (for Week 96 extension). Subjects must sign and date a revised informed consent document prior to inclusion in this study extension.

At the end of 120 weeks of reboxetine treatment, the primary investigator or designee at each site shall interview the patient, review the subject's history, current mental and physical symptoms, and again determine if further reboxetine treatment is warranted. If it is decided that the patient should continue on reboxetine treatment, the investigator, or designee, should complete the Continuation Assessment Case Report Form (for Week 120 extension). Subjects must sign and date a revised informed consent document prior to inclusion in this study extension.

5.3 Appendix 1: Study Flow-Chart, page 5 of Amendment B

Reason for change: Incorporation of additional 48 week study period

From (page 5 of Amendment B): **APPENDIX 1: Study Flow-Chart**

Week	Screen (2-14 days)	1	2	4	8	12	16	20	24	32,40	48	56, 64	72	80, 88	96	104, 112	120 or Study Termination whenever it occurs
Sign consent	✓												✓		**X**		
PI or designee to determine need to continue RBX after interview with subject (Continuation Assessment)									✓				✓		**X**		
Brief Medical Hx and PE	✓																**X**†
ECG-12 lead	✓			✓		✓			✓		✓		**X**		✓		**X**
Serum chemistry	✓			✓		✓			✓		✓		**X**		✓		**X**
Hematology	✓			✓		✓			✓		✓		**X**		✓		**X**
Urinalysis	✓			✓		✓			✓		✓		**X**		✓		**X**
Serum pregnancy test	✓			✓		✓			✓		✓		**X**		✓		**X**
Urine drug screen	✓																
Vital signs and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**
HAMD-25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**
CGI or CGI-I	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**
Adverse events	✓**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**
Dispensing/returning medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**‡

* Procedures and forms listed for "Final Visit" should be completed whenever a patient withdraws from the study

** Please briefly review medical history again before medication is dispensed

‡ Collect study medication, containers and dosing diaries at the final visit

† At study end, only PE is performed

X = new assessments per Amendment B

NOTE: All the Screen activities (except signing the Informed Consent) do not need to be repeated if done at the final study visit of the previous reboxetine protocol within a 14 day window.

To: **APPENDIX 1: Study Flow-Chart**

Week	Screen (2-14 days)	1	2	4	8	12	16	20	24	32,40	48	56, 64	72	80, 88	96	104, 112	120	128, 136	144 or Study Termination whenever it occurs
Sign consent	✓												✓		**X**				
PI or designee to determine need to continue RBX after interview with subject (Continuation Assessment)									✓				✓		**X**				
Brief Medical Hx and PE	✓																		**C**[†]
ECG-12 lead	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Serum chemistry	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Hematology	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Urinalysis	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Serum pregnancy test	✓			✓		✓			✓		✓		**X**		✓		**X**		**C**
Urine drug screen	✓																		
Vital signs and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**
HAMD-25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**
CGI or CGI-I	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**C**	**C**
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**
Adverse events	✓**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**
Dispensing/returning medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**C**	**C**[‡]

[*] Procedures and forms listed for "Final Visit" should be completed whenever a patient withdraws from the study
[**] Please briefly review medical history again before medication is dispensed
[‡] Collect study medication, containers and dosing diaries at the final visit
[†] At study end, only PE is performed
X = new assessments per Amendment B
C = new assessments per Amendment C
NOTE: All the Screen activities (except signing the Informed Consent) do not need to be repeated if done at the final study visit of the previous reboxetine protocol within a 14 day window.

6 APPROVAL (AMENDMENT #C; 15 FEB 2002)

Study Management
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(908) 901-1944 (fax)

Karen A Richard 2/21/02
Signature Date

Site Management
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02/19/2002
Signature Date

Medical Director
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Feb 13, 02
Signature Date

Amendment

1 IDENTIFYING INFORMATION FOR AMENDMENT

Amendment Number: 3

Amendment Date: 7 February 2001

Product: PNU-155950E (Reboxetine)

2 IDENTIFYING INFORMATION FOR ORIGINAL DOCUMENT

Document Number:

Document Type: Study Protocol

Title: Open-label Reboxetine Rescue and Continuation Therapy

Protocol Number: 950ECNS0005-071

Project / Product Identifier: 53,206

Author(s) / Study Director: Christopher P. Cirillo

Issue / Approval Date: 11 May 1999

3 PREVIOUS AMENDMENTS

Amendment Number:	1	2
Amendment Date:	7 July 1999	10 March 2000

4 AMENDMENT SUMMARY

The reason for this Amendment is to update the changes in study personnel and to define the visit windows for the extension protocol.

5 SPECIFIC CHANGES

5.1 Change in Study Personnel, page 1.

Reason for change: Study management moved from Kalamazoo to Peapack.

From:
Clinical Study Team Leader
Saeeduddin Ahmed, MD
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To:
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From:
Trial Conduct Team Leader
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From:
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To:
Program Management, Operational
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5.2 Define Visit Windows

Reason for Change: Visit windows were never defined for this extension protocol but were taken from M2020-0034.

From:
M2020-0034 carried over visit windows:

Weekly Visits (weeks 1, 2, & 4)	+/- 1 day
Monthly Visits (weeks 8, 12, 16, 20, 24)	+/- 2 days
Extended Visits (weeks 32, 40, 48….)	unspecified

To:
Newly Defined 950ECNS0005-071 Visit Windows:

Weekly Visits (weeks 1, 2, & 4)	+/- 3 days
Monthly Visits (weeks 8, 12, 16, 20, 24)	+/- 7 days
Extended Visits (weeks 32, 40, 48….)	+/- 7 days

6 APPROVAL (AMENDMENT #3; 07 FEB 2001)

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Signature 2/13/01 Date

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Signature 2/12/01 Date

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Signature 2/12/01 Date

Amendment

1 IDENTIFYING INFORMATION FOR AMENDMENT

Amendment Number:	A
Amendment Date:	10 May 2001
Product:	PNU-155950E (Reboxetine)

2 IDENTIFYING INFORMATION FOR ORIGINAL DOCUMENT

Document Number:	950ECNS0005-071
Document Type:	Study Protocol
Title:	Open-label Reboxetine Rescue and Continuation Therapy
Protocol Number:	950ECNS0005-071
Project / Product Identifier:	53,206
Author(s) / Study Director:	Monica Froeschke, RN
Issue / Approval Date:	11 May 1999

3 PREVIOUS AMENDMENTS

Amendment Number:	1	2	3
Amendment Date:	7 July 1999	10 March 2000	7 February 2001

4 AMENDMENT SUMMARY

The original protocol, then which was modified by Amendment 2, was written to allow subjects previously enrolled in another reboxetine trial to continue reboxetine treatment for an additional 72 weeks or until 3 months after reboxetine received FDA approval, whichever occurred first. This amendment would allow site physicians to assess the need for continued reboxetine therapy on a case-by-case basis. If both the physician and the subject agree that continued therapy with reboxetine is warranted, reboxetine treatment for an additional 24 weeks and continued routine safety assessments may be provided (up to 96 weeks total treatment per subject). The other stipulations for subject termination in section 5.1 of the protocol still apply. It is the responsibility of the

Investigator to obtain signed and dated consent from subjects prior to inclusion in this second study extension (Amendment #A). After IRB approval of this amendment, all subjects who enter the study at the site should sign the most recent version of the informed consent form (allowing reboxetine treatment for up to 96 weeks).

A new consent form template is provided to sites in this mailing with changes from the previous template noted: deletions marked by ~~strikethrough~~, and additions noted by double underlines.

5 SPECIFIC CHANGES

5.1 Change in Study Personnel, page 1.

Reason for change: Change in Pharmacia statistician work assignments.

From: John Landry

To: Cynthia Bartlett
Pharmacia Canada
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5.2 Change in Section 5.1, Duration/Schedule of Events, page 8

Reason for change: Extension of protocol an additional 24 weeks for subjects benefiting from reboxetine (per investigator's and subject's assessment).

a. Description of Change
From: Treatment will continue for 72 weeks or until (which ever is **sooner**):

To: Treatment will continue for 96 weeks or until (which ever is **sooner**): …

5.3 Change in Section 7.2, Treatment Schedule, page 11

Reason for change: An additional 24 weeks are added to the section added by Amendment #2. The total number of weeks a subject can be enrolled in this protocol will now be 96 weeks. *After IRB approval of this amendment, all subjects who enter the study at the site should sign the most recent version of the informed consent form (allowing reboxetine treatment for up to 96 weeks).*

a. Description of Change

From: At the end of 24 weeks of reboxetine treatment, the primary investigator or designee at each site shall interview the patient, review the subject's history, current mental and physical symptoms, and determine if further reboxetine treatment is warranted. Subjects must sign and date a revised informed consent document prior to inclusion in this study extension (Amendment #2).

To: At the end of 72 weeks of reboxetine treatment, the primary investigator or designee at each site shall interview the patient, review the subject's history, current mental and physical symptoms, and determine if further reboxetine treatment is warranted. If it is decided that the patient should continue on reboxetine treatment, the investigator, or designee, should complete the Continuation Assessment Case Report Form (for Week 72 extension). Subjects must sign and date a revised informed consent document prior to inclusion in this study extension.

5.4 Appendix 1: Study Flow-Chart, page 5 of Amendment 2

Reason for change: Incorporation of additional 24 week study period

From (page 5 of Amendment 2): **APPENDIX 1: Study Flow-Chart**

Week	Screen/Day 1 (2-14 days)	1	2	4	8	12	16	20	24	32,40	48	56,64	72 or Study Termination whenever it occurs
Visit	Screen/Baseline												Final visit*
Sign consent	✓												
PI or designee to determine need to continue RBX after interview with subject (Continuation Assessment)									✓				
Brief Medical Hx and PE	✓												✓†
ECG-12 lead	✓			✓		✓			✓		✓		✓
Serum chemistry	✓			✓		✓			✓		✓		✓
Hematology	✓			✓		✓			✓		✓		✓
Urinalysis	✓			✓		✓			✓		✓		✓
Serum pregnancy test	✓			✓		✓		✓			✓		✓
Urine drug screen	✓												
Vital signs and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HAMD-25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CGI or CGI-I	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispensing/returning medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓‡

* Procedures and forms listed for "Final Visit" should be completed whenever a patient withdraws from the study

** Please briefly review medical history again before medication is dispensed

‡ Collect study medication, containers and dosing diaries at the final visit

† At study end, only PE is performed

NOTE: All the Screen/Day 1 activities (except signing the Informed Consent) do not need to be repeated if done at the final study visit of the previous reboxetine protocol within a 14 day window.

To: **APPENDIX 1: Study Flow-Chart**

Week	Screen (2-14 days)	1	2	4	8	12	16	20	24	32, 40	48	56, 64	72	80	88	96 or Study Termination whenever it occurs
Sign consent	✓															
PI or designee to determine need to continue RBX after interview with subject (Continuation Assessment)									✓				✓			
Brief Medical Hx and PE	✓															✓†
ECG-12 lead	✓			✓		✓			✓		✓					✓
Serum chemistry	✓			✓		✓			✓		✓					✓
Hematology	✓			✓		✓			✓		✓					✓
Urinalysis	✓			✓		✓			✓		✓					✓
Serum pregnancy test	✓			✓		✓		✓			✓					✓
Urine drug screen	✓															
Vital signs and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HAMD-25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CGI or CGI-I	✓	✓	✓	✓	✓	✓	✓	✓	✓							✓
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispensing/returning medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓‡

* Procedures and forms listed for "Final Visit" should be completed whenever a patient withdraws from the study

** Please briefly review medical history again before medication is dispensed

‡ Collect study medication, containers and dosing diaries at the final visit

† At study end, only PE is performed

NOTE: All the Screen activities (except signing the Informed Consent) do not need to be repeated if done at the final study visit of the previous reboxetine protocol within a 14 day window.

6 APPROVAL (AMENDMENT #A; 07 MAY 2001)

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5/7/2001
Signature Date

Amendment

1 IDENTIFYING INFORMATION FOR AMENDMENT

Amendment Number:	B
Amendment Date:	13 September 2001
Product:	PNU-155950E (Reboxetine)

2 IDENTIFYING INFORMATION FOR ORIGINAL DOCUMENT

Document Number:	950ECNS0005-071
Document Type:	Study Protocol
Title:	Open-label Reboxetine Rescue and Continuation Therapy
Protocol Number:	950ECNS0005-071
Project / Product Identifier:	53,206
Author(s) / Study Director:	Monica Froeschke, RN
Issue / Approval Date:	11 May 1999

3 PREVIOUS AMENDMENTS

Amendment Number:	1	2	3	A
Amendment Date:	7 July 1999	10 March 2000	7 February 2001	10 May 2001

4 AMENDMENT SUMMARY

The original protocol, which was modified by Amendment 2 and Amendment A, was written to allow subjects previously enrolled in another reboxetine trial to continue reboxetine treatment for an additional 72 weeks and 96 weeks, respectively or until 3 months after reboxetine received FDA approval, whichever occurred first. This amendment would further extend of the protocol period from 96 weeks to 120 weeks. Site physicians will again assess the need for continued reboxetine therapy on a case-by-case basis. If both the physician and the subject agree that continued therapy with reboxetine is warranted, reboxetine treatment for an additional 24 weeks and continued routine safety assessments may be provided (up to 120 weeks total treatment per

subject). The other stipulations for subject termination in section 5.1 of the protocol still apply. It is the responsibility of the Investigator to obtain signed and dated consent from subjects prior to inclusion in this third study extension (Amendment #B). After IRB approval of this amendment, all subjects who enter the study at the site should sign the most recent version of the informed consent form (allowing reboxetine treatment for up to 144 weeks).

5 SPECIFIC CHANGES

5.1 Change in Section 5.1, Duration/Schedule of Events, page 8

Reason for change: Extension of protocol an additional 48 weeks for subjects benefiting from reboxetine (per investigator's and subject's assessment).

a. Description of Change
From: Treatment will continue for 96 weeks or until (which ever is **sooner**):

To: Treatment will continue for 120 weeks or until (which ever is **sooner**): …

5.2 Change in Section 7.2, Treatment Schedule, page 11

Reason for change: An additional 24 weeks are added to the section added by Amendment #A. The total number of weeks a subject can be enrolled in this protocol will now be 120 weeks. *After IRB approval of this amendment, all subjects who enter the study at the site should sign the most recent version of the informed consent form (allowing reboxetine treatment for up to 120 weeks).*

a. Description of Change
From: At the end of 72 weeks of reboxetine treatment, the primary investigator or designee at each site shall interview the patient, review the subject's history, current mental and physical symptoms, and determine if further reboxetine treatment is warranted. If it is decided that the patient should continue on reboxetine treatment, the investigator, or designee, should complete the Continuation Assessment Case Report Form (for Week 72 extension). Subjects must sign and date a revised informed consent document prior to inclusion in this study extension.

To: At the end of 72 weeks of reboxetine treatment, the primary investigator or designee at each site shall interview the patient, review the subject's history, current mental and physical symptoms, and determine if further reboxetine treatment is warranted. If it is decided that the patient should continue on reboxetine treatment, the investigator, or designee, should complete the Continuation Assessment Case Report Form (for Week 72 extension). Subjects must sign and date a revised informed consent document prior to inclusion in this study extension.

At the end of 96 weeks of reboxetine treatment, the primary investigator or designee at each site shall interview the patient, review the subject's history, current mental and physical symptoms, and again determine if further reboxetine treatment is warranted. If it is decided that the patient should continue on reboxetine treatment, the investigator, or designee, should complete the Continuation Assessment Case Report Form (for Week 96 extension). Subjects must sign and date a revised informed consent document prior to inclusion in this study extension.

5.3 Additional Safety Assessments

Reason for Change: During the preparation of Amendment B, it was discovered that Amendment A inadvertently omitted Laboratory and ECG assessments to be completed at the Week 72 Visit.

a. Description of Change

From: Laboratory and ECG assessments from Week 72 Visit should be postponed to the Week 96 or Early Termination Visit.

To: Laboratory and ECG assessments will be completed at the Weeks 72, 96, and 120 or at any Early Termination Visit.

5.4 Additional Efficacy Assessments

Reason for Change: During the preparation of Amendment B, it was discovered that Amendment 2 inadvertently omitted the completion of CGI-I assessments after Week 24.

b. Description of Change

From: (new section)

To: CGI-I assessments will now be completed at all visits. If a patient has already completed visits that now require the CGI, the corresponding CGI case report form should be marked NOT DONE.

5.5 Appendix 1: Study Flow-Chart, page 5 of Amendment A

Reason for change: Incorporation of additional 48 week study period

From (page 5 of Amendment A): **APPENDIX 1: Study Flow-Chart**

Week	Screen (2-14 days)	1	2	4	8	12	16	20	24	32, 40	48	56, 64	72	80	88	96 or Study Termination whenever it occurs
Sign consent	✓															
PI or designee to determine need to continue RBX after interview with subject (Continuation Assessment)									✓				✓			
Brief Medical Hx and PE	✓															✓†
ECG-12 lead	✓			✓		✓			✓		✓					✓
Serum chemistry	✓			✓		✓			✓		✓					✓
Hematology	✓			✓		✓			✓		✓					✓
Urinalysis	✓			✓		✓			✓		✓					✓
Serum pregnancy test	✓			✓		✓			✓		✓					✓
Urine drug screen	✓															
Vital signs and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HAMD-25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CGI or CGI-I	✓	✓	✓	✓	✓	✓	✓	✓	✓							✓
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispensing/returning medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓‡

* Procedures and forms listed for "Final Visit" should be completed whenever a patient withdraws from the study

** Please briefly review medical history again before medication is dispensed

‡ Collect study medication, containers and dosing diaries at the final visit

† At study end, only PE is performed

NOTE: All the Screen/Day 1 activities (except signing the Informed Consent) do not need to be repeated if done at the final study visit of the previous reboxetine protocol within a 14 day window.

To: **APPENDIX 1: Study Flow-Chart**

Week	Screen (2-14 days)	1	2	4	8	12	16	20	24	32,40	48	56, 64	72	80, 88	96	104, 112	120 or Study Termination whenever it occurs
Sign consent	✓												✓		**X**		
PI or designee to determine need to continue RBX after interview with subject (Continuation Assessment)									✓				✓		**X**		
Brief Medical Hx and PE	✓																**X**†
ECG-12 lead	✓			✓		✓			✓		✓		**X**		✓		**X**
Serum chemistry	✓			✓		✓			✓		✓		**X**		✓		**X**
Hematology	✓			✓		✓			✓		✓		**X**		✓		**X**
Urinalysis	✓			✓		✓			✓		✓		**X**		✓		**X**
Serum pregnancy test	✓			✓		✓			✓		✓		**X**		✓		**X**
Urine drug screen	✓																
Vital signs and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**
HAMD-25	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**
CGI or CGI-I	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**
Adverse events	✓**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**
Dispensing/returning medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**X**	**X**‡

* Procedures and forms listed for "Final Visit" should be completed whenever a patient withdraws from the study

** Please briefly review medical history again before medication is dispensed

‡ Collect study medication, containers and dosing diaries at the final visit

† At study end, only PE is performed

X = new assessments per Amendment B

NOTE: All the Screen activities (except signing the Informed Consent) do not need to be repeated if done at the final study visit of the previous reboxetine protocol within a 14 day window.

6 APPROVAL (AMENDMENT #B; 13 SEPT 2001)

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Karen A Richard 9/13/01
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Signature Date

950E-CNS-0005-071

APPENDIX 1.1 PROTOCOL AND AMENDMENTS

1.1	Amendment C	15-Feb-2002
1.2	Amendment B	13-Sep-2001
1.3	Amendment A	10-May 2001
1.4	Amendment 3	07-Feb-2001
1.5	Amendment 2	10-Mar-2000
1.6	Amendment 1	17-Jul-1999
1.7	Protocol	11-May-1999

950E-CNS-0005-071

APPENDIX 1.2 SAMPLE CASE REPORT FORMS

950E-CNS-0005-071

APPENDIX 1.3 SAMPLE INFORMED CONSENT

950E-CNS-0005-071

APPENDIX 1.4 LIST OF INVESTIGATORS AND INDEPENDENT ETHICS COMMITTEES

1.4 Investigator and IRB Information

950E-CNS-0005-071

APPENDIX 1 STUDY INFORMATION

Appendix 1.1 Protocol and Amendments
Appendix 1.2 Sample Case Report Forms
Appendix 1.3 Sample Informed Consent
Appendix 1.4 List of Investigators and Independent Ethics Committees
Appendix 1.5 Curriculum Vitae for Investigators
Appendix 1.6 List of Subjects Receiving Drug by Batch
Appendix 1.7 Randomization Scheme – Not Applicable
Appendix 1.8 Audit Certificates – Not Applicable
Appendix 1.9 Documentation of Statistical Methods
Appendix 1.10 Inter-Laboratory Standardization Methods – Not Applicable
Appendix 1.11 List of Publications Based on the Study – None
Appendix 1.12 Supporting Documentation Referenced in the Report

APPENDIX 2 SUPPORTIVE STATISTICAL TABLES AND FIGURES

Appendix 2.1 Subject Disposition, Demographics, and Baseline Characteristics Summary Tables

Appendix 2.2 Efficacy Data Summary Tables

Appendix 2.3 Safety Data Summary Tables

950E-CNS-0005-071

APPENDIX 3 PATIENT CLINICAL DATA LISTINGS

TABLE T1
Subject Disposition
All Enrolled Subjects
Date Produced: August 25, 2003

Population	Reboxetine (N=69)	
	N	%
Number of Subjects Enrolled	69	100.0
Number in Safety Population	69	100.0
Number in Modified Intention to Treat Population	68	98.6
Number of Subjects Completed 24 Weeks of Treatment	37	53.6
Number of Subjects Continuing Beyond 24 Weeks of Treatment	31	44.9
Number of Subjects Completed 72 Weeks of Treatment	17	24.6
Number of Subjects Continuing Beyond 72 Weeks of Treatment	13	18.8
Number of Subjects Completed 96 Weeks of Treatment	9	13.0
Number of Subjects Continuing Beyond 96 Weeks of Treatment	8	11.6
Number of Subjects Completed 120 Weeks of Treatment	7	10.1
Number of Subjects Continuing Beyond 120 Weeks of Treatment	6	8.7
Number of Subjects Completed 144 Weeks of Treatment	2	2.9
Number of Subjects Who Terminated Study Early	55	79.7

Program: ds1.sas

TABLE T1
Subject Disposition
All Enrolled Subjects
Date Produced: August 25, 2003

Population	Reboxetine (N=69)	
	N	%
Reasons for Early Termination: *-Adverse event	11	15.9
*-Protocol violation	7	10.1
*-Consent withdrawn	6	8.7
*-Lost to follow-up	4	5.8
*-Protocol specific withdrawal criteria	2	2.9
*-Lack of efficacy	12	17.4
*-Progression of disease	1	1.4
*-Improvement	1	1.4
*-Other	11	15.9

Program: ds1.sas

TABLE T2
Demographics - Sex and Race
All Enrolled Subjects
Date Produced: August 25, 2003

		Reboxetine	
		N	%
Sex	Male	22	31.9
	Female	47	68.1
	Total Reported	69	100.0
Race	Caucasian	61	88.4
	Black	6	8.7
	Hispanic	2	2.9
	Total Reported	69	100.0

Program: dm1.sas

TABLE T3
Demographics - Age
All Enrolled Subjects
Date Produced: August 25, 2003

Variable	Statistic	Reboxetine
Age (yr)	N	69
	Mean	46.7
	SD	10.35
	Min	20
	Max	66

Program: dm2.sas

TABLE T4
Demography: Marital Status
All Enolled Subjects
Date Produced: August 25, 2003

MARITAL STATUS	# of Pts	Percent
Never married/Single	18	26.1
Currently married	26	37.7
Separated	2	2.9
Widowed	4	5.8
Divorced	19	27.5
Total	69	100.0

Program: dm3_5.sas

TABLE T5
Demography: Current Employment Status
All Enolled Subjects
Date Produced: August 25, 2003

EMPLOYMENT STATUS	# of Pts	Percent
Full-time	37	53.6
Part-time	9	13.0
Not employed (by choice)	17	24.6
Not employed (other)	6	8.7
Total	69	100.0

Program: dm3_5.sas