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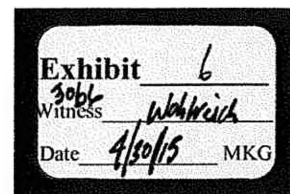
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Protocol F1J-MC-HMBU(a)

Duloxetine Versus Venlafaxine Extended Release in the Treatment of Major Depressive Disorder

Duloxetine Hydrochloride (LY248686)

Eli Lilly and Company
Protocol Approved by Lilly: 03 December 2002
Protocol Amendment (a) Approved by Lilly : 26 February 2003



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Duloxetine Versus Venlafaxine extended release in the Treatment of Major Depressive Disorder

1. Introduction

Major depressive disorder (MDD) is a common and debilitating condition with a lifetime prevalence ranging from 10% to 25% in females and 5% to 12% in males (APA 1994). Aside from the considerable morbidity associated with the disease, there is also a substantial mortality, with an associated lifetime risk of suicide estimated at 15% (Buda and Tsuang 1981; Guze and Robins 1970).

The introduction of the selective serotonin reuptake inhibitors (SSRIs) set a new standard for safety and ease of use in the drug treatment of MDD. Compared with earlier classes of antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), SSRIs are better tolerated, have a more benign side-effect profile, and have a lower potential for drug-drug interactions. Despite their advantages, however, patient response to SSRIs is modest, estimated to be between 55% and 65% (Hirschfeld 1999). Furthermore, the proportion of SSRI-treated patients achieving full remission of their symptoms is considerably lower still, estimated at 35% (Thase et al. 2001).

Evidence suggests that both the serotonergic and noradrenergic neurotransmitter systems play a role in the pathophysiology of depression. Venlafaxine is a serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI), and a number of studies have indicated the potential therapeutic superiority of this antidepressant over SSRIs (Feighner 1999). Furthermore, a recent meta-analysis of eight randomised, double-blind studies in MDD (Thase et al. 2001) concluded that the use of venlafaxine is associated with significantly higher remission rates than SSRIs.

Duloxetine hydrochloride (hereafter referred to as "duloxetine") is a potent and balanced dual reuptake inhibitor of serotonin and norepinephrine in vitro and in vivo. It exhibits low affinity for other neurotransmitter receptors (Wong and Bymaster 2002), suggesting a low side effect potential.

A global development program is underway to evaluate the efficacy of duloxetine in the treatment of MDD. Initial studies (conducted in Europe and the United States in the 1990s) examined the efficacy of duloxetine at doses up to 30 mg/day. These studies failed to demonstrate statistically significant superiority over placebo on prospectively defined primary efficacy analyses, but showed evidence of clinical effects on both primary and secondary measures. Subsequent work has determined that the dose range examined in these earlier studies was insufficient to test the efficacy of duloxetine, and eight large scale, double-blind, placebo-controlled clinical trials have since been completed evaluating duloxetine at doses from 40 to 120 mg/day in the acute and continuation treatment of MDD. Four of these have been clearly positive, three

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supportive (that is, $p > .05$ on the primary efficacy analysis, but other numerical differences and analyses were consistent with efficacy), and one where duloxetine and placebo were equivocal.

The safety and pharmacokinetic profile of duloxetine has been studied in more than 25 clinical pharmacological studies (15 multiple-dose studies) to date, at doses up to 160 mg/day (80 mg twice daily). Duloxetine is safe and well tolerated in this dose range.

To date, there have been no randomized, controlled studies directly comparing the safety and efficacy of duloxetine and venlafaxine. While these two agents share some pharmacodynamic similarities, there are significant differences in their receptor binding affinities, leading to potentially different benefit/risk ratios. Duloxetine is a more balanced inhibitor with a NE to 5-HT human receptor binding affinity ratio of 9, whereas venlafaxine's human receptor binding affinity ratio is 30 (Bymaster et al. 2001).

Consequently, there is value in conducting a study to investigate the comparative efficacy and safety of these two SNRI antidepressants in the treatment of MDD.

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2. Objectives

2.1 Primary Objective

The primary objective of this study is to test the hypothesis that duloxetine 60 mg daily is statistically significantly superior to venlafaxine extended release 150 mg daily during the 6 weeks of Study Period II using global benefit-risk assessment, in outpatients with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV)-defined major depressive disorder (MDD). Benefit is defined as remission (total score of ≤ 7 at endpoint of Study Period II) on the 17-item Hamilton Depression Rating Scale (HAM-D₁₇). Risk is defined by four categories: no Association for Methodology and Documentation in Psychiatry (AMDP-5) collected adverse events (AMDPAE), mild or moderate AMDPAE, severe AMDPAE, and discontinued with a reason of self-reported adverse event. Data from this study and a similar study, F1J-MC-HMCQ, will be combined for this comparison.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To test the hypothesis that duloxetine 60 mg daily is not inferior to venlafaxine extended release 150 mg daily during 6 weeks of therapy, and that duloxetine 60 to 120 mg is not inferior to venlafaxine extended release 150 to 225 mg during 12 weeks of therapy, in the efficacy of treating MDD as measured by the mean change from baseline to endpoint on the HAM-D₁₇ total score. Data from this study and a similar study, F1J-MC-HMCQ, will be combined for this comparison.
- To test the hypothesis that duloxetine 60 to 120 mg daily is statistically significantly superior to venlafaxine extended release 150 to 225 mg daily during 12 weeks of therapy using global benefit-risk assessment. Data from this study and a similar study, F1J-MC-HMCQ, will be combined for this comparison.
- To assess the efficacy of duloxetine 60 mg daily versus venlafaxine extended release 150 mg daily during 6 weeks of therapy, and duloxetine 60 to 120 mg daily versus venlafaxine extended release 150 to 225 mg daily during 12 weeks of therapy, as measured by:
 - HAM-D₁₇ subscales including the Core, Maier, Anxiety/Somatization, Retardation/Somatization, and Sleep; and the depressed mood item (Item 1)
 - Response rates, as defined by a $\geq 50\%$ change from baseline to endpoint on the HAM-D₁₇ total score

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- Remission rates, as defined by a HAMD₁₇ score of ≤ 7 at endpoint
 - Total score Hamilton Anxiety Rating Scale (HAMA)
 - Clinical Global Impressions of Severity Rating Scale (CGI-Severity)
 - Patient's Global Impression of Improvement Rating Scale (PGI-Improvement).
- To assess the impact of duloxetine 60 mg daily versus venlafaxine extended release 150 mg daily during 6 weeks of therapy, and duloxetine 60 to 120 mg daily versus venlafaxine extended release 150 to 225 mg daily during 12 weeks of therapy on quality of life and health outcomes as measured by:
 - SF-36 Health Status Survey (SF-36)
 - Quality of Life in Depression Scale (QLDS)
 - EuroQOL (EQ-5D)
 - Sheehan Disability Scale (SDS)
 - Patient Health Questionnaire (PHQ) – physical component
 - Resource Use and Hospitalization Module.
 - To assess duloxetine 60 mg daily versus venlafaxine extended release 150 mg daily during 6 weeks of therapy, and duloxetine 60 to 120 mg daily versus venlafaxine extended release 150 to 225 mg daily during 12 weeks of therapy on time-to-first:
 - Visit that sustained 30% improvement on the Maier subscale of the HAMD₁₇ is achieved
 - Visit that the HAMD₁₇ total is ≤ 7 .
 - To evaluate the safety and tolerability of duloxetine 60 mg daily versus venlafaxine extended release 150 mg daily during 6 weeks of therapy, and duloxetine 60 to 120 mg daily versus venlafaxine extended release 150 to 225 mg daily during 12 weeks of therapy on safety and tolerability as measured by:
 - Spontaneously reported treatment-emergent adverse events
 - Vital signs
 - Electrocardiograms (ECGs)
 - Laboratory analytes
 - Solicited adverse events using the AMDP-5

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- Change in Sexual Functioning Questionnaire (CSFQ)
 - Pittsburgh Sleep Quality Index (PSQI).
- To evaluate the incidence of adverse events occurring during Study Period IV using spontaneously reported adverse events and the AMDP-5.
- To evaluate the effects of duloxetine 60 mg daily versus venlafaxine extended release 150 mg daily during 6 weeks of therapy, and duloxetine 60 to 120 mg daily versus venlafaxine 150 to 225 mg daily during 12 weeks of therapy on cognition using a composite cognitive score derived from the Verbal Learning and Recall Test (VLRT), the Symbol Digit Substitution Test (SDST), 2-Digit Cancellation Test (2DCT), and the Letter-Number Sequencing Test (LNST).

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3. Investigational Plan

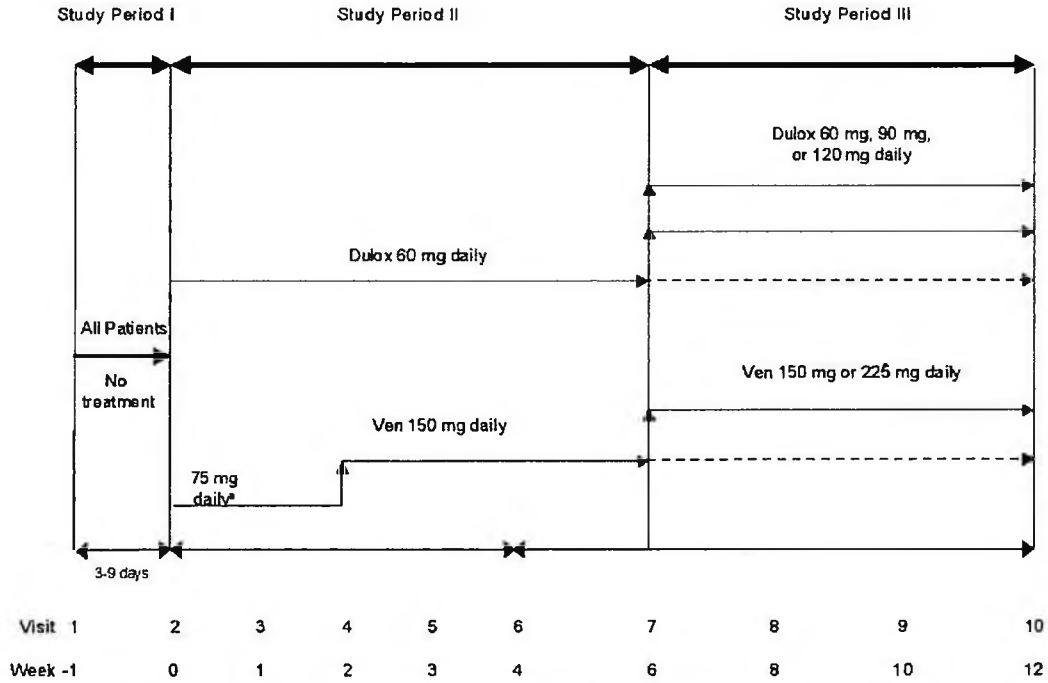
3.1. Summary of Study Design

Study F1J-MC-HMBU is a multicenter, randomized, double-blind, parallel study of approximately 320 outpatients diagnosed with major depressive disorder (MDD). The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998) will be used to determine whether patients meet criteria for MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV).

- Screening (Study Period I): Visit 1 to 2. This is a screening phase during which patients will be screened for eligibility. Visit 2 will occur 3 to 9 days after Visit 1.
- Double-Blind Fixed Dose (Study Period II): Visits 2 to 7. This is a 6-week period of double-blind treatment. Patients who meet entry criteria will be enrolled and randomized at Visit 2 to one of two treatment groups: duloxetine 60 mg daily or venlafaxine extended release 150 mg daily. The venlafaxine group will begin treatment with venlafaxine 75 mg daily for the first 2 weeks, increasing to 150 mg daily for the remainder of Study Period II. Patients who complete Study Period II will be eligible to enter Study Period III.
- Double-Blind Dose (Study Period III): Visits 7 to 10. This is a 6-week, double-blind period for patients who complete Study Period II. At Visit 7, Visit 8, or Visit 9, patients may have their dose increased during an additional 6 weeks of therapy, based on the investigator's discretion. Duloxetine may be increased up to 120 mg daily. Venlafaxine extended release may be increased up to 225 mg daily. The dose of study medication may not be reduced at anytime. See Section 5.5.3 for a description of study drug administration during this study period.
- Taper (Study Period IV): Visits 10 through 303. This is a 3-week taper period. Patients who discontinue the study at Visit 4 or thereafter or complete Study Period III may enter the taper period at the investigator's discretion to assess discontinuation-emergent adverse events (DEAEs) and other safety measures. Study medication will be tapered in a double-blind manner. See Section 5.5.4 for a description of study drug administration during this study period.

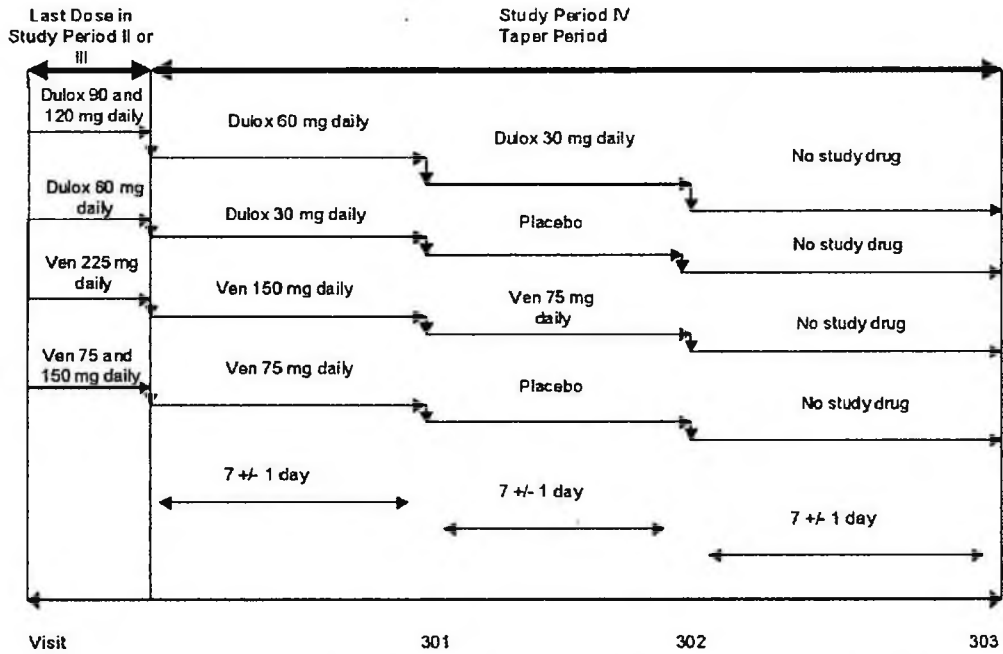
Figure HMBU.1 illustrates the study design.

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* Initial Venlafaxine extended release dose is 75 mg/day for 2 weeks, then increases to 150 mg/day.

Note: The dose may be increased at any visit in Study Period III.



Note: Dulox = duloxetine; Ven = venlafaxine extended release.

Figure HMBU.1. Illustration of study design for Protocol F1J-MC-HMBU.

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See Protocol Attachment HMBU.1 for allowed and suggested visit intervals.

3.1.1. Study Extensions

There are no extensions to this study.

3.2. Discussion of Design and Control

Study Period I is designed to determine if patients meet all of the inclusion criteria and none of the exclusion criteria.

Study Period II is designed to assess the benefit-risk ratio of duloxetine versus venlafaxine extended release at usual doses for patients with depression.

Study Period III is designed to allow investigators to increase the dose of study medication for patients who have not responded to usual doses to determine if the patient will respond to higher doses.

Study Period IV is designed to ensure that patients are treated with a reducing regimen of study drug (taper) rather than experiencing an abrupt cessation of treatment. The intention is to reduce the likelihood of DEAEs, which are recognized to occur following abrupt interruption of therapy.

Even when antidepressants are discontinued by way of a taper rather than abrupt discontinuation, DEAEs are still known to occur, albeit with reduced frequency or severity. It is for this reason that Study Period IV features a one-week, study drug-free period, followed by a final visit to assess DEAEs. In this way, the propensity for patients to experience DEAEs despite the use of a taper, an important and increasingly widely-recognized phenomenon, can be compared for duloxetine and venlafaxine extended release.

Venlafaxine extended release was chosen as a comparator since it is the most widely used and prescribed member of the serotonin and norepinephrine reuptake inhibitor (SNRI) drug class approved for antidepressant use. To date, there have been no randomized, controlled studies directly comparing the safety and efficacy of duloxetine and venlafaxine. While these two agents share some pharmacodynamic similarities, there are significant differences in their receptor binding affinities, leading to potentially different benefit/risk ratios. Duloxetine is a more balanced inhibitor with a NE to 5-HT human receptor binding affinity ratio of 9, whereas venlafaxine's human receptor binding affinity ratio is 30 (Bymaster et al. 2001). Consequently, there is value in conducting a study to make head-to-head comparisons for the efficacy and safety of these two SNRI antidepressants in the treatment of MDD.

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3.3 Investigator Information

Approximately 35 physicians with experience in treating patients with depression and conducting clinical trials of psychiatric medications will participate as investigators in this protocol.

Each investigator and staff member who will perform efficacy ratings in this study must be evaluated and approved by Lilly prior to participating as an efficacy rater in this study. In most cases, evaluation and notification will occur at the start-up meeting. Individuals who do not attend the rater evaluation and training portion of the start-up meeting and who wish to perform efficacy ratings in this study must be evaluated and approved by Lilly prior to performing any ratings.

Evaluation and approval are study-specific. Individuals who have been approved to perform efficacy ratings for another study sponsored by Lilly are not automatically approved to perform efficacy ratings in this study. Approval is based on an assessment of inter-rater reliability of the primary efficacy measure, as well as evaluation of the clinical interview skills of each rater. It is desirable that investigators and site staff will have documented statistical evidence of ongoing inter-rater reliability assessments at their site and clear mechanisms to manage outliers.

Inter-rater reliability assessments that would involve participation by all efficacy raters at a site may occur on one or more occasions during the course of the study.

If possible, the measurements should be performed on a given patient by the same rater at each visit. The primary investigator has the responsibility of selecting who will administer the instruments at the site, as long as all training requirements have been met by those raters.

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4. Study Population

4.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

- [1] Outpatients at least 18 years of age who meet criteria for major depressive disorder (MDD) as defined by Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria and confirmed by the Mini International Neuropsychiatric Interview (MINI).
- [2] Hamilton Depression Rating Scale (HAM-D₁₇) total score ≥ 18 at Visit 1.
- [3] Sign the informed consent document (ICD).
- [4] Have had at least one other major depressive episode, prior to the current episode as determined by the MINI.
- [5] Have a level of understanding sufficient to provide informed consent and to communicate with the investigators and site personnel.
- [6] Are judged to be reliable and agree to keep all appointments for clinic visits, tests, and procedures required by the protocol.

4.1.1. Disease Diagnostic Criteria

Patients must meet DSM-IV criteria for major depression. The MINI for DSM-IV will be used to establish the diagnosis and exclude other psychiatric illnesses. The MINI is a standardized diagnostic interview based on DSM-IV criteria that was developed as a more concise and easily administered alternative to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (Spitzer et al. 1990). Additionally, patients must have a total score ≥ 18 at Visit 1 on the HAM-D₁₇.

4.2. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- [7] Are investigator site personnel directly affiliated with the study, or are immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

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- [8] Are employed by Lilly (that is, employees, temporary contract workers, or designees responsible for the conduct the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical trials, but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- [9] Women of childbearing potential who are not using a medically accepted means of contraception when engaging in sexual intercourse (for example, intrauterine device, oral contraceptive, contraceptive patch, implant, Depo-Provera® [medroxyprogesterone acetate injectable suspension, Pharmacia & Upjohn], or barrier devices). Women who are pregnant or breast-feeding may not participate in the study.
- [10] Have received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.
- [11] Have previously completed or withdrawn from this study or any other study investigating duloxetine.
- [12] Any current primary Axis I disorder other than major depressive disorder (MDD), including but not limited to dysthymia.
- [13] Previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorders.
- [14] Any anxiety disorder as a primary diagnosis within the past year (including panic disorder, agoraphobia, obsessive-compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and social phobia).
- [15] Lack of response of the current episode of major depression to two or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks or, in the judgment of the investigator, the patient meets criteria for treatment-resistant depression.
- [16] History of a lack of response, at any time, to an adequate trial of venlafaxine, venlafaxine extended release, or other serotonin and norepinephrine reuptake inhibitor (SNRI) for the treatment of depression (defined as treatment with at least 75 mg/day of venlafaxine or equivalent dose of other SNRI for a minimum of 4 weeks).
- [17] Presence of an Axis II disorder that, in the judgment of the investigator, would interfere with study compliance.

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- [18] DSM-IV-defined history of substance abuse or dependence within the past year, excluding nicotine and caffeine.
- [19] Have a positive urine drug screen for any substances of abuse. Note: If the patient has a positive drug screen at Visit 1, a retest may be performed prior to Visit 2 if, in the judgment of the investigator, there is an acceptable explanation for the positive result. If the retest is positive for active metabolites, the investigator must document that the patient has discontinued taking the medication. If the retest is positive for the parent compound, the patient will be excluded.
- [20] Patients judged to be at serious suicidal risk in the opinion of the investigator, or if the patient's HAMD₁₇ score on Item 3 Suicide is ≥ 3 .
- [21] Serious medical illness or clinically significant laboratory abnormalities that, in the judgment of the investigator, are likely to require intervention/ hospitalization/ excluded medication during the course of the study.
- [22] Electroconvulsive therapy (ECT) or Transcranial Magnetic Stimulation (TMS) within the past year.
- [23] Patients who require initiation or discontinuation of psychotherapy within 6 weeks prior to enrollment or at any time during the study.
- [24] Taking any excluded medications listed in Protocol Attachment HMBU.3 within 7 days prior to Visit 2.
- [25] Treatment with a monoamine oxidase inhibitor (MAOI) within 14 days prior to Visit 2 or potential need to use a MAOI within 14 days after discontinuation of study drug.
- [26] Treatment with fluoxetine within 30 days prior to Visit 2.
- [27] Frequent and/or severe allergic reactions with multiple medications.
- [28] Abnormal thyroid stimulating hormone (TSH) concentration (outside the reference range of the performing laboratory). Note: Patients diagnosed with hyperthyroidism or hypothyroidism who have been treated on a stable dose of thyroid supplement for at least the past 3 months, have medically appropriate TSH concentration, and are clinically euthyroid are allowed.
- [29] Have at Visit 1 an ALT, AST, or GGT >1.5 times upper limit of normal, based on the performing laboratory's reference ranges.

4.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusions [7] and [8] reduce the potential bias that may be introduced at the study site. Exclusion [9] is meant to reduce potential risk to the fetus or infant by preventing in utero or lactation exposure, because risks to fetuses and infants are unknown. Exclusion [10]

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excludes drugs that cannot be mapped to a standard drug dictionary or for which little data are known to analyze the potential relationship of adverse events or drug interactions. Exclusion [11] ensures accurate exposure data to duloxetine, thus avoiding bias in safety evaluation. Exclusions [12], [13], [14], [15], [16], [17], [19], [21], and [29] exclude patients that may have significant medical events that are unrelated to therapy but may need to be treated during the course of the study by excluded medications or procedures. Exclusion [18] excludes patients who are likely to use central nervous system (CNS)-active drugs that might adversely affect the safety or efficacy assessments. Exclusion [20] excludes patients who might be better served/optimally dosed without the constraints of a research protocol. Exclusion [22] is to avoid enrolling patients with a history of major depression non-responsive to drug treatment, who may experience ECT- or TMS-associated adverse events, affecting the interpretation of safety and efficacy. Exclusion [23] avoids a change in variables that also treat the condition under study which might confound the efficacy assessments. Exclusion [24] excludes medications that might cause adverse events/interactions or obscure the determination of duloxetine- or venlafaxine extended release-induced adverse events. Exclusions [25] and [26] reinforce patient safety and reduce the risk of serotonin syndrome. Exclusion [27] excludes patients who would be more likely to have an allergic reaction or less likely to tolerate duloxetine or venlafaxine extended release. Exclusion [28] excludes patients with abnormal TSH which may be indicative of the symptoms of depression or may complicate existing MDD.

4.3. Discontinuations

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the study and Lilly or its designee must be contacted. An exception may be granted in very rare circumstances where there is a compelling safety reason to allow the patient to continue. In these rare cases, the investigator must obtain documented approval from Lilly to allow the patient to continue in the study.

In addition, patients will be discontinued from the study drug and/or from the study in the following circumstances.

- The investigator decides that the patient should be withdrawn. If this decision is made because of a serious adverse event or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be notified immediately. See Safety Section (Section 6.4).
- The patient or attending physician requests that the patient be withdrawn from the study.

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- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The investigator or Lilly, for any reason, stops the study or stops the patient's participation in the study.
- The patient becomes pregnant.

Patients who discontinue study drug early will have end-of-therapy and/or end-of-study procedures performed as shown in the Study Schedule (Protocol Attachment HMBU.2).

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5. Treatment

5.1. Treatments Administered

This study involves a comparison of duloxetine 60 to 120 mg daily administered orally versus venlafaxine extended release 150 to 225 mg daily administered orally.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to Lilly at the end of the study.

5.2. Materials and Supplies

The sponsor will provide 30 mg capsules of duloxetine and 75 mg capsules of venlafaxine extended release.

Matching placebo will be utilized to maintain the integrity of the blind during the study.

Proper measures have been taken to ensure duloxetine, venlafaxine extended release, and placebo are indistinguishable. Over-encapsulated venlafaxine extended release is tested against unblinded venlafaxine extended release to ensure there are no changes to dissolution.

5.3. Method of Assignment to Treatment

A patient number will be assigned to each patient after the informed consent document is signed and dated (Study Period I). Randomization will occur in a 1:1 ratio to either duloxetine or venlafaxine extended release at Visit 2 (Study Period II). Assignment to treatment groups will be determined by a computer-generated random sequence using an Interactive Voice Response System (IVRS). Site personnel will confirm they have located the correct blister card by entering a confirmation number found on the card into the IVRS. In Study Period III patients will continue on the treatment assignment given at Visit 2. While the dose may be increased at the discretion of the investigator during Study Period III, dose decreases are not permitted. Study Period IV is the taper period of the study; patients will have their study medication decreased until they have completely tapered off study drug.

5.4. Rationale for Selection of Doses in the Study

The duloxetine dose regimens in this study were selected based on current clinical, preclinical, and pharmacokinetic data. Previous studies have demonstrated that duloxetine administered at doses of 60 mg to 120 mg daily for the treatment of major depressive disorder (MDD) is safe and efficacious. Dosing regimens of venlafaxine extended release selected for this study are based upon recommendations for treatment of MDD within the venlafaxine extended release Summary of Product Characteristics,

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namely the use of a dose of 75 mg daily for at least 2 weeks prior to increasing the dose up to a maximum of 225 mg daily. The use of 150 mg daily of venlafaxine extended release as a fixed-dose comparison in Study Period II is based upon the desire to compare duloxetine at a dose of 60 mg daily with the mean prescribed dose of venlafaxine extended release used in actual clinical practice. Dual reuptake inhibition is believed to occur with venlafaxine at doses in excess of 150 mg daily. With duloxetine, however, dual reuptake inhibition is believed to occur at a dose of 60 mg daily. Dose increases are permitted in Study Period III in order to allow a comparison of duloxetine and venlafaxine at doses where dual reuptake inhibition is thought to occur.

5.5. Selection and Timing of Doses

5.5.1. Study Period I

Study Period I is the screening period of the study; no study medication will be administered.

5.5.2. Study Period II

Patients should be instructed to begin study drug the day after Visit 2. Four capsules of study medication should be taken once daily at approximately the same time. It is strongly recommended that it be taken in the morning. Study medication should be taken with food and swallowed whole. Capsules should not be crushed or broken.

Those patients unable to tolerate their starting dose or their full treatment group dose will be discontinued from the study. No dose reductions are allowed in Study Period II.

5.5.3. Study Period III

Investigators are permitted to increase the dose of study medication at Visit 7, Visit 8, or Visit 9. Dose increases should be made based upon the investigator's clinical assessment of need up to a maximum of 120 mg daily of duloxetine or 225 mg daily of venlafaxine extended release. If the subject is not showing a response, dose increases may be made in the following manner: duloxetine 60 mg daily may titrate to 90 mg daily then to 120 mg daily; venlafaxine extended release 150 mg daily may titrate to venlafaxine extended release 225 mg daily. While patients assigned to duloxetine may have their dose increased twice, patients assigned to venlafaxine extended release will only have their dose increased the first time. As investigators and patients are blinded, a choice for a second increase can occur for venlafaxine; however, patients will continue on the 225 mg dose. Those patients unable to tolerate the increased dose of study medication will be discontinued from the study. No dose reductions are allowed in Study Period III.

Patients whose dose is increased will take 7 capsules daily, given as 5 capsules in the morning and 2 capsules in the evening. Patients on duloxetine 90 mg will take 60 mg in the morning and 30 mg in the evening. Patients on duloxetine 120 mg will take 60 mg in

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the morning and 60 mg in the evening. Patients on venlafaxine extended release 225 mg will take the entire dose in the morning with placebo capsules in the evening.

5.5.4 Study Period IV

Patients who discontinue the study at Visit 4 or thereafter, or who complete Study Period III, may enter the taper period at the investigator's discretion. Discontinuation effects are known to occur with the abrupt withdrawal of antidepressants. It is therefore recommended that the dose be gradually reduced to minimize the risk of withdrawal reactions. During the taper period, four capsules of study medication should be taken once daily at approximately the same time. It is strongly recommended that it be taken in the morning. Reduction of study medication should occur at 7-day intervals in the following manner (see Figure HMBU.1): duloxetine 120 mg daily should titrate to duloxetine 60 mg daily, then to duloxetine 30 mg daily, then to no study drug; duloxetine 90 mg daily should titrate to duloxetine 60 mg daily, then to duloxetine 30 mg daily, then to no study drug; duloxetine 60 mg daily should titrate to duloxetine 30 mg daily, then to placebo, then to no study drug; venlafaxine extended release 225 mg daily should titrate to venlafaxine extended release 150 mg daily, then to venlafaxine extended release 75 mg daily, then to no study drug; venlafaxine extended release 150 mg daily should titrate to venlafaxine extended release 75 mg daily, then to placebo, then to no study drug, and venlafaxine extended release 75 mg daily should continue on 75 mg venlafaxine extended release daily, then titrate to placebo, then to no study drug. In order to maintain the blind, patients will appear to be tapered equally.

5.6. Blinding

This is a double-blind study. Patients who meet all the criteria for randomization will be randomly allocated to double-blind treatment at Visit 2 by the IVRS.

In order to preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency codes, generated by a computer drug-labeling system, will be available to the investigator. These codes, which reveal the patient's treatment group when opened, may be opened during the study ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All codes, whether sealed or opened, must be returned to Lilly.

The investigator should make every effort to contact the Lilly clinical research physician prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or patient are unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician for the patient to continue in the study.

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5.7 Concomitant Therapy

In general, concomitant medications with primarily central nervous system activity are not allowed in this protocol. Protocol Attachment HMBU.3 contains a list of some allowed and excluded medications for this study. This is not an exhaustive list. If an investigator is uncertain as to the appropriateness of a certain medication, the investigator should contact the Lilly clinical research physician or a designee. Any changes to this list will be communicated to investigators and will not constitute a protocol amendment. Patients must sign the informed consent document before stopping any excluded medications.

All concomitant medication taken during the study will be recorded on the case report form (CRF). Patients will be instructed to consult with the investigator or study coordinator at the site before taking any new prescribed medications, over-the-counter (OTC) medications, or supplements.

Cough and cold medications containing pseudoephedrine or the sedating antihistamine, diphenhydramine, are excluded.

Patients will be allowed the episodic use of benzodiazepines or certain hypnotics during Study Periods II and III as displayed in Table HMBU.1 below; no more than 8 total days (intermittent or consecutive) are allowed. Any changes to Table HMBU.1 will be communicated to investigators and will not constitute a protocol amendment. Benzodiazepine/hypnotic use during Study Period IV is at the discretion of the investigator. If a patient exceeds the prescribed limits of benzodiazepine use, they must be discontinued from the study. Patients will be strongly encouraged not to use benzodiazepines or hypnotics the night before a scheduled visit and not to alter their intake of caffeine or nicotine during the course of the study.

Table HMBU.1. List of Benzodiazepine/Hypnotic Maximum Daily Doses

Benzodiazepine/Hypnotic	Maximum Daily Dose
Lorazepam	8 mg
Temazepam	30 mg
Diazepam	40 mg
Oxazepam	80 mg
Flunitrazepam	0.5-2 mg
Lormetazepam	4 mg
Chlordiazepoxide	80 mg
Loprazolam	4 mg
Chloral Hydrate	1000 mg
Zolpidem	10 mg
Zopiclone	7.5 mg

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5.8. Treatment Compliance

Compliance for each visit interval is defined as taking between 80% and 120% of the study drug dosage prescribed for that interval. The first time a patient is noncompliant, the patient will be counseled on the importance of taking the prescribed amount of study medication. The second time (either consecutive or nonconsecutive) that a patient is noncompliant, Lilly or its representative will be notified. Patients who are significantly noncompliant will be discontinued.

The following procedures will be employed to assure appropriate drug accountability:

- Drug accountability will be emphasized at the start-up meeting.
- Drug accountability forms will be provided in the clinical trial records binder or similar file.
- Drug accountability will be monitored throughout the study.
- Each patient should be instructed to return all study drug packaging and unused material to the study site at each visit. The study site will keep a record of all drug dispensed to and returned by the patients throughout the study. The study site will return all unused study drug for all patients to Lilly or its designee.

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6. Efficacy, Health Outcome/Quality of Life Measures, and Safety Evaluations

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Protocol Attachment HMBU.2).

6.1. Primary Outcome Measure

The primary outcome measure is the linear measure of global benefit-risk assessment (Chuang-Stein et al. 1991). In this assessment, benefit is defined as remission at endpoint (HAMD₁₇ total score ≤ 7), a virtually symptom-free state; risk is defined by four categories: no AMDP-5 collected adverse events (AMDPAE), mild or moderate AMDPAE, severe AMDPAE, and discontinue with a reason of self-reported adverse event. For each patient, the severity level is determined as the maximum severity of all the treatment-emergent adverse events, collected using AMDP-5, that the patient might experience during the study.

6.2. Efficacy Measures

6.2.1. Primary Efficacy Measure

- 17-item Hamilton Depression Rating Scale (HAMD₁₇) (Hamilton 1960, 1967) is a widely used observational rating measure of depression severity. The HAMD₁₇ will be used to assess the severity of depression and its improvement during the course of the study. The HAMD₁₇ total score ranges from 0 (not at all depressed) to 52 (severely depressed). See Section 3.3 for a discussion of methodological approaches taken to ensure inter-rater reliability in the implementation of the HAMD₁₇ scale. For the primary outcome, remission is defined as a HAMD₁₇ total score ≤ 7 at endpoint.

6.2.2. Secondary Efficacy Measures

- HAMD₁₇ Response Rates: Response is defined as a $\geq 50\%$ reduction in HAMD₁₇ total score from baseline to endpoint.
- HAMD₁₇ Time-to-First Response: Time-to-first response is defined as the visit where a sustained $\geq 30\%$ reduction in the Maier subscale of the HAMD₁₇.
- HAMD₁₇ Remission Rates: Remission is defined as a HAMD₁₇ total score of ≤ 7 at endpoint.

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- The Hamilton Anxiety Rating Scale (HAMA) (Hamilton 1959; Riskind et al. 1987) is a widely used clinician-rated instrument that measures the presence and severity of anxiety. The 14-item version of this scale will be used to assess the severity of anxiety and its improvement during the course of therapy. Each symptom is rated on a defined step scale (0 to 4). The HAMA total score ranges from 0 (not at all anxious) to 56 (severely anxious).
- The Clinical Global Impressions of Severity (CGI-Severity) Scale (Guy 1976) must be administered by the physician, in the presence of the subject, to record the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).
- The Patient's Global Impressions of Improvement (PGI-Improvement) Scale (NIMH 1976) is a patient-rated instrument that measures the improvement of the patient's symptoms. Scores range from 1 (very much improved) to 4 (no change) to 7 (very much worse).
- HAMD₁₇ Subscales (Faries et al. 2000) include the Core subscale (Items 1, 2, 3, 7, and 8) and the Maier subscale (Items 1, 2, 7, 8, 9, and 10), which consist of items thought to represent the "core" symptoms of depression. The Anxiety/Somatization subscale of the HAMD₁₇ (Items 10, 11, 12, 13, 15, and 17) evaluates severity of psychic and somatic manifestations of anxiety, as well as agitation. The Retardation/Somatization subscale (Items 1, 7, 8, and 14) evaluates dysfunction in mood, work, and sexual activity, as well as overall motor retardation. The Sleep subscale (Items 4, 5, and 6) evaluates initial, middle, and late insomnia.

6.2.3. Cognitive Assessment Battery

The composite cognitive score will be based on the four cognitive tests described below. Higher scores correlate to better cognitive functioning. The composite score, ranging from 0-51, is defined as the sum of:

- the average number of words recalled per trial on the 3 learning trials of the Verbal Learning and Recall Test (VLRT) (score 0-15).
- the number of words recalled on the delayed recall for VLRT (score 0-15).
- the fraction of all possible targets correct on the Symbol Digit Substitution Test (SDST) multiplied by 7 (score 0-7).

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- the number of targets hit minus the number incorrect minus the number of times the patient had to be reminded of the task, divided by the possible number correct (40) on the 2DCT, multiplied by 7 (score 0-7). If the resulting number is less than zero, it will be set to a zero value.
- the total score on the Letter-Number Sequencing (LNST) (0-21) divided by 3 (score 0-7).

The four tests were designed to challenge the patient's abilities in the following areas: verbal learning and memory; attention to visually presented material; and working memory and executive function. Numerous studies have demonstrated that depressed patients perform more poorly than matched comparison subjects on tests of new learning and delayed recall (Burt et al. 1995; King et al. 1998). Both depressed patients and those with a history of depressive episodes have decreased hippocampal volume as measured by magnetic resonance imaging (MRI) (Bremner et al. 2000; Sheline et al. 1996). Hippocampal damage due to chronic hypercortisolemia has been proposed as a possible mechanism responsible for the learning and memory deficits associated with depression (Sheline et al. 1996). Performance of depressed persons is also impaired on a variety of tasks requiring substantial cognitive effort (Tancer et al. 1990) and on some tasks placing demands on attention and executive functions that are associated with activation of prefrontal cortical brain regions (Tancer et al. 1990). Cognitive deficits observed in depressed patients usually become less severe when the depressive episode resolves, but some residual cognitive deficits might remain (Beats et al. 1996; Fromm and Schopflocher 1984). The brief cognitive battery selected for this protocol was designed to assess the cognitive domains that are the most impaired in depressed patients.

- The Verbal Learning and Recall Test (VLRT) is a test of verbal learning and recall adapted from the Rey Auditory Verbal Learning Test (RAVLT; Lezak 1995; Rey 1941), will be used to assess verbal learning and memory. For the verbal learning portion of this test, patients will be given three trials to learn a list of 15 words taken from the RAVLT lists (Lezak 1995). On each of the trials, patients will first be asked to read the words out loud as they are presented on the cards one at a time. After all 15 words have been read, the test administrator asks the patient to say as many of the words as he/she can recall. The test administrator then records the number of words recalled correctly. This procedure is repeated for each of the three learning trials. The test administrator then proceeds with the other tests in the cognitive assessment battery. After the remaining tests in the cognitive assessment battery are completed, the patient is asked to recall as many of the words as possible from the list that was presented at the start of the testing session. The learning trial score is the average number of words recalled for the three trials. The delayed recall score is the total number of words correctly repeated from the original list.

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- The Symbol Digit Substitution Test (SDST) is an attention-demanding psychomotor component of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler 1997). The patient is given a symbol-digit code in which each of the digits 1 through 9 is paired with a different symbol. Below the code, a series of symbols selected from those in the code are presented in an irregular order. The patient is instructed to draw the number that is appropriate for each symbol in the space below each symbol and to complete as many correct digits as possible within a 90-second test period. The SDST score is the number correct. The number attempted will also be recorded.
- The Two Digit Cancellation Test (2DCT) is a clinical adaptation of the visual search tasks that have been used to investigate cognitive processes involved in attention and visual information processing (Neisser 1964). The version used in this protocol was designed to assess drug effects on attention to visual stimuli in persons with mild cognitive impairment (Mohs et al. 1997). For this test, the patient is presented with a piece of paper containing rows of digits. At the top of the page are two target digits. The patient is instructed to examine each row of digits working from top to bottom and left to right, crossing off each number that matches either of the two numbers at the top of the page. The patient is given a 30 second practice trial on a practice form, then is given 45 seconds to complete the actual test form. The 2DCT score is the number of targets hit minus the number incorrectly marked (errors) minus the number of times the patient had to be reminded of the task.
- The Letter-Number Sequencing Test (LNST) (Wechsler 1997) is a verbally administered test designed to tax the patient's working memory and executive functioning. The test administrator instructs the patient to listen to a group of numbers and letters and then to repeat them back after rearranging them so that they say the numbers first, in order from smallest to largest, followed by the letters in alphabetical order. For example, if the test administrator gives the sequence B-7, the correct response is 7-B; if the sequence given is 9-C-3, the correct response is 3-9-C. The patient is given 5 practice trials. The test administrator reads the stimuli from the Letter-Number Sequencing worksheet at the rate of 1 item per second, and records the patient's response to each trial verbatim. The patient receives 3 trials for each item (sequence lengths of 2 through 8 number/letter combinations), and each trial is scored (0 = incorrect; 1 = correct). The sum of the 3 trials is recorded as the item score. If a patient fails all 3 trials of an item, the test is discontinued. The LNST score is the sum of the seven item scores. The maximum score is 21; the minimum score is 0.

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6.3. Health Outcome/Quality of Life Measures

- The SF-36 Health Status Survey (SF-36) (Ware et al. 1993) is used to assess general quality of life. The SF-36 consists of 36 questions covering the following 8 health domains (subscales): physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each subscale is scored by summing the individual items and transforming the scores into a 0 to 100 scale, with higher scores indicating better health status or functioning. No overall total score is calculated. Two summary scores, the physical component summary (PCS) and the mental component summary (MCS), have been constructed based on the eight SF-36 subscales. The equations are provided in SF-36 Physical and Mental Health Summary Scales: A User's Manual (Ware et al. 1993). The two summary scores represent independent (orthogonal) indices based on factor analysis of SF-36 scale scores using Medical Outcomes Study data.
- The Quality of Life in Depression Scale (QLDS) (Hunt and McKenna 1992) is a patient-reported, depression-specific, Health-Related Quality of Life instrument. This scale, which measures subjective well-being, consists of 34 yes/no items. The QLDS scores range from 0 (good quality of life) to 34 (very poor quality of life). Contents for the measure were derived from a needs-based approach, where individual's lives gain quality from the ability and impact of disease on their lives in terms of the capacity of the individual to satisfy their needs. Basic needs include companionship, love, conversation, pleasure, self-care, and nutrition. There is evidence that the QLDS is sensitive to differences in severity of depression. The QLDS has demonstrated significant differences between treatment groups in previous duloxetine clinical trials. The instrument has been well validated and there are a number of international translations that have shown excellent reliability and construct validity.
- The EuroQOL (EQ-5D) (Kind 1996) is a 5-item patient reported measure of health status developed for use in evaluating health and healthcare. It produces a numeric score for health status on which full health has a value of 1 and death has a value of 0. EQ-5D describes health status in terms of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Three types of data are generated for each patient: a profile, a weighted health index, and a score on the self-rated thermometer, indicating self-assessment of health state.

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- The Sheehan Disability Scale (SDS) (Sheehan 1996) is a self-rated instrument used to measure the effect of the patient's symptoms on work/school, social life, and family life/home responsibilities. The visual analog scale uses spatiovisual, numeric, and verbal descriptive anchors simultaneously to assess disability across the three domains. The number most representing how much each area was disrupted by symptoms is marked along the line from 0 = not at all, to 10 = extremely. Scores of 5 and above are associated with significant functional impairment. Two additional questions will measure the number of days lost and days underproductive.
- The Patient Health Questionnaire (PHQ) is a self-administered version of the PrimeMD (Spitzer et al. 1994, 1999). The physical complaints module consists of 13-items that capture complaints of common physical symptoms seen in primary care settings. Each symptom (for example, headache, back pain, dizziness) will be graded by the patients as: "bothered not at all" = 0, "bothered a little" = 1, "bothered a lot" = 2. The scores range from 0-26 with higher scores indicating more bothersome physical complaints. A subscale of items associated with pain will also be assessed
- The Resource Use and Hospitalization Modules (Broadhead et al. 1990; Revicki et al. 1994) are designed to measure direct and indirect costs. Direct costs include inpatient and outpatient costs, while indirect costs include lost days of work and caregiver time spent with patients. Inpatient costs include costs associated with hospitalizations and time spent in emergency rooms and psychiatric rooms. Outpatient costs include costs associated with visits to various health care providers, home health care by health care providers, and partial care. Patients will be asked a set of standard questions on missed work, bed disability, and restricted activity days. They will self-report on the number of days over the past month that they have been either late to work, missed work, or missed usual activities due to symptoms. These questions will assist with defining the indirect cost of MDD and have been used widely in epidemiological studies.

6.4. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate healthcare option, adverse events that are serious or that caused the patient to discontinue before

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completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up is left to the discretion of the investigator.

6.4.1. Adverse Events

Lilly has standards for reporting adverse events that are to be followed regardless of applicable regulatory requirements that may be less stringent. For purposes of collecting and evaluating all information about Lilly drugs used in clinical trials, a clinical trial adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship. Cases of pregnancy should be reported for tracking purposes. Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

Prior to enrollment, study site personnel will note the occurrence and nature of each patient's medical condition(s) in the appropriate section of the case report form (CRF). During the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

If a patient experiences an adverse event after the informed consent document is signed (entry) but the patient is never assigned to treatment (enrollment), the event will ONLY be reported if the investigator believes that the event may have been caused by a protocol procedure.

All adverse events occurring after enrollment must be reported to Lilly or its designee by CRF.

In addition, study site personnel must report to Lilly or its designee immediately, any serious adverse event or any instance where the investigator unblinds a patient's treatment group assignment for any other reason.

If a patient's dosage is reduced or treatment is discontinued as a result of an adverse event, study site personnel must clearly document the circumstances and data leading to any such dosage reduction or discontinuation of treatment, using the case report form.

If clinically significant abnormal electrocardiograms (ECGs) or laboratory values lead to, or are associated with, clinical symptom(s), the diagnosis should be reported as an adverse event.

In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should enter "unexpected benefit" with the actual event term (for example, the complete actual term would be "unexpected benefit—sleeping longer").

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6.4.1.1. Serious Adverse Events

Study site personnel must report immediately to Lilly or its designee by the designated transmission method any adverse event from this study that results in one of the following outcomes, or is significant for any other reason:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect.

Serious adverse events occurring after a patient is discontinued from the study will ONLY be reported if the investigator believes that the event may have been caused by the study drug or a protocol procedure.

6.4.1.2. Adverse Event Monitoring with a Systematic Questionnaire

The Association for Methodology and Documentation in Psychiatry (AMDP-5) (CIPS 1996) is a tool to collect adverse events and the severity of the events during treatment. Each event listed can be rated as absent, mild, moderate, severe, or not evaluated.

The AMDP-5 is to be administered after study site personnel have questioned the patient and noted any change in the presenting condition(s), any change in the preexisting condition(s), and the occurrence and nature of any adverse events. All adverse events obtained during this routine questioning must be reported to Lilly in the adverse event section of the CRF.

Only serious adverse events elicited through the AMDP-5 questionnaire are to be recorded in the adverse event section of the CRF. Serious adverse events from the AMDP-5 questionnaire are also reported to Lilly immediately, by the designated transmission method.

Non-serious adverse events obtained through use of the AMDP-5 questionnaire are not recorded in the adverse event section of the CRF. They are reported and analyzed separately.

6.4.1.3. Other Safety Measures

In addition to patient and physician reported adverse events, the following adverse event measures will be used in this study:

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- The Changes in Sexual Functioning Questionnaire (CSFQ) (Clayton et al. 1997) was designed to evaluate the effects of illness and medication on the quality of sex life. The CSFQ has two versions, a 36-item version for men and a 34-item version for women. In addition to a total score, 5 subscale scores can be computed reflecting the following factors: sexual desire/frequency, sexual desire/interest, sexual pleasure, sexual ability/excitement, and sexual release/orgasm. The items are rated using a 5-point Likert scale (1 through 5). Lower scores indicate greater sexual dysfunction.
- The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989) is a 19-item, subject-completed questionnaire designed to assess sleep quality and sleep disturbances. Seven components are created from the 19 items. When the components are added together, a global score (range 0-21) is created. Higher scores indicated poorer sleep quality.

6.4.2. Laboratory Tests

Standard laboratory tests including chemistry, hematology, and urinalysis panels will be performed at the times specified in the Study Schedule (Protocol Attachment HMBU.2). Clinical laboratory tests (Protocol Attachment HMBU.4) will be analyzed by a central laboratory.

Investigators must document their review of each laboratory report by signing or initialing and dating each report.

6.4.3. Electrocardiograms (ECGs)

Twelve-lead ECGs will be obtained according to the Study Schedule (Protocol Attachment HMBU.2).

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, for immediate patient management and to determine whether the patient meets entry criteria. If a clinically significant increase in the QTc interval from baseline is present, then the investigator should assess the patient for symptoms (such as palpitations, near syncope, and syncope).

The ECGs will subsequently be sent for analysis to the centralized ECG vendor designated by Lilly. ECGs will be interpreted by the ECG vendor cardiologist for data analysis and report writing purposes.

Once the overread ECG is returned from the centralized ECG vendor, the investigator or qualified designee is responsible to determine if any change to the patient management is needed and document his/her review by signing and dating the confirmed ECG. Any clinically significant findings that result in a diagnosis should be recorded on the Adverse Events/Pre-existing Condition page of the CRF.

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If there are differences in ECG interpretation between the investigator or qualified designee and the ECG vendor cardiologist, the investigator or qualified designee's interpretation will prevail for study entry and immediate patient management purposes and the ECG vendor cardiologist's interpretation will prevail for data analysis purposes.

6.4.4. Safety Monitoring

The Lilly clinical research physician will monitor safety data throughout the course of the study.

The Lilly clinical research physician will review serious adverse events within time frames mandated by company procedures and will review trends, laboratory analytes, and adverse events at periodic intervals.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring board (an advisory group for this study formed to protect the integrity of data; see Section 8.2.11) can conduct additional analyses of the safety data.

6.5. Appropriateness of Measurements

The measures of efficacy and safety are standard measures used in clinical trials of depression and are well documented and reliable.

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7. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the case report forms (CRFs), and study procedures.
- Make periodic visits to the study site.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- Review and evaluate CRF data and use standard computer edits to detect errors in data collection.
- Verify the quality of the data.

In addition, Lilly or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. Lilly Medical Quality Assurance (MQA) and/or regulatory agencies may audit the study at any time. Investigators will be given notice before an MQA audit occurs.

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ethical review boards with direct access to original source documents.

7.1. Data Entry

Symptomologic and psychiatric rating scales will be used in this trial. Some or all of a patient's rating scale data may be directly entered into the CRF at the time that the information is obtained. In these instances where there is no prior written record of the data, the CRF will serve as the source document. Any data for which the CRF will serve as the source document will be identified and documented by each site in that site's study file.

CRF data will be encoded and stored in a database on the AS400 platform.

Central laboratory data will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the contract laboratory to the Lilly generic labs system.

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8. Sample Size and Statistical Methods

8.1. Determination of Sample Size

Approximately 320 patients will be enrolled to either duloxetine 60 mg daily or venlafaxine extended release 150 mg daily treatment group at the randomization visit with 1:1 ratio. The sample size was determined based on the consideration that data from this study and Study F1J-MC-HMCQ, which is similar in design, will be combined for testing the primary objective. With 320 patients per arm (duloxetine 60 mg daily or venlafaxine extended release 150 mg daily) in the pooled data, it is anticipated to have at least 80% power to detect a treatment group difference of 0.74 points in the Global Benefit-Risk assessment score between duloxetine and venlafaxine treatment groups at the endpoint of Study Period II. The sample size was determined using a two-sided test with $\alpha=0.05$, assuming a common standard deviation of 3.16 and a discontinuation rate of 10%.

8.2. Statistical and Analytical Plans

8.2.1. General Considerations

All analyses will be conducted on an intent-to-treat basis. An intent-to-treat analysis is an analysis of data by the groups to which patients are assigned by random allocation, even if the patient might not take the assigned treatment, might not receive the correct treatment, or might not follow the protocol.

Treatment effects will be evaluated based on a two-sided significance level of 0.05 and interaction effects at a significance level of 0.10. No adjustments will be made for multiple comparisons. Unless otherwise specified, when a total score is calculated from individual items, it will be considered missing if any of the individual items are missing. When an average score is computed from individual items, it is calculated from nonmissing values.

Unless otherwise specified, when an analysis of variance (ANOVA) model is used to analyze a continuous efficacy variable, the model will contain the terms of treatment, investigator, and treatment-by-investigator interaction. The interaction will be tested at a significance level of 0.10. When the interaction is not statistically significant, treatment effect will be evaluated using the model without the interaction term. Similar logic is applied to an analysis of covariance (ANCOVA), which in general refers to the model that consists of the terms used in the ANOVA with baseline score added as a covariate. Type II sum-of-squares for the least-squares means will be used for the statistical comparison using ANOVA or ANCOVA.

According to the Objectives of this protocol, similar statistical evaluation will be conducted for data obtained from Study Period II (of 6 weeks therapy) and for those from Study Periods II and III (of 12 weeks therapy) as long as data collection is performed at

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corresponding visits. Thus, unless otherwise specified, the statistical methods described in each section below will be applied to the analyses for Study Period II as well as to those for Study Period II and III. In all the comparisons where baseline and endpoint are used, unless otherwise specified, baseline refers to the last nonmissing observation at or before the randomization visit (Visit 2), and endpoint refers to the last nonmissing observation in the time frame of comparison (Visit 3 to Visit 7 for the 6-week comparison; Visit 3 to Visit 10 for the 12-week comparison).

When the investigator sites are used in the analyses, the sites having less than 10 randomized patients with at least one nonmissing value for baseline-to-endpoint change on HAMD₁₇ total score will be pooled and considered a single site. If a pooled site still has less than 10 randomized patients, these patients will be pooled with the smallest remaining site. This pooling procedure will continue until every site used in the analyses has at least 10 patients. All pooling will occur within the same country.

Any changes to the proposed analyses made prior to unblinding the data, with the exception of the primary efficacy analysis, will not necessitate a protocol amendment. All changes to the analysis plan, both those prior to unblinding the data and those subsequent to unblinding the data, will be documented and justified in the final study report.

Exploratory analyses of the data will be conducted as deemed appropriate. Statistical analysis of this protocol will be the responsibility of Eli Lilly and Company. Statistical Application Software (SAS, Version 8.0) will be used to perform all statistical analyses. SAS programs will be run either under the MVS operation system or in the PC environment.

Section 8.2.2 to Section 8.2.11 below elaborate the data analysis methods for the data collected in the Study Period II (6 weeks therapy) and Study Period III (12 weeks therapy). Data analysis methods for Study Period IV (for study drug tapering) are stated in Section 8.2.12.

8.2.2. Patient Disposition

The reasons for patient disposition (completed the study period, discontinued due to adverse events, discontinued due to lack of efficacy, etc.) will be summarized by percentage within each treatment group. The treatment group differences will be evaluated using a Fisher's exact test.

8.2.3. Patient Characteristics

Patient characteristics (age, origin, height, weight, baseline HAMD₁₇ total score, CGI score) will be summarized by treatment group. In addition, historical diagnosis and psychiatric/depression history will also be summarized for all randomized patients by treatment group. For the continuous measures, the baseline comparability between

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treatment groups will be examined using an ANOVA model with the terms of treatment and investigator. Categorical variables will be assessed using a Fisher's exact test.

8.2.4. Previous and Concomitant Therapy

Previous medications will be summarized by treatment group.

Concomitant medication used during the therapy phase will be summarized by treatment group. For each of the summaries, the differences between the treatment groups in the frequency of usage for each medication will be analyzed by a Fisher's exact test. In addition, the percentage of patients who use benzodiazepines/hypnotics concomitantly will be summarized separately from other concomitant medication by visit and by at least once across all visits, and will be analyzed by a Fisher's exact test. The mean daily dose of benzodiazepines/hypnotics for each patient will be calculated across the therapy phase and will be evaluated using the ANCOVA model. The distribution of the residuals will be checked. When the assumptions of normality and homogeneity are violated, rank-transformed change scores will be analyzed using an ANOVA model with the terms of treatment and investigator, and will be reported. Otherwise, the inference from the analysis on raw data will be reported.

8.2.5. Study Drug Exposure and Treatment Compliance

Days of full study drug exposure will be calculated for each patient as the difference between the randomization date and the last dose date at or before Visit 10. The exposure days will be summarized by treatment group and analyzed using the ANOVA model.

At each visit, the status of treatment compliance will be collected based on the percentage of capsules taken over the total capsules prescribed. A patient is considered to be compliant if the percentage is between 80% and 120%. A patient is considered to be compliant overall in a study period if he or she is compliant for each nonmissing observation in that particular study period. The percentage of patients who are compliant to treatment at each individual visit and overall will be summarized by treatment group and analyzed by a Fisher's exact test.

Dose escalation might occur for some patients during Study Period III. The percentage of patients who will experience the dosage increase will be summarized by treatment group.

8.2.6. Primary Outcome and Methodology

The primary outcome measure is the linear measure of Global Benefit-Risk (GBR) assessment. The approach was first proposed by Chuang-Stein et al. (1991). In this assessment, benefit is defined as remission at endpoint (HAMD₁₇ total score ≤ 7), a virtually symptom-free state; risk is defined by four categories: no AMDP-5 collected adverse events (AMDPAE), mild or moderate AMDPAE, severe AMDPAE, and

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discontinue with a reason of self-reported adverse event. For each patient, the severity level is determined as the maximum severity of all the treatment-emergent adverse events, collected using AMDP-5, that the patient might experience during the study. The concept of "treatment-emergent" refers to the events that first occurred or worsened during the treatment period. Considering the benefit and the risk a patient can have when taking the study drug, there are eight mutually exclusive categories listed in Table HMBU.2.

Table HMBU.2. Global Benefit-Risk Assessment Categories

	No AMDPAE	Mild or Moderate AMDPAE	Severe AMDPAE	DC due to self-reported adverse event
Remission	I	II	III	IV
Non-remission	V	VI	VII	VIII

Abbreviation: AMDPAE = Association for Methodology and Documentation in Psychiatry collected adverse events, DC= discontinue.

The overall benefit and risk impact on the patients moves from overwhelmingly beneficial in Category I to least beneficial, or least desirable, in Category VIII. With observed proportions in each category, a weight function of $W = (5, 4, 3, 1, -1, -3, -4, -5)$ will be applied to compute the linear GBR score (Chuang-Stein 1991). The weight function is chosen to reflect the benefit-risk impact on the patients along those categories. In mathematics, the linear GBR score is defined as $M = \sum w_i * p_i$, where w_i is the weight for category i and p_i is the observed proportion of patients in category i , $i=1,2,\dots,8$.

When the score is positive, the benefit outweighs the risk. The higher the score, the more benefit over risk the therapy can provide.

The primary objective of this study will be tested by a Z-test created from the linear GBR scores from duloxetine and venlafaxine extended release treatment groups, where the statistics

$$Z = (M_1 - M_2) / \sqrt{(\text{estimated variance of } M_1 + \text{estimated variance of } M_2)},$$

where 1 refers to duloxetine treatment group, and 2 refers to venlafaxine extended release treatment group.

In addition, analysis for GBR scores will be stratified based on the country of investigator to control for the potential variation in GBR scores across countries that might result from the differences in geographic regions. The mathematical details for the estimated variance and the stratification method will be described in the Statistical Analyses Plan, which will be available and locked before the data is unblinded.

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As specified by the Primary Objective of this study, this primary analysis will be conducted using combined data from this study and the similar designed Study F1J-MC-HMCQ. Data from the patients taking the same medication and dosage from the two studies will be pooled for the analysis. To preserve the integrity of the data, neither study will be unblinded prior to the unblinding of the other study.

8.2.7. Secondary Efficacy Analyses

8.2.7.1. Non-inferiority Test on HAMD₁₇ Total Score

To perform the non-inferiority test, data from this study will be combined with data from similar designed Study F1J-MC-HMCQ according to the principle described above.

Change from baseline to endpoint on HAMD₁₇ total score will be analyzed using an ANCOVA model as described in Section 8.2.1, General Consideration. The 97.5% one-sided confidence interval (CI) will be created for the difference in mean change between duloxetine and venlafaxine extended release. It will be declared that duloxetine is non-inferior to venlafaxine extended release if the upper bound of the 97.5% CI is less than or equal to 1.15. The non-inferiority margin of 1.15 is determined as one half of the absolute gain of venlafaxine extended release over placebo reported from study by Rudolph and Feiger (1999).

8.2.7.2. Analyses on Secondary Efficacy Outcome Measures

Table HMBU.3 presents the analyses for the secondary efficacy variables, either collected directly from CRFs or derived from raw observations.

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Table HMBU.3. Analysis for the Secondary Efficacy Variables

Efficacy Variable	Derivation and Details	Analysis
1. Change from baseline to endpoint: a. HAM D ₁₇ total score b. HAM D ₁₇ depressed item (Item 1) c. HAM D ₁₇ subscales of Core, Maier, Anxiety, Retardation and Sleep d. HAMA total score e. CGI – Severity	a. Sum of 17-HAMD items c. Refer to Section 6.12 for the composition of the subscales d. Sum of HAMA 14 items	Variables 1a to 1e will be analyzed by the ANCOVA models as described in Section 8.2.1, General Considerations

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Table HMBU.3. Analysis for the Secondary Efficacy Variables (continued)

Efficacy Variable	Derivation and Details	Analysis
2. All baseline and postbaseline data at the Visits in the acute therapy for: a. HAMD ₁₇ total score b. HAMD ₁₇ depressed item (Item 1) c. HAMD ₁₇ subscales of Core, Maier, Anxiety, Retardation and Sleep d. CGI – Severity	(The same as above)	Variables 2a to 2d will be analyzed by a repeated measures analysis. The model details will be described in text beneath the table.
3. All post-baseline data for PGI-Improvement		The observed scores at each postbaseline visit as well the last nonmissing score (defined as endpoint) will be analyzed by the ANOVA model as described in Section 8.2.1, General Considerations. In addition, the data will also be analyzed by a repeated measures analysis. The model will be similar to the one used for the variables in the above group, with the modifications that there are no baseline or baseline-by-visit effects in the model.
4. Categorical variable: a. Response rate at endpoint b. Remission rate at endpoint c. Sustained 30% improvement on Maier subscale	a. Response: at least 50% reduction from baseline to endpoint in HAMD ₁₇ total score b. Remission: HAMD ₁₇ total score ≤ 7 at endpoint c. Sustained 30% improvement on Maier subscale: a reduction on Maier subscale of at least 30% from baseline at endpoint, at an earlier visit prior to the last visit of the study period, and at all the visits in between.	For variables 4a to 4c, proportions will be summarized by treatment group and will be analyzed by a Fisher's exact test.

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Table HMBU.3. Analysis for the Secondary Efficacy Variables (concluded)

Efficacy Variable	Derivation and Details	Analysis
<p>5. Time-to-event variable:</p> <p>a. Time-to-first visit that sustained 30% improvement on Maier subscale is achieved</p> <p>b. Time-to-first visit that HAMD₁₇ total is ≤ 7</p>	<p>a. The earliest visit at which the sustained 30% improvement on Maier subscale is observed.</p> <p>For both 5a and 5b, the time-to-event variables are calculated by the algorithm: for those who meet the criterion, time = the date of the visit at which the event occurred – randomization date; for those who do not meet the criterion, time = the last dose date – randomization date.</p>	<p>- For variables 5a and 5b, the Kaplan-Meier survival curves of time-to-event will be calculated by treatment group. In the calculation, patients who do not have the event will be considered as right-censored observation. The comparison of the survival curves between treatment groups will be conducted by a log-rank test and the Wilcoxon test (using PROC LIFETEST).</p> <p>- Additionally for 5a, the time at which 50% of the patients achieve the sustained 30% reduction by the K-M estimation, defined as time-to-onset, will be presented by treatment group.</p> <p>- Analysis on 5a will only be conducted for the data from 12-week study periods</p>

Note: Baseline is defined as the last measurement taken at, or prior to, Visit 2; endpoint is defined as the last nonmissing measurement taken in the comparison study period (Study Period II: Visit 3 to Visit 7; Study Periods II and III: Visit 3 to Visit 10); last visit is defined as the visit where the endpoint is assessed. Abbreviations: CGI-Severity = Clinical Global Impressions of Severity; PGI-Improvement = Patient's Global Impression of Improvement; HAMD₁₇ = 17-item Hamilton Depression Rating Scale.

A repeated measures analysis refers to a likelihood-based, mixed-effects repeated measures analysis using all the longitudinal observations at each postbaseline visit. The model will include the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline score and baseline-by-visit interaction. The following covariance structures will be used to estimate within-patient errors in preliminary analyses on HAMD₁₇ total score: unstructured, spatial power, Toeplitz, compound symmetric, and simple structures, with and without heterogeneous variances by visit. The covariance structure converging to the best fit among those preliminary analyses, as determined by Akaike's information criterion, will be chosen as the covariance in the model of repeated measures analyses for all efficacy variables exclusively. The Kenward-Roger method will be used to estimate denominator degrees of freedom. Type III sum-of-squares for the least-squares means will be used. Analyses will be implemented using SAS PROC MIXED (Version 8.0).

When analyzing an efficacy variable using the repeated measures analysis, the primary comparison will be the contrast between duloxetine and venlafaxine extended release treatment groups at the last visit of the study period for which the comparison is performed. Secondary comparison will be the contrast between duloxetine and venlafaxine extended release treatment groups at each postbaseline visit where the specific efficacy assessment is conducted.

8.2.7.3. Analysis for Cognitive Outcome Measure

The cognitive outcome measure will be the composite cognitive score, ranging from 0-51. This score will be the total computed from the data collected from the four cognitive tests described below:

- the average number of words recalled per trial on the 3 learning trials of the VLRT (score 0-15)
- the number of words recalled on the delayed recall for VLRT (score 0-15)
- the fraction of all possible targets correct on the SDST multiplied by 7 (score 0-7)
- the number of targets hit minus the number incorrect minus the number of times the patient had to be reminded of the task, divided by the possible number correct (40) on the 2DCT, multiplied by 7 (score 0-7). If the resulting number is less than zero, it will be set to a zero value
- the total score on the LNST (0-21) divided by 3 (score 0-7).

Change from baseline to endpoint on the cognitive composite score will be analyzed by the ANCOVA model as described in Section 8.2.1.

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8.2.8. Health Outcome/Quality of Life Analyses

Patient self-reported health outcomes include the following:

- The Medical Outcomes Study Short Form-36 (SF-36) Questionnaire
- Quality of Life in Depression Scale (QLDS)
- The EuroQoL instrument version EQ-5D (EQ-5D)
- Sheehan Disability Scale (SDS)
- Patient Health Questionnaire (PHQ)
- Resource Utilization Questionnaire

The SF-36 consists of 36 questions covering eight health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each domain is scored by summing the individual items and transforming the scores into a scale from 0 to 100, with higher scores indicating better health status or functioning. No overall total score is calculated. Moreover, two summary scores, the physical component summary (PCS) and the mental component summary (MCS), have been constructed based on the eight SF-36 domains. The equations are provided in the SF-36 Physical and Mental Health Summary Scales: A User's Manual. The two summary scores represent independent (orthogonal) indices based on factor analysis of SF-36 scale scores using Medical Outcomes Study data (Ware et al. 1993).

For each of the domains as well as the PCS and the MCS, the treatment group differences will be evaluated by the analyzing the change from baseline to endpoint using the ANCOVA model.

The total score from QLDS will be calculated from 34 items and the baseline-to-endpoint change in QLDS total score will be analyzed by the ANCOVA model.

The EQ-5D questionnaire consists of five items: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. For each item patients choose one of the three options that will best describe the status. The three options reflecting increasing degrees of difficulty are coded as 1, 2, and 3. Scores from the five items form a 5-digit code that describes the respondent's health state. This 5-digit code is then converted to a weighted index (called EQ-5D index) using population values provided by the EuroQoL group. The change from baseline to endpoint in EQ-5D index will be analyzed by the ANCOVA model.

SDS assesses the effect of disability in three areas: work, social life and family life using a 0 to 10 scale. Changes from baseline to endpoint in each of the areas will be analyzed using the ANCOVA model. The total of the three areas will also be analyzed using the ANCOVA model. When the data for the item of Work is entered as "N/A" for a patient,

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it will be imputed by using the average score from the other two items of social life and family life from that patient.

PHQ is used to collect the bothersome level on a range of physical symptoms. The Resource Utilization Questionnaire is used to collect information for the analysis of comparing resource utilization between treatment groups. Data collected by the Resource Utilization Questionnaire and PHQ do not directly impact the clinical evaluation of the study drug, and thus will not be reported in the study report. The data from the Resource Utilization Questionnaire and PHQ will be summarized in an independent report, while the data analysis plan will be available to regulatory agencies prior to the completion of the study.

8.2.9. Safety Analyses

8.2.9.1. Adverse Events

8.2.9.1.1. Serious Adverse Events, Discontinuation due to Adverse Events, and Treatment-Emergent Adverse Events

Treatment group differences in the incidence rates of serious adverse events will be evaluated using Fisher's exact test.

The adverse events reported as reasons for discontinuation will be summarized by treatment group and compared among the treatment groups using Fisher's exact test.

Preexisting conditions will be summarized and compared between the treatment groups using Fisher's exact tests.

Treatment-emergent adverse events (also called treatment-emergent signs and symptoms [TESS]) are the reported events that first occurred or worsened during the treatment period. For each treatment-emergent adverse event, the severity level is recorded according to the patient's perceived severity of the event (mild, moderate, or severe). The incidence rates of treatment-emergent adverse events will be analyzed by Fisher's exact tests. Moreover, treatment-emergent adverse events will be summarized by their maximum severity as reported and analyzed by a Fisher's exact test, where the maximum severity of an event is defined as the maximum among all the severity reported for that particular event during the treatment.

When analyzing patient-reported adverse events, the Medical Dictionary for Regulatory Activities (MedDRA) will be used as the mapping dictionary between the terms collected on the case report form (CRF) and the terms used in analysis. The most updated version of MedDRA at the time of conducting data analysis will be used.

Treatment-emergent adverse events collected by AMDP-5 will also be analyzed by frequency and by the maximum severity. In those analyses, the concepts of "treatment-emergent" and "maximum severity" are the same as used for analyzing patient self-reported adverse events, as described above.

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8.2.9.2. Vital Signs, Weight, and ECG Evaluation

Change from baseline to endpoint in vital signs (sitting heart rate and blood pressure, including diastolic and systolic) will be analyzed using the ANOVA model. Change from baseline to endpoint in weight will also be analyzed by the ANOVA model.

A patient is considered to have hypertension if his or her blood pressure after randomization meets the following criteria:

- Sitting diastolic blood pressure ≥ 90 mm Hg and increase from baseline (defined as the highest of the measures across all the visits prior to randomization) of 10 mm Hg for 3 consecutive visits, or
- Sitting systolic blood pressure ≥ 140 mm Hg and increase from baseline (defined as the highest of the measures across all the visits prior to randomization) of 10 mm Hg for 3 consecutive visits.

The percentage of patients with hypertension will be summarized by therapy group and will be analyzed using Fisher's exact tests.

In addition, the percentage of patients who had 3 consecutive elevations on sitting diastolic blood pressure (defined above) and the percentage of patients who had 3 consecutive elevation on sitting systolic blood pressure (defined above) will also be summarized and compared using Fisher's exact test, separately.

8.2.9.3. Clinical Laboratory Evaluation

Change from baseline to endpoint (of Study Period II and Study Period III) for the chemistry and electrolyte group and the hematology group (including prolactin) will be analyzed by the ANOVA model. Change from baseline to endpoint of Study Period III for the urinalysis group will be analyzed by the same model. Rank-transformed data will be used in the analysis given the view that the change scores for most of the laboratory analytes are not normally distributed.

A treatment-emergent high laboratory value is a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at endpoint. A treatment-emergent low laboratory value is a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at endpoint. The performing laboratory's reference ranges will be used to determine limits for abnormal laboratory values. The incidence of treatment-emergent high/low values will be computed by therapy group and evaluated using Fisher's exact test. Patients with a high/low laboratory value for a specific laboratory test at baseline will be excluded from the analysis of treatment-emergent high/low values for that analyte.

8.2.9.4. Sexual Functioning and Sleep Quality Evaluation

Sexual functioning will be assessed by the Changes in Sexual Functioning Questionnaire (CSFQ) of 14 items. The CSFQ has two versions, a 36-item version for men and a 34-item version for women. The following six variables will be obtained from the CSFQ:

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Total score (range: 14 - 70), Sexual desire/frequency score (range: 2 – 10), Sexual desire/interest (range: 3 – 15), Sexual pleasure (range: 1 – 5), Sexual arousal/excitement (range: 3 - 15), and Sexual orgasm/complete (range: 3 – 15). For all the measures, the lower the score, the more severe the sexual dysfunction.

Change from baseline to endpoint for each of the scores will be analyzed by the ANCOVA model as described in Section 8.2.1 separately for male and female patient groups

Sleep quality will be evaluated using Pittsburgh Sleep Quality Index (PSQI). This questionnaire consists of nine questions collecting information related to sleep hours and quality of sleep. The global PSQI score is the sum of the seven components which are either collected by the questionnaire or derived from the variables collected from the questionnaire. Each component results in a score ranging from 0 to 3 with the higher the score, the more difficult or less quality with sleep. These seven components are defined as

- Subjective sleep quality (Item 6)
- Sleep latency (Categorize PSQI Item 2, Minutes to fall asleep, into 0, if ≤ 15 , 1 if > 16 and ≤ 30 , 2 if > 31 and ≤ 60 , 3 if > 60 . Add this score with Item 5a. Determine the Difficulty score by the sum [ranges from 0 to 6]: 0 if sum = 0; 1 if sum = 1 or 2; 2 if sum = 3 or 4; 3 if sum = 5 or 6)
- Sleep duration (determined by the integer of actual sleep hours by Item 4: 0 if hours ≥ 7 ; 1 if hours = 6; 2 if hours = 5; and 3 if hours ≤ 4)
- Habitual sleep efficiency (Calculate the percentage of real hours of sleep over hours in bed. The Efficiency score is determined as: 0 if the percentage is $\geq 85\%$; 1 if $\geq 75\%$ and $< 85\%$; 2 if $\geq 65\%$ and $< 75\%$; and 3 if $< 65\%$.)
- Sleep disturbances (Calculate the sum of Items 5b to 5j and the sum ranges from 0 to 27. Frequency of trouble sleep score is determined as: 0 if the sum = 0; 1 if sum is between 1 and 9; 2 if the sum is between 10 and 18, and 3 if the sum is between 19 and 27.)
- Use of sleep medication (Item 7)
- Daytime dysfunction (Calculate the sum of Items 8 and 9. The Energy level score is determined by the sum [ranges from 0 to 6]: 0 if sum = 0; 1 if sum = 1 or 2; 2 if sum = 3 or 4; 3 if sum = 5 or 6.)

The change from baseline to endpoint for the global PSQI score will be analyzed by the ANCOVA model as described in Section 8.2.1.

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8.2.10. Subgroup Analyses

Table HMBU.4 lists all the subgroups by which the subgroup analyses for the HAMD₁₇ total score will be conducted.

Table HMBU.4. Definition for the Subgroups

Subgroup Variable	Categories
a. Age	a. < 55 or ≥ 55
b. Gender	b. Female or Male
c. Ethnic Origin	c. Caucasian African Descent East/Southeast Asian Western Asian Hispanic Other
d. Baseline severity of depression	d. Baseline HAMD ₁₇ total < 25 or ≥ 25
e. Baseline severity of anxiety	e. Baseline HAMA total < 20 or ≥ 20

To analyze a specific subgroup's impact, change from baseline to endpoint will be analyzed using an ANCOVA model with all the terms described generally in Section 8.2.1 with additional terms of the subgroup and the subgroup-by-treatment interaction. The primary statistical testing will be for the treatment-by-subgroup interaction, which will be tested at the significance level of 0.10. Furthermore, treatment group differences will be evaluated within each category of a subgroup regardless of the significance level of the treatment-by-subgroup interaction.

For the subgroup of racial origin, all the categories that have less than 10% of the randomized patients in the study will be combined as Other in the analysis.

Subgroup analysis for safety variables and quality of life variables will be conducted as deemed appropriate and necessary.

8.2.11. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, a Data Monitoring Committee (DMC) will be formed and the interim analysis will be conducted under the auspices of the DMC. The DMC will disseminate interim results, if it is necessary, in a manner that will not affect the conduct of the ongoing study.

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8.2.12. Analysis Plan for Study Period IV: Tapering Period

Patients who complete Study Period III have the option to enter Study Period IV, the tapering period. Patients who discontinue from the study before the last visit of Study Period III and on or after Visit 4 also have the option to enter Study Period IV.

Regardless of the last dose taken in Study Period III, all patients taking duloxetine or venlafaxine extended release will be grouped as duloxetine or venlafaxine extended release treatment group, and these two treatment groups will be used in all the analyses conducted for this study period.

Data from this study will be combined with data from similar designed Study F1J-MC-HMCQ according to the principle described in Section 8.2.6.

Since Study Period IV is an option for the patients, statistical inferences might not be valid if the number of patients is too small or not balanced between the two treatment groups. Thus, the statistical comparisons will only be made when each treatment group has at least 100 patients. Nevertheless, the statistical models will be provided in the following sections.

When performing the data analysis for this period, when the investigator is used as a factor in an analysis, it will be the one used in the analysis for Study Period II.

8.2.12.1. Patient Characteristics

The characteristics (as detailed in Section 8.2.3) of those patients who enter Study Period IV will be summarized and compared between the treatment groups using the model and the test as described in Section 8.2.2.

8.2.12.2. Concomitant Medication and Treatment Compliance

Concomitant medication used during this study period will be summarized by treatment group. The treatment group difference in the frequency of usage for each medication will be analyzed by a Fisher's exact test. In addition, the percentage of patients who use benzodiazepines/hypnotics concomitantly will be summarized separately from other concomitant medication by visit and by at least once across the three visits in Study Period IV, and will be analyzed by a Fisher's exact test.

At each visit, the status of treatment compliance will be collected based on the percentage of capsules taken over the total capsules prescribed. A patient is considered to be compliant if the percentage is between 80% and 120%. A patient is considered to be compliant overall in this study period if he or she is compliant for each nonmissing observation in the study period. The percentage of patients who are compliant to treatment at each individual visit and overall will be summarized by treatment group and analyzed by a Fisher's exact test.

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8.2.12.3. Discontinuation-emergent Adverse Events

Discontinuation-emergent adverse event is defined as the reported events that first occurred or worsened during Study Period IV (compared with all the visits prior to Visit 301). The incidence rates of discontinuation-emergent adverse events will be analyzed by Fisher's exact tests. Moreover, discontinuation-emergent adverse events will be summarized by their maximum severity as reported and analyzed by a Fisher's exact test.

Discontinuation-emergent adverse events collected by AMDP-5 will also be analyzed by frequency and by the maximum severity. In those analyses, the concept of "discontinuation-emergent" is the same as above.

8.2.12.4. Evaluation of Cognition Outcome Measure

The composite cognitive score will be analyzed for its change from baseline (the last non-missing value in Study Period II and III) to the last visit of Study Period IV (Visit 303) by the ANCOVA model as described in Section 8.2.1.

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9. Informed Consent, Ethical Review, and Regulatory Considerations

9.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing any new information that may be relevant to the patient's willingness to continue his or her participation in the trial in a timely manner.

The informed consent document (ICD) will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

9.2. Ethical Review

The investigator will provide Lilly with documentation of ethical review board (ERB) approval of the protocol and the ICD before the study may begin at the investigative site(s). Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol. The ERB(s) will review the protocol as required.

The investigator will supply the following to the study site's ERB(s):

- the current Clinical Investigator's Brochure or package labeling and updates during the course of the study
- Informed Consent Document
- Relevant Curricula Vitae.

9.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices (GCP) and the applicable laws and regulations. The investigator or designee will promptly submit the protocol to applicable ERB(s).

Duloxetine is the subject of NDA #21-427, which was submitted to the FDA on 12 November 2001.

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An identification code assigned by the investigative site to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting adverse events and/or other trial-related data.

9.3.1. Investigator Information

Contact information for investigators, clinical laboratories, other medical and/or technical department(s) and/or institutions involved in the trial is provided in the Contacts for Protocol F1J-MC-HMBU document provided with this protocol.

9.3.2. Protocol Signatures

After reading the protocol, each investigator will sign two protocol signature pages and return one of the signed pages to a Lilly representative (see Protocol Attachment HMBU.6).

9.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

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Protocol Attachment HMBU.1.
Targeted and Suggested Visit Intervals Table

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Protocol Attachment HMBU.1

Targeted and Suggested Intervals Between Visits Study Period I, II, & III

Study Period	Targeted Cumulative Days from Visit 2	Targeted Interval (in Days) from Prior Visit
Study Period I		
Visit 1	-3 to -9	NA
Visit 2	0	3 to 9
Study Period II		
Visit 3	5 to 9	7
Visit 4	12 to 16	7
Visit 5	19 to 23	7
Visit 6	26 to 30	7
Visit 7	40 to 44	14
Study Period III		
Visit 8	54 to 58	14
Visit 9	68 to 72	14
Visit 10	82 to 86	14

Note: If a patient's visit occurs early within the visit interval, the patient's subsequent visit should occur later in the suggested interval, if possible. For example, if the visit interval between Visit 2 and Visit 3 is 5 days, the investigator should attempt to schedule Visit 4 for 9 days after Visit 3.

Targeted and Suggested Intervals Between Visits Study Period IV

Study Period	Targeted Cumulative Days from Last Visit in Study Period II or III	Targeted Interval (in Days) from Prior Visit
Study Period IV		
Visit 301	6 to 8	7
Visit 302	13 to 15	7
Visit 303	20 to 22	7

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**Protocol Attachment HMBU.2.
Study Schedule**

Study Schedule, Protocol F1J-MC-HMBU

CRF Visit No.	1	2	3	4	5	6	7	8	9	10	301	302	303	Early D/C
Week Number	-1	0	1	2	3	4	6	8	10	12				
Procedure														
Informed Consent	X													
Demographics	X													
Psychiatric/Depression History		X												
MINI	X													
Historical Diagnosis	X													
Previous Drug/Non-Drug Therapy		X												
Height	X													
Physical Exam	X													
Weight	X									X			X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X			X	X
ECG	X						X			X				X
Pre-existing Conditions and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Summary										X				X
Taper Summary													X ^b	
Efficacy Measurements														
HAMD ₁₇	X	X	X	X	X	X	X	X	X	X				X
Hamilton Anxiety Rating Scale		X					X			X				X
CGI-Severity		X	X	X	X	X	X	X	X	X				X
PGI-Improvement			X	X	X	X	X	X	X	X				X

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Study Schedule, Protocol F1J-MC-HMBU (concluded)

CRF Visit No	1	2	3	4	5	6	7	8	9	10	301	302	303	Early D/C
Week Number	-1	0	1	2	3	4	6	8	10	12				
Procedure														
Health Outcome Measurements														
SF-36		X					X			X				X
Quality of Life in Depression Scale		X					X			X				X
EuroQOL		X					X			X				X
Sheehan Disability Scale		X					X			X				X
Patient Health Questionnaire		X					X			X				X
Resource Use and Hospitalization		X					X			X				X
Cognitive Assessments														
VLRT		X					X			X			X	X
SDST		X					X			X			X	X
2DCT		X					X			X			X	X
LNST		X					X			X			X	X
Other Safety Measures														
AMDP-5		X	X	X	X	X	X	X	X	X	X	X	X	X
CSFQ		X					X			X				X
Pittsburgh Sleep Quality Index		X					X			X				X
Laboratory Tests														
Chemistry and Electrolytes	X						X			X				X
Hematology	X						X			X				X
Prolactin	X						X			X				X
Urinalysis ^a	X									X				
Urine Drug Screen ^a	X													
Pregnancy Test (all females) ^a	X													
Thyroid Function Test (TSH)	X													
Study Drug and Concomitant Medications														
Study Drug Dispensed		X	X	X	X	X	X	X	X	X	X			
Study Drug Compliance			X	X	X	X	X	X	X	X	X	X		X
Date of Last Dose							X			X	X	X		X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Benzodiazepine/Hypnotic Use	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: 2DCT= 2-Digit Cancellation Test; AMDP-5 = Association for Methodology and Documentation in Psychiatry; CGI-Severity = Clinical Global Impressions of Severity; CSFQ = Change in Sexual Functioning Questionnaire; DESS= Discontinuation Emergent Signs and Symptoms; Early D/C= early discontinuation; ECG= electrocardiogram; EuroQOL = European Quality of Life Scale; HAMD₁₇ = 17-item Hamilton Depression Rating Scale; LNST = Letter-Number Sequencing Test; MINI = Mini International Neuropsychiatric Interview; SDST = Symbol Digit Substitution Test; SF-36 = Medical Outcomes Study Short Form 36;; VLRT = Verbal Learning and Recall Test.

^a To be performed at the investigator's discretion throughout the study.

^b If patient discontinues at Visit 301 or 302 complete the taper summary at the taper discontinuation visit.

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Protocol Attachment HMBU.3.
Concomitant Medications Table

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Drugs Allowed (Y) and Drugs Not Allowed (N) As Concomitant Medications

Drug Class	Episodic Use	Chronic Use
ACE inhibitors	N	Y ^a
Alpha blockers	N	Y ^a
Analgesics non-prescription (except narcotics)	Y	Y
Antacids	Y	Y
Antiarrhythmics	N	Y ^a
Antiasthma agents (except theophylline and aminophylline)	Y	Y
Antibiotics	Y	Y
Anticoagulants	N	N
Anticonvulsants	N	N
Antidepressants	N	N
Antidiarrheals	Y	Y ^a
Antiemetics	Y	N
Antihistamines (nonsedating)	Y	Y
Antihistamines (sedating)	Y ^b	N
Antimanics	N	N
Antimigraines (triptans)	N	N
Antipsychotics	N	N
Benzodiazepines	Y ^b	N
Beta blockers	N	Y ^a
Birth control medication	Y	Y
Calcium channel blockers	N	Y ^a
Cough/cold preparations	Y ^b	Y ^a
Diuretics	N	Y ^a
Guanabenz, Guanfacine, Guanethidine	N	N
Guanadrel	N	N
Herbal preparations with no known CNS activity	Y ^c	Y ^c
Hormones	N	Y ^a
Hypnotics	Y ^b	N
Insulin	N	Y ^a
Laxatives	Y	Y ^a
MAOIs	N	N
Methyldopa	N	Y ^a
Multivitamins	Y	Y
Narcotics/Opioids	Y ^c	N
Psychostimulants	N	N
Reserpine	N	N
Sedatives	N	N
Steroids (inhaled, topical, ophthalmic only)	Y	Y
Tryptophan	N	N

^a Medication is allowed provided the patient is on a stable dose for a minimum of 3 months prior to study enrollment and remains on the medication for the duration of the study.

^b As described in Section 5.7 of this protocol.

^c Use of some herbal preparations with no known CNS effects and narcotics are allowed if approved by the Lilly physician.

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Protocol Attachment HMBU.4.
Clinical Laboratory Tests

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Clinical Laboratory Tests

Hematology:	Clinical Chemistry -
Hemoglobin	Serum Concentrations of:
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Alanine aminotransaminase (ALT/SGPT)
Monocytes	Aspartate transaminase (AST/SGOT)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Serum creatinine
Platelets	Uric acid
	Phosphorus
	Calcium
Urinalysis ^a :	Glucose, nonfasting
Specific gravity	Total Protein
Protein	Albumin
Ketones	
Blood	Cholesterol
Nitrite	
Color	Creatine kinase (CK)
Urine Drug Screen ^a	Hepatic monitoring tests ^{a,b}
	Hepatic serology panel (A,B,C)
Prolactin	Thyroid Function Test:
	Thyroid-stimulating hormone (TSH)
	Pregnancy Test (all females) ^a

^a To be performed at the investigator's discretion throughout the study.

^b To be performed at sponsor request for selected patients

Protocol Attachment HMBU.5.
Abbreviations and Definitions

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Abbreviations and Definitions

Study Entry Terms	<p>Screen The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial.</p> <p>Enter/Consent The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.</p> <p>Enroll/Randomize The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.</p>
2DCT	2-Digit Cancellation Test
AMDP-5	Association for Methodology and Documentation in Psychiatry
AMDPAE	Association for Methodology and Documentation in Psychiatry collected Adverse Events
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
Blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor(s), and in some cases, select sponsor personnel being unaware of the treatment assignment(s).
Compliance	Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements and the applicable regulatory requirements.
CGI-Severity	Clinical Global Impressions of Severity
CRF	Case Report Form (sometimes referred to as Clinical Report Form). A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CSFQ	Changes in Sexual Functioning Questionnaire
DEAE	Discontinuation-emergent adverse event

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ECG	Electrocardiogram
EuroQOL	European Quality of Life Scale
HAMD17	17-item Hamilton Depression Rating Scale
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IVRS	Interactive Voice Response System
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the patient's participation in the clinical trial.
LNST	Letter-Number Sequencing Test
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
MQA	Lilly Medical Quality Assurance
Patient	A subject with a defined disease.
PGI-Improvement	Patient's Global Impression of Improvement
PSQI	Pittsburgh Sleep Quality Index
QLDS	Quality of Life in Depression Scale
SDS	Sheehan Disability Scale
SDST	Symbol Digit Substitution Test
SF-36	Medical Outcomes Study Short Form-36
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control.
TSH	Thyroid-stimulating hormone
Treatment-Emergent Adverse Event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms).
VLRT	Verbal Learning and Recall Test

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Protocol Attachment HMBU.6.
Protocol Signatures

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Protocol Signatures Protocol F1J-MC-HMBU

I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with Eli Lilly and Company (or subsidiary). I will promptly submit the protocol to applicable ethical review board(s). I confirm that if I or any of my staff are members of the ethical review board, we will abstain from voting on this protocol.

Instructions to the investigator: Please SIGN and DATE both copies of this signature page. PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the signed copies to Lilly.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator Title

Name of Facility

Location of Facility
(City, State (if applicable), Country)

Signature of Representative of
Eli Lilly and Company (or Subsidiary)

Date

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Protocol Signatures Protocol F1J-MC-HMBU

I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. I will accept the monitor's overseeing of the study. I will abide by the publication plan set forth in my agreement with Eli Lilly and Company (or subsidiary). I will promptly submit the protocol to applicable ethical review board(s). I confirm that if I or any of my staff are members of the ethical review board, we will abstain from voting on this protocol.

Instructions to the investigator: Please SIGN and DATE both copies of this signature page. PRINT your name, title, and the name of the facility in which the study will be conducted on both copies. Return one of the signed copies to Lilly.

Signature of Investigator

Date

Investigator Name

Investigator Title

Name of Facility

Location of Facility
(City, State (if applicable), Country)

Signature of Representative of
Eli Lilly and Company

Date

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Confidential Information

The information contained in this protocol amendment summary is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of duloxetine hydrochloride (LY248686), unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

**Protocol Amendment Summary F1J-MC-HMBU(a)
Duloxetine Versus Venlafaxine Extended Release in the
Treatment of Major Depressive Disorder**

Duloxetine Hydrochloride (LY248686)

Eli Lilly and Company
Amendment (a) Approved by Lilly: 26 February 2003

Note to Investigators: The new protocol is indicated by Amendment (a) Approved by Lilly: 26 February 2003 on the bottom of every page. Amendment (a) will be used to conduct the study in place of any preceding version of this protocol.

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Overview

The overall changes and rationale for the changes made to this protocol are as follows:

- It was determined that the Visual Analog Scale was not needed in this protocol and it was removed.
- The word flexible has been removed when describing Study Period III for clarification. Figure HMBU.1 was updated to reflect this as well. Drug dosing is not allowed to be decreased during this Study Period. Directions on not decreasing the dose are also included in the appropriate sections of the protocol. Clarification was also made that the dose of drug could only be increased at a Study Visit. Patients who are not able to tolerate the increase in study drug dose will be discontinued from the study.
- Exclusion [19] stated that a urine drug screen would be performed for both substances of abuse and excluded medication. The urine drug screen will be performed for substances of abuse only, not excluded medication.
- Exclusion [21] was clarified to state that patients likely to need excluded medication during the study are excluded from the study
- All laboratory references ranges in the study will be the reference ranges of the performing laboratory.
- A double-dummy design will be used to ensure blinding during the study. The total number of capsules taken in the Study Periods was updated.
- Protocol F1J-MC-HMBU will use emergency codes in envelopes for necessary unblinding and not the interactive voice response system.
- Clarification for not allowing dose decreases was added.
- The use of both benzodiazepines and hypnotics is allowed as specified in the protocol. When benzodiazepines are referenced, hypnotics were added for clarification.
- The Symbol Digit Substitution Test was updated to show a length of 90 seconds instead of 120 seconds
- The analysis plan for the Sheehan Disability Scale was added to the protocol.
- Prolactin levels were listed under the Hematology subheading for the Clinical Laboratory Tests. It must be listed separately and has been updated in the text of the protocol as a separate test.

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- Typographical errors were corrected if found in the text. Not all of these typographical changes are reflected in the summary.
- For European Studies, the final report is signed by the coordinating investigator. This has been clarified in Section 9.3.3.
- Patient can enter Study Period IV at any time in Study Period III or after Visit 4 in Study Period II. This has been clarified in the protocol. Dosing for patients who enter Study Period IV on venlafaxine extended release 75 mg daily has been explained.
- The Study Schedule was updated to include the necessary items described above. In addition, the Study Summary, Taper Summary, and Date of Last Dose were added. The PGI-Improvement was incorrectly marked as being taken at Visit 2. Since the scale measures improvement, it does not give any relevant data at baseline.

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Revised Protocol Sections

Note: The page numbers listed are the "Document Page" numbers found in the upper right corner of the page in the revised protocol.
 All deletions have been identified by ~~strikethroughs~~
 All additions have been identified by the use of underline.

2.2. Secondary Objectives (page 8)

The secondary objectives of the study are:

- To assess the efficacy of duloxetine 60 mg daily versus venlafaxine extended release 150 mg daily during 6 weeks of therapy, and duloxetine 60 to 120 mg daily versus venlafaxine extended release 150 to 225 mg daily during 12 weeks of therapy, as measured by:
 - HAMD₁₇ subscales including the Core, Maier, Anxiety/Somatization, Retardation/Somatization, and Sleep; and the depressed mood item (Item 1)
 - Response rates, as defined by a $\geq 50\%$ change from baseline to endpoint on the HAMD₁₇ total score.
 - Remission rates, as defined by a HAMD₁₇ score of ≤ 7 at endpoint
 - Total score Hamilton Anxiety Rating Scale (HAMA)
 - Clinical Global Impressions of Severity Rating Scale (CGI-Severity)
 - Patient's Global Impression of Improvement Rating Scale (PGI-Improvement)
 - ~~Visual Analog Scales for Pain (VAS).~~
- To assess the impact of duloxetine 60 mg daily versus venlafaxine extended release 150 mg daily during 6 weeks of therapy, and duloxetine 60 to 120 mg daily versus venlafaxine extended release 150 to 225 mg daily during 12 weeks of therapy on quality of life and health outcomes as measured by:
 - SF-36 Health Status Survey (SF-36)
 - Quality of Life in Depression Scale (QLDS)
 - EuroQOL (EQ-5D)
 - Sheehan Disability Scale (SDS)

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- Patient Health Questionnaire (PHQ) – physical component
- Resource Use and Hospitalization Module.

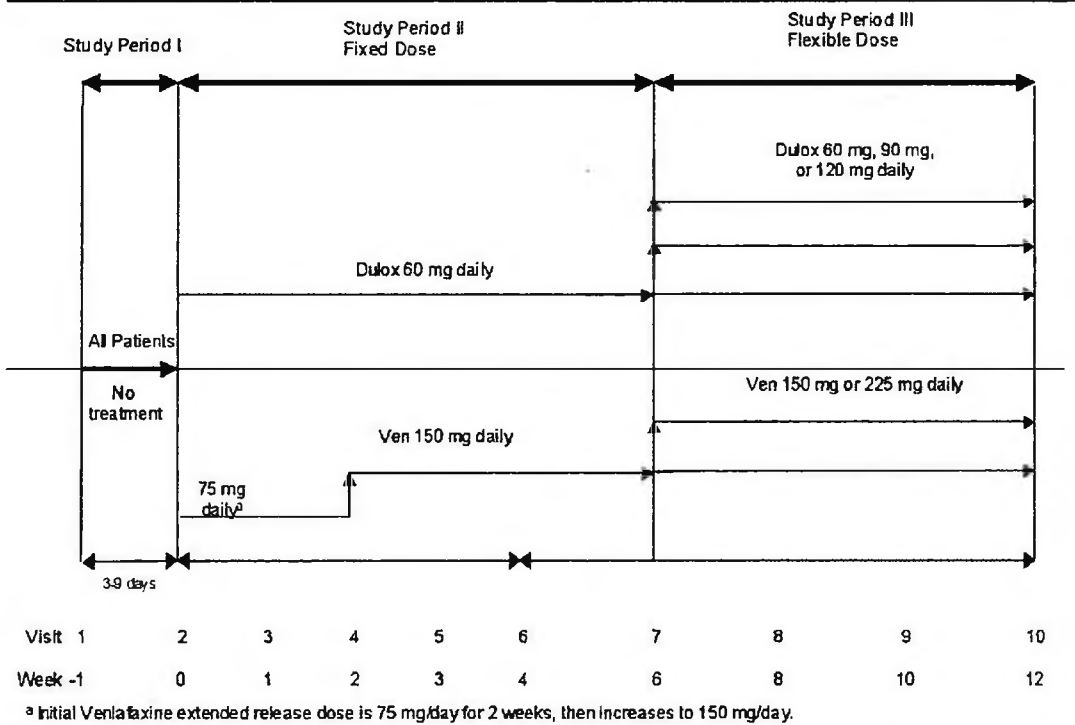
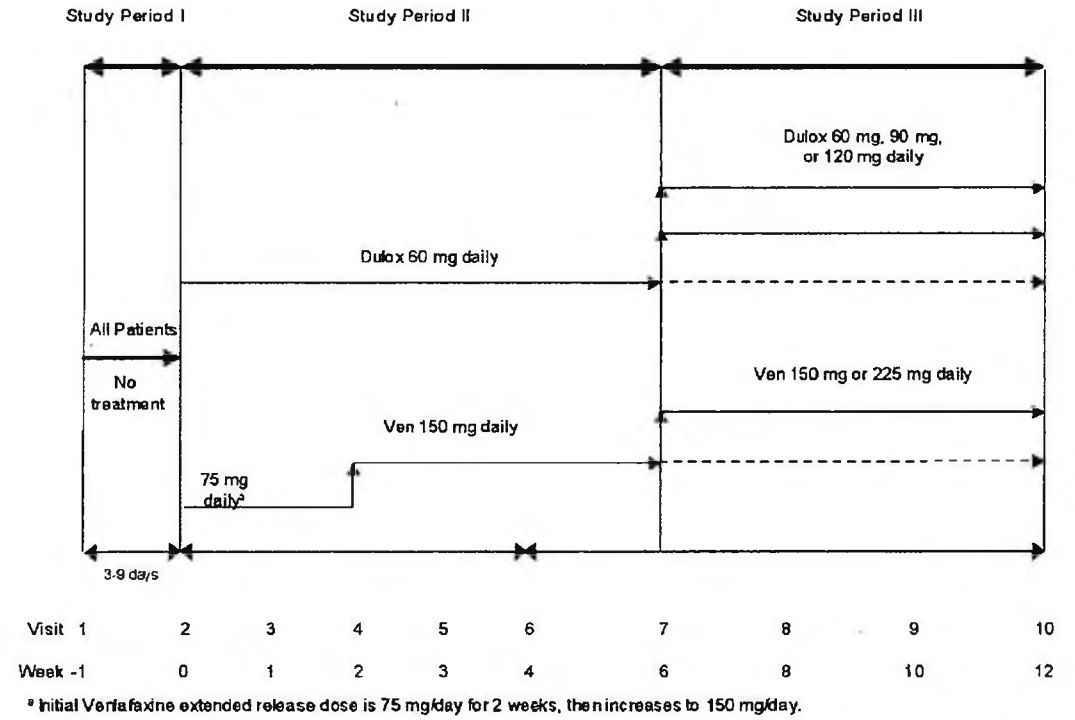
3.1. Summary of Study Design (page 11)

Study F1J-MC-HMBU is a multicenter, randomized, double-blind, parallel study of approximately 320 outpatients diagnosed with major depressive disorder (MDD). The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998) will be used to determine whether patients meet criteria for MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV).

- Screening (Study Period I): Visit 1 to 2. This is a screening phase during which patients will be screened for eligibility. Visit 2 will occur 3 to 9 days after Visit 1.
- Double-Blind Fixed Dose (Study Period II): Visits 2 ~~through~~ 7. This is a 6-week period of double-blind treatment. Patients who meet entry criteria will be enrolled and randomized at Visit 2 to one of two treatment groups: duloxetine fixed-dose 60 mg daily or venlafaxine extended release 150 mg daily. The venlafaxine group will begin treatment with venlafaxine 75 mg daily for the first 2 weeks, increasing to 150 mg daily for the remainder of Study Period II. Patients who complete Study Period II will be eligible to enter Study Period III.
- Double-Blind ~~Variable~~ Dose (Study Period III): Visits 7 ~~through~~ 10. This is a 6-week, double-blind period for patients who complete Study Period II. At Visit 7, Visit 8, or Visit 9 or thereafter, patients may have their dose increased during an additional 6 weeks of therapy, based on the investigator's discretion. Duloxetine may be increased up to 120 mg daily. Venlafaxine extended release may be increased up to 225 mg daily. The dose of study medication may not be reduced at anytime. See Section 5.5.3 for a description of study drug administration during this study period.
- Taper (Study Period IV): Visits 10 through 303. This is a 3-week taper period. Patients who discontinue the study at Visit 4 or thereafter or complete Study Period III may enter the taper period at the investigator's discretion to assess discontinuation-emergent adverse events (DEAEs) and other safety measures. Study medication will be tapered in a double-blind manner. See Section 5.5.4 for a description of study drug administration during this study period.

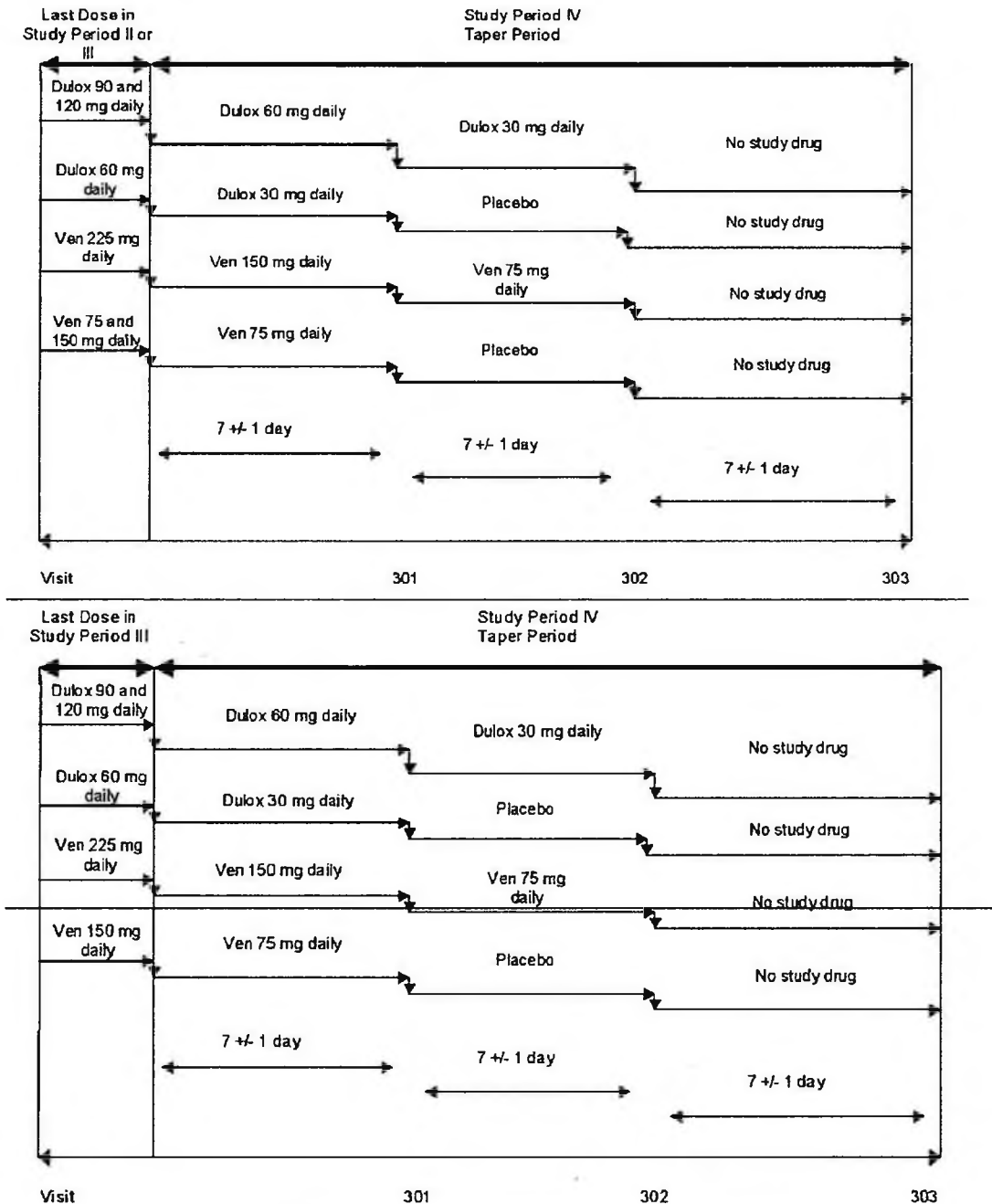
Figure HMBU.1 illustrates the study design.

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Note: The dose may be increased at any visit in Study Period III.

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Note: Dulox = duloxetine; Ven = venlafaxine extended release.

Figure HMBU.1. Illustration of study design for Protocol F1J-MC-HMBU.

See Protocol Attachment HMBU.1 for allowed and suggested visit intervals.

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3.2. Discussion of Design and Control (page 13)

Study Period I is designed to determine if patients meet all of the inclusion criteria and none of the exclusion criteria.

Study Period II is designed to assess the benefit-risk ratio of duloxetine versus venlafaxine extended release at usual doses for patients with depression.

Study Period III is designed to allow investigators to increase the dose of study medication for patients who have not responded to usual doses to determine if the patient will respond to higher doses.

Study Period IV is designed to ensure that patients are treated with a reducing regimen of study drug (taper) rather than experiencing an abrupt cessation of treatment. The intention is to reduce the likelihood of DEAEs, which are recognized to occur following abrupt interruption of therapy.

Even when antidepressants are discontinued by way of a taper rather than abrupt discontinuation, DEAEs are still known to occur, albeit with reduced frequency or severity. It is for this reason that Study Period IV features a one-week, study drug-free period, followed by a final visit to assess DEAEs. In this way, the propensity for patients to experience DEAEs despite the use of a taper, an important and increasingly widely-recognized phenomenon, can be compared for duloxetine and venlafaxine extended release.

Venlafaxine extended release was chosen as a comparator since it is the most widely used and prescribed member of the serotonin and norepinephrine reuptake inhibitor (SNRI) drug class approved for antidepressant use. To date, there have been no randomized, controlled studies directly comparing the safety and efficacy of duloxetine and venlafaxine. While these two agents share some pharmacodynamic similarities, there are significant differences in their receptor binding affinities, leading to potentially different benefit/risk ratios. Duloxetine is a more balanced inhibitor with a NE to 5-HT human receptor binding affinity ratio of 9, whereas venlafaxine's human receptor binding affinity ratio is 30 (Bymaster et al. 2001). Consequently, there is value in conducting a study to make head-to-head comparisons for the efficacy and safety of these two SNRI antidepressants in the treatment of MDD.

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4.2. Exclusion Criteria (page 17)

- [19] Have a positive urine drug screen for any substances of abuse or excluded medication. Note: If the patient has a positive drug screen at Visit 1, ~~for an excluded medication that may not have had an adequate washout period,~~ a retest may be performed prior to Visit 2 if, in the judgment of the investigator, there is an acceptable explanation for the positive result. If the retest is positive for active metabolites, the investigator must document that the patient has discontinued taking the excluded medication. If the retest is positive for the parent compound, the patient will be excluded.
- [21] Serious medical illness or clinically significant laboratory abnormalities that, in the judgment of the investigator, are likely to require ~~medication/ intervention/ hospitalization/~~ excluded medication during the course of the study.
- [28] Abnormal thyroid stimulating hormone (TSH) concentration (outside the reference range of the performing laboratory), ~~as per Lilly reference range (0.32-5.00 mIU/L).~~ Note: Patients diagnosed with hyperthyroidism or hypothyroidism who have been treated on a stable dose of thyroid supplement for at least the past 3 months, have medically appropriate TSH concentration, and are clinically euthyroid are allowed.
- [29] Have at Visit 1 an ALT, AST, or GGT >1.5 times upper limit of normal, ~~based on Lilly reference ranges~~ the performing laboratory's reference ranges.

4.3. Discontinuations (page 18)

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the study and Lilly or its designee must be contacted. An exception may be granted in very rare circumstances where there is a compelling safety reason to allow the patient to continue. In these rare cases, the investigator must obtain documented approval from Lilly to allow the patient to continue in the study.

In addition, patients will be discontinued from the study drug and/or from the study in the following circumstances.

- The investigator decides that the patient should be withdrawn. If this decision is made because of a serious adverse event or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. Lilly or its designee is to be notified immediately. See Safety Section (Section 6.4).
- The patient or attending physician requests that the patient be withdrawn from the study.

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- The patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The investigator or Lilly, for any reason, stops the study or stops the patient's participation in the study.
- The patient becomes pregnant.

Patients who discontinue study drug early will have end-of-therapy and/or end-of-study procedures performed as shown in the Study Schedule (Protocol Attachment HMBU.2).

5.3. Method of Assignment to Treatment (page 20)

A patient number will be assigned to each patient after the informed consent document is signed and dated (Study Period I). Randomization will occur in a 1:1 ratio to either duloxetine or venlafaxine extended release at Visit 2 (Study Period II). Assignment to treatment groups will be determined by a computer-generated random sequence using an Interactive Voice Response System (IVRS). Site personnel will confirm they have located the correct blister card by entering a confirmation number found on the card into the IVRS. In Study Period III is the flexible dose period of the study during which patients will continue on the treatment assignment given at Visit 2. While the dose may be increased at the discretion of the investigator during Study Period III, dose decreases are not permitted. Duloxetine during this period is available in the dose range of 60 to 120 mg daily; venlafaxine extended release during this period is available in the dose range of 150 to 225 mg daily. Study Period IV is the taper period of the study; patients will have their study medication decreased until they have completely tapered off study drug.

5.4. Rationale for Selection of Doses in the Study

The duloxetine dose regimens in this study were selected based on current clinical, preclinical, and pharmacokinetic data. Previous studies have demonstrated that duloxetine administered at doses of 60 mg to 120 mg daily for the treatment of major depressive disorder (MDD) is safe and efficacious. Dosing regimens of venlafaxine extended release selected for this study are based upon recommendations for treatment of MDD within the venlafaxine extended release Summary of Product Characteristics, namely the use of a dose of 75 mg daily for at least 2 weeks prior to increasing the dose up to a maximum of 225 mg daily. The use of 150 mg daily of venlafaxine extended release as a fixed-dose comparison in Study Period II is based upon the desire to compare duloxetine at a dose of 60 mg daily with the mean prescribed dose of venlafaxine extended release used in actual clinical practice. Dual reuptake inhibition is believed to occur with venlafaxine at doses in excess of 150 mg daily. With duloxetine, however, dual reuptake inhibition is believed to occur at a dose of 60 mg daily. Dose increases are

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permitted in Study Period III in order to allow a comparison of duloxetine and venlafaxine at doses where dual reuptake inhibition is thought to occur.

5.5.2. Study Period II (page 21)

Patients should be instructed to begin study drug the day after Visit 2. Four capsules of Study medication should be taken once daily at approximately the same time. It is strongly recommended that it be taken in the morning. Study medication should be taken with food and swallowed whole. Capsules should not be crushed or broken.

Those patients unable to tolerate their starting dose or their full treatment group dose will be discontinued from the study. No dose reductions are allowed in Study Period II .

5.5.3. Study Period III (page 21)

Patients Investigators are permitted flexible to increase the dose of dosing of study medication at any time on or after Visit 7, Visit 8, or Visit 9, provided the patient has been on the current dose for at least 7 days. Dose increases should be made based upon the investigator's clinical assessment of need up to a maximum of 120 mg daily of duloxetine or 225 mg daily of venlafaxine extended release. If the subject is not showing a response, dose increases may be made in the following manner: duloxetine 60 mg daily may titrate to 90 mg daily then to 120 mg daily; venlafaxine extended release 150 mg daily may titrate to venlafaxine extended release 225 mg daily. While patients assigned to duloxetine may have their dose increased twice, patients assigned to venlafaxine extended release will only have their dose increased the first time. As investigators and patients are blinded, a choice for a second increase can occur for venlafaxine; ~~but however,~~ patients will continue on the 225 mg dose with the same administration to maintain the blind. Those patients unable to tolerate the increased dose of study medication will be discontinued from the study. No dose reductions are allowed in Study Period III.

Patients whose dose is increased will take 75 capsules daily, given as 3-5 capsules in the morning and 2 capsules in the evening. Patients on duloxetine 90 mg will take 60 mg in the morning and 30 mg in the evening. Patients on duloxetine 120 mg will take 60 mg in the morning and 60 mg in the evening. Patients on venlafaxine extended release 225 mg will take the entire dose in the morning with placebo capsules in the evening.

5.5.4 Study Period IV (page 22)

Patients who discontinue the study at Visit 4 or thereafter, or who complete Study Period III, may enter the taper period at the investigator's discretion. Discontinuation effects are known to occur with the abrupt withdrawal of antidepressants. It is therefore recommended that the dose be gradually reduced to minimize the risk of withdrawal reactions. During the taper period, four capsules of study medication should be taken once daily at approximately the same time. It is strongly recommended that it be taken in

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the morning. Reduction of study medication should occur at 7-day intervals in the following manner (see Figure HMBU.1): duloxetine 120 mg daily should titrate to duloxetine 60 mg daily, then to duloxetine 30 mg daily, then to no study drug; duloxetine 90 mg daily should titrate to duloxetine 60 mg daily, then to duloxetine 30 mg daily, then to no study drug; duloxetine 60 mg daily should titrate to duloxetine 30 mg daily, then to placebo, then to no study drug; venlafaxine extended release 225 mg daily should titrate to venlafaxine extended release 150 mg daily, then to venlafaxine extended release 75 mg daily, then to no study drug; and venlafaxine extended release 150 mg daily should titrate to venlafaxine extended release 75 mg daily, then to placebo, then to no study drug; and venlafaxine extended release 75 mg daily should continue on 75 mg venlafaxine extended release daily, then titrate to placebo, then to no study drug. In order to maintain the blind, patients will appear to be tapered equally.

5.6. Blinding (page 22)

This is a double-blind study. Patients who meet all the criteria for randomization will be randomly allocated to double-blind treatment at Visit 2 by the IVRS.

In order to preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Emergency codes, generated by a computer drug-labeling system, will be available to the investigator. These codes, which reveal the patient's treatment group when opened, may be opened during the study ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All codes, whether sealed or opened, must be returned to Lilly.

~~Emergency unblinding for adverse events may be performed through an IVRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IVRS.~~

The investigator should make every effort to contact the Lilly clinical research physician prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or patient are unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician for the patient to continue in the study.

5.7 Concomitant Therapy (page 22)

In general, concomitant medications with primarily central nervous system activity are not allowed in this protocol. Protocol Attachment HMBU.3 contains a list of some

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allowed and excluded medications for this study. This is not an exhaustive list. If an investigator is uncertain as to the appropriateness of a certain medication, the investigator should contact the Lilly clinical research physician or a designee. Any changes to this list will be communicated to investigators and will not constitute a protocol amendment. Patients must sign the informed consent document before stopping any excluded medications.

All concomitant medication taken during the study will be recorded on the case report form (CRF). Patients will be instructed to consult with the investigator or study coordinator at the site before taking any new prescribed medications, over-the-counter (OTC) medications, or supplements.

Cough and cold medications containing pseudoephedrine or the sedating antihistamine, diphenhydramine, are excluded.

Patients will be allowed the episodic use of benzodiazepines or certain hypnotics during Study Periods II and III as displayed in Table HMBU.1 below; no more than 8 total days (intermittent or consecutive) are allowed. Any changes to Table HMBU.1 will be communicated to investigators and will not constitute a protocol amendment. Benzodiazepine/hypnotic use during Study Period IV is at the discretion of the investigator. If a patient exceeds the prescribed limits of benzodiazepine use, they must be discontinued from the study. Patients will be strongly encouraged not to use benzodiazepines or hypnotics the night before a scheduled visit and not to alter their intake of caffeine or nicotine during the course of the study.

6.2.2. Secondary Efficacy Measures (page 25)

- HAMD₁₇ Response Rates: Response is defined as a $\geq 50\%$ reduction in HAMD₁₇ total score from baseline to endpoint.
- HAMD₁₇ Time-to-First Response: Time-to-first response is defined as the visit where a sustained $\geq 30\%$ reduction in the Maier subscale of the HAMD₁₇.
- HAMD₁₇ Remission Rates: Remission is defined as a HAMD₁₇ total score of ≤ 7 at endpoint.
- The Hamilton Anxiety Rating Scale (HAMA) (Hamilton 1959; Riskind et al. 1987) is a widely used clinician-rated instrument that measures the presence and severity of anxiety. The 14-item version of this scale will be used to assess the severity of anxiety and its improvement during the course of therapy. Each symptom is rated on a defined step scale (0 to 4). The HAMA total score ranges from 0 (not at all anxious) to 56 (severely anxious).

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- The Clinical Global Impressions of Severity (CGI-Severity) Scale (Guy 1976) must be administered by the physician, in the presence of the subject, to record the severity of illness at the time of assessment. The score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).
- The Patient's Global Impressions of Improvement (PGI-Improvement) Scale (NIMH 1976) is a patient-rated instrument that measures the improvement of the patient's symptoms. Scores range from 1 (very much improved) to 4 (no change) to 7 (very much worse).
- ~~Visual Analog Scales (VAS) for Pain consists of six questions regarding the experience of overall pain, headache, back pain, shoulder pain, pain interference with daily activities, and proportion of the day with pain. Visual analog scales are widely used in the assessment of pain (DeLoach et al. 1998).~~
- HAM D₁₇ Subscales (Faries et al. 2000) include the Core subscale (Items 1, 2, 3, 7, and 8) and the Maier subscale (Items 1, 2, 7, 8, 9, and 10), which consist of items thought to represent the "core" symptoms of depression. The Anxiety/Somatization subscale of the HAM D₁₇ (Items 10, 11, 12, 13, 15, and 17) evaluates severity of psychic and somatic manifestations of anxiety, as well as agitation. The Retardation/Somatization subscale (Items 1, 7, 8, and 14) evaluates dysfunction in mood, work, and sexual activity, as well as overall motor retardation. The Sleep subscale (Items 4, 5, and 6) evaluates initial, middle, and late insomnia.

6.2.3. Cognitive Assessment Battery (page 26)

- The Symbol Digit Substitution Test (SDST) is an attention-demanding psychomotor component of the Wechsler Adult Intelligence Scale (WAIS-III; Wechsler 1997). The patient is given a symbol-digit code in which each of the digits 1 through 9 is paired with a different symbol. Below the code, a series of symbols selected from those in the code are presented in an irregular order. The patient is instructed to draw the number that is appropriate for each symbol in the space below each symbol and to complete as many correct digits as possible within a 42090-second test period. The SDST score is the number correct. The number attempted will also be recorded.

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6.3. Health Outcome/Quality of Life Measures (page 29)

- The Quality of Life in Depression Scale (QLDS) (Hunt and McKenna 1992) is a patient-reported, depression-specific, Health-Related Quality of Life HRQoL instrument. This scale, which measures subjective well-being, consists of 34 yes/no items. The QLDS scores range from 0 (good quality of life) to 34 (very poor quality of life). Contents for the measure were derived from a needs-based approach, where individual's lives gain quality from the ability and impact of disease on their lives in terms of the capacity of the individual to satisfy their needs. Basic needs include companionship, love, conversation, pleasure, self-care, and nutrition. There is evidence that the QLDS is sensitive to differences in severity of depression. The QLDS has demonstrated significant differences between treatment groups in previous duloxetine clinical trials. The instrument has been well validated and there are a number of international translations that have shown excellent reliability and construct validity.

6.4.1.2. Adverse Event Monitoring with a Systematic Questionnaire (page 32)

The Association for Methodology and Documentation in Psychiatry (AMDP-5) (CIPS 1996) is a tool to collect adverse events and the severity of the events during treatment. Each event listed can be rated as absent, mild, moderate, severe, or not evaluated.

The AMDP-5 is to be administered after study site personnel have questioned the patient and noted any change in the presenting condition(s), any change in the preexisting condition(s), and the occurrence and nature of any adverse events. All adverse events obtained during this routine questioning must be reported to Lilly in the adverse event section of the CRF.

Only serious adverse events elicited through the AMDP-5 questionnaire are to be recorded in the adverse event section of the CRF. Serious adverse events from the AMDP-5 questionnaire are also reported to Lilly immediately, by the designated transmission method.

Non-serious adverse events obtained through use of the AMDP-5 questionnaire are not recorded in the adverse event section of the CRF. They are reported and analyzed separately.

6.4.1.3.2. Other Safety Measures (page 32)

In addition to patient and physician reported adverse events, the following adverse event measures will be used in this study:

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- ~~The Association for Methodology and Documentation in Psychiatry (AMDP-5) (CIPS 1996) is a tool to collect adverse events and the severity of the events during treatment. Each event listed can be rated as absent, mild, moderate, severe, or not evaluated.~~
- The Changes in Sexual Functioning Questionnaire (CSFQ) (Clayton et al. 1997) was designed to evaluate the effects of illness and medication on the quality of sex life. The CSFQ has two versions, a 36-item version for men and a 34-item version for women. In addition to a total score, 5 subscale scores can be computed reflecting the following factors: sexual desire/frequency, sexual desire/interest, sexual pleasure, sexual ability/excitement, and sexual release/orgasm. The items are rated using a 5-point Likert scale (1 through 5). Lower scores indicate greater sexual dysfunction.
- The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989) is a 19-item, subject-completed questionnaire designed to assess sleep quality and sleep disturbances. Seven components are created from the 19 items. When the components are added together, a global score (range 0-21) is created. Higher scores indicated poorer sleep quality.

8.2.4. Previous and Concomitant Therapy (page 38)

Previous medications will be summarized by treatment group.

Concomitant medication used during the therapy phase will be summarized by treatment group. For each of the summaries, the differences between the treatment groups in the frequency of usage for each medication will be analyzed by a Fisher's exact test. In addition, the percentage of patients who use benzodiazepines/hypnotics concomitantly will be summarized separately from other concomitant medication by visit and by at least once across all visits, and will be analyzed by a Fisher's exact test. The mean daily dose of benzodiazepines/hypnotics for each patient will be calculated across the therapy phase and will be evaluated using the ANCOVA model. The distribution of the residuals will be checked. When the assumptions of normality and homogeneity are violated, rank-transformed change scores will be analyzed using an ANOVA model with the terms of treatment and investigator, and will be reported. Otherwise, the inference from the analysis on raw data will be reported.

8.2.6. Primary Outcome and Methodology (page 38)

The primary outcome measure is the linear measure of Global Benefit-Risk (GBR) assessment. The approach was first proposed by Chuang-Stein et al. (1991). In this assessment, benefit is defined as remission at endpoint (HAMD₁₇ total score ≤ 7), a virtually symptom-free state; risk is defined by four categories: no AMDP-5 collected adverse events (AMDPAE), mild or moderate AMDPAE, severe AMDPAE, and

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discontinue with a reason of self-reported adverse event. For each patient, the severity level is determined as the maximum severity of all the treatment-emergent adverse events, collected using AMDP-5, that the patient might experience during the study. The concept of "treatment-emergent" refers to the events that first occurred or worsened during the treatment period. Considering the benefit and the risk a patient can have when taking the study drug, there are eight mutually exclusive categories listed in Table HMBU.2.

Table HMBU.2. Global Benefit-Risk Assessment Categories

	No AMDPAE	Mild or Moderate AMDPAE	Severe AMDPAE	DC due to self-reported adverse event
Remission	I	II	III	IV
Non-remission	V	VI	VII	VIII

Abbreviation: AMDPAE = Association for Methodology and Documentation in Psychiatry collected adverse events, DC= discontinue.

The overall benefit and risk impact on the patients moves from overwhelmingly beneficial in Category I to least beneficial, or least desirable, to in Category VIII. With observed proportions in each category, a weight function of $W = (5, 4, 3, 1, -1, -3, -4, -5)$ will be applied to compute the linear GBR score (Chuang-Stein 1991). The weight function is chosen to reflect the benefit-risk impact on the patients along those categories. In mathematics, the linear GBR score is defined as $M = \sum w_i * p_i$, where w_i is the weight for category i and p_i is the observed proportion of patients in category i , $i=1,2,\dots,8$.

When the score is positive, the benefit outweighs the risk. The higher the score, the more benefit over risk the therapy can provide.

The primary objective of this study will be tested by a Z-test created from the linear GBR scores from duloxetine and venlafaxine extended release treatment groups, where the statistics

$$Z = (M_1 - M_2) / \sqrt{(\text{estimated variance of } M_1 + \text{estimated variance of } M_2)},$$

where 1 refers to duloxetine treatment group, and 2 refers to venlafaxine extended release treatment group.

In addition, analysis for GBR scores will be stratified based on the country of investigator to control for the potential variation in GBR scores across countries that might result from the differences in geographic regions. The mathematical details for the estimated variance and the stratification method will be described in the Statistical Analyses Plan, which will be available and locked before the data is unblinded.

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As specified by the Primary Objective of this study, this primary analysis will be conducted using combined data from this study and the similar designed Study F1J-MC-HMCQ. Data from the patients taking the same medication and dosage from the two studies will be pooled for the analysis. To preserve the integrity of the data, neither study will be unblinded prior to the unblinding of the other study.

8.2.7.2. Analyses on Secondary Efficacy Outcome Measures (page 40)
Table HMBU.3 presents the analyses for the secondary efficacy variables, either collected directly from CRFs or derived from raw observations.

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F1J-MC-HMBU Synopsis

Table HMBU.3. Analysis for the Secondary Efficacy Variables

Efficacy Variable	Derivation and Details	Analysis
1. Change from baseline to endpoint: a. HAMD ₁₇ total score b. HAMD ₁₇ depressed item (Item 1) c. HAMD ₁₇ subscales of Core, Maier, Anxiety, Retardation and Sleep d. HAMA total score e. CGI – Severity f. VAS – Six assessments	a. Sum of 17-HAMD items c. Refer to Section 6.12 for the composition of the subscales d. Sum of HAMA 14 items f. Six assessments will be analyzed separately: overall, headaches, back pain, shoulder pain, pain interference, awake due to pain.	Variables 1a to 4f 1e will be analyzed by the ANCOVA models as described in Section 8.2.1, General Considerations

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F1J-MC-HMBU Synopsis

Table HMBU.3. Analysis for the Secondary Efficacy Variables (continued)

Efficacy Variable	Derivation and Details	Analysis
2. All baseline and postbaseline data at the Visits in the acute therapy for: <ul style="list-style-type: none"> a. HAMD₁₇ total score b. HAMD₁₇ depressed item (Item 1) c. HAMD₁₇ subscales of Core, Maier, Anxiety, Retardation and Sleep d. CGI – Severity ◆ VAS – Six assessments 	(The same as above)	Variables 2a to 2e-2d will be analyzed by a repeated measures analysis. The model details will be described in text beneath the table.
3. All post-baseline data for PGI-Improvement		The observed scores at each postbaseline visit as well the last nonmissing score (defined as endpoint) will be analyzed by the ANOVA model as described in Section 8.2.1, General Considerations. In addition, the data will also be analyzed by a repeated measures analysis. The model will be similar to the one used for the variables in the above group, with the modifications that there are no baseline or baseline-by-visit effects in the model.
4. Categorical variable: <ul style="list-style-type: none"> a. Response rate at endpoint b. Remission rate at endpoint c. Sustained 30% improvement on Maier subscale 	<ul style="list-style-type: none"> a. Response: at least 50% reduction from baseline to endpoint in HAMD₁₇ total score b. Remission: HAMD₁₇ total score ≤ 7 at endpoint c. Sustained 30% improvement on Maier subscale: a reduction on Maier subscale of at least 30% from baseline at endpoint, at an earlier visit prior to the last visit of the study period, and at all the visits in between. 	For variables 4a to 4c, proportions will be summarized by treatment group and will be analyzed by a Fisher's exact test.

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F1J-MC-HMBU Synopsis

Table HMBU.3. Analysis for the Secondary Efficacy Variables (concluded)

Efficacy Variable	Derivation and Details	Analysis
5. Time-to-event variable: a. Time-to-first visit that sustained 30% improvement on Maier subscale is achieved b. Time-to-first visit that HAMD ₁₇ total is ≤ 7	a. The earliest visit at which the sustained 30% improvement on Maier subscale is observed. For both 5a and 5b, the time-to-event variables are calculated by the algorithm: for those who meet the criterion, time = the date of the visit at which the event occurred – randomization date; for those who do not meet the criterion, time = the last dose date – randomization date.	<ul style="list-style-type: none"> - For variables 5a and 5b, the Kaplan-Meier survival curves of time-to-event will be calculated by treatment group. In the calculation, patients who do not have the event will be considered as right-censored observation. The comparison of the survival curves between treatment groups will be conducted by a log-rank test and the Wilcoxon test (using PROC LIFETEST). - Additionally for 5a, the time at which 50% of the patients achieve the sustained 30% reduction by the K-M estimation, defined as time-to-onset, will be presented by treatment group. - Analysis on 5a will only be conducted for the data from 12-week study periods

Note: Baseline is defined as the last measurement taken at, or prior to, Visit 2; endpoint is defined as the last nonmissing measurement taken in the comparison study period (Study Period II: Visit 3 to Visit 7; Study Periods II and III: Visit 3 to Visit 10); last visit is defined as the visit where the endpoint is assessed.

Abbreviations: CGI-Severity = Clinical Global Impressions of Severity; PGI-Improvement = Patient's Global Impression of Improvement; HAMD₁₇ = 17-item Hamilton Depression Rating Scale; VAS = Visual Analog Scale

A repeated measures analysis refers to a likelihood-based, mixed-effects repeated measures analysis using all the longitudinal observations at each postbaseline visit. The model will include the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline score and baseline-by-visit interaction. The following covariance structures will be used to estimate within-patient errors in preliminary analyses on HAMD₁₇ total score: unstructured, spatial power, Toeplitz, compound symmetric, and simple structures, with and without heterogeneous variances by visit. The covariance structure converging to the best fit among those preliminary analyses, as determined by Akaike's information criterion, will be chosen as the covariance in the model of repeated measures analyses for all efficacy variables exclusively. The Kenward-Roger method will be used to estimate denominator degrees of freedom. Type III sum-of-squares for the least-squares means will be used. Analyses will be implemented using SAS PROC MIXED (Version 8.0).

When analyzing an efficacy variable using the repeated measures analysis, the primary comparison will be the contrast between duloxetine and venlafaxine extended release treatment groups at the last visit of the study period for which the comparison is performed. Secondary comparison will be the contrast between duloxetine and venlafaxine extended release treatment groups at each postbaseline visit where the specific efficacy assessment is conducted.

8.2.8. Health Outcome/Quality of Life Analyses (page 45)

Patient self-reported health outcomes include the following:

- The Medical Outcomes Study Short Form-36 (SF-36) Questionnaire
- Quality of Life in Depression Scale (QLDS)
- The EuroQoL instrument version EQ-5D (EQ-5D)
- Sheehan Disability Scale (SDS)
- Patient Health Questionnaire (PHQ)
- Resource Utilization Questionnaire

The SF-36 consists of 36 questions covering eight health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each domain is scored by summing the individual items and transforming the scores into a scale from 0 to 100, with higher scores indicating better health status or functioning. No overall total score is calculated. Moreover, two summary scores, the physical component summary (PCS) and the mental component summary (MCS), have been constructed based on the eight SF-36 domains. The equations are provided in the SF-36 Physical and Mental Health Summary Scales: A User's Manual. The two summary scores represent

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independent (orthogonal) indices based on factor analysis of SF-36 scale scores using Medical Outcomes Study data (Ware et al. 1993).

For each of the domains as well as the PCS and the MCS, the treatment group differences will be evaluated by the analyzing the change from baseline to endpoint using the ANCOVA model.

The total score from QLDS will be calculated from 34 items and the baseline-to-endpoint change in QLDS total score will be analyzed by the ANCOVA model.

The EQ-5D questionnaire consists of five items: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. For each item patients choose one of the three options that will best describe the status. The three options reflecting increasing degrees of difficulty are coded as 1, 2, and 3. Scores from the five items form a 5-digit code that describes the respondent's health state. This 5-digit code is then converted to a weighted index (called EQ-5D index) using population values provided by the EuroQoL group. The change from baseline to endpoint in EQ-5D index will be analyzed by the ANCOVA model.

SDS assesses the effect of disability in three areas: work, social life and family life using a 0 to 10 scale. Changes from baseline to endpoint in each of the areas will be analyzed using the ANCOVA model. The total of the three areas will also be analyzed using the ANCOVA model. When the data for the item of Work is entered as "N/A" for a patient, it will be imputed by using the average score from the other two items of social life and family life from that patient.

PHQ is used to collect the bothersome level on a range of physical symptoms. The Resource Utilization Questionnaire is used to collect information for the analysis of comparing resource utilization between treatment groups. Data collected by the Resource Utilization Questionnaire and PHQ do not directly impact the clinical evaluation of the study drug, and thus will not be reported in the study report. The data from the Resource Utilization Questionnaire and PHQ will be summarized in an independent report, while the data analysis plan will be available to regulatory agencies prior to the completion of the study.

8.2.9.2. Vital Signs, Weight, and ECG Evaluation (page 47)

Change from baseline to endpoint in vital signs (sitting heart rate and blood pressure, including diastolic and systolic) will be analyzed using the ANOVA model. Change from baseline to endpoint in weight will also analyzed by the ANOVA model.

A patient is considered to have hypertension if his or her blood pressure after randomization meets the following criteria:

- Sitting diastolic blood pressure ≥ 90 mm Hg and increase from baseline (defined as the highest of the measures across all the visits prior to randomization) of 10 mm Hg for 3 consecutive visits, or

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- Sitting systolic blood pressure ≥ 140 mm Hg and increase from baseline (defined as the highest of the measures across all the visits prior to randomization) of 10 mm Hg for 3 consecutive visits.

The percentage of patients with hypertension will be summarized by therapy group and will be analyzed using Fisher's exact tests.

In addition, the percentage of patients who had 3 consecutive elevations on sitting diastolic blood pressure (defined above) and the percentage of patients who had 3 consecutive elevation on sitting systolic blood pressure (defined above) will also be summarized and compared with using Fisher's exact test, respectively separately.

8.2.9.3. Clinical Laboratory Evaluation (page 47)

Change from baseline to endpoint (of Study Period II and Study Period III) for the chemistry and electrolyte group and the hematology group (including prolactin) will be analyzed by the ANOVA model. Change from baseline to endpoint of Study Period III for the urinalysis group will analyzed by the same model. Rank-transformed data will be used in the analysis given the view that the change scores for most of the laboratory analytes are not normally distributed.

A treatment-emergent high laboratory value is a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at endpoint. A treatment-emergent low laboratory value is a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at endpoint. Lilly The performing laboratory's reference ranges will be used to determine limits for abnormal laboratory values. The incidence of treatment-emergent high/low values will be computed by therapy group and evaluated using Fisher's exact test. Patients with a high/low laboratory value for a specific laboratory test at baseline will be excluded from the analysis of treatment-emergent high/low values for that analyte.

8.2.9.4. Sexual Functioning and Sleep Quality Evaluation (page 47)

Sexual functioning will be assessed by the Clayton Changes in Sexual Functioning Questionnaire (CSFQ) of 14 items. The CSFQ has two versions, a 36-item version for men and a 34-item version for women. The following six variables will be obtained from the CSFQ: Total score (range: 14 - 70), Sexual desire/frequency score (range: 2 - 10), Sexual desire/interest (range: 3 - 15), Sexual pleasure (range: 1 - 5), Sexual arousal/excitement (range: 3 - 15), and Sexual orgasm/complete (range: 3 - 15). For all the measures, the lower the score, the more severe the sexual dysfunction.

Change from baseline to endpoint for each of the scores will be analyzed by the ANCOVA model as described in Section 8.2.1 separately for male and female patient groups.

Sleep quality will be evaluated using Pittsburgh Sleep Quality Index (PSQI). This questionnaire consists of nine questions collecting information related to sleep hours and

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quality of sleep. The global PSQI score is the sum of the seven components which are either collected by the questionnaire or derived from the variables collected from the questionnaire. Each component results in a score ranging from 0 to 3 with the higher the score, the more difficult or less quality with sleep. These seven components are defined as:

- Subjective sleep quality (Item 6)
- Sleep latency (Categorize PSQI Item 2, Minutes to fall asleep, into 0, if ≤ 15 , 1 if > 16 and ≤ 30 , 2 if > 31 and ≤ 60 , 3 if > 60 . Add this score with Item 5a. Determine the Difficulty score by the sum [ranges from 0 to 6]: 0 if sum = 0; 1 if sum = 1 or 2; 2 if sum = 3 or 4; 3 if sum = 5 or 6)
- Sleep duration (determined by the integer of actual sleep hours by Item 4: 0 if hours ≥ 7 ; 1 if hours = 6; 2 if hours = 5; and 3 if hours ≤ 4)
- Habitual sleep efficiency (Calculate the percentage of real hours of sleep over hours in bed. The Efficiency score is determined as: 0 if the percentage is $\geq 85\%$; 1 if $\geq 75\%$ and $< 85\%$; 2 if $\geq 65\%$ and $< 75\%$; and 3 if $< 65\%$.)
- Sleep disturbances (Calculate the sum of Items 5b to 5j and the sum ranges from 0 to 27. Frequency of trouble sleep score is determined as: 0 if the sum = 0; 1 if sum is between 1 and 9; 2 if the sum is between 10 and 18, and 3 if the sum is between 19 and 27.)
- Use of sleep medication (Item 7)
- Daytime dysfunction (Calculate the sum of Items 8 and 9. The Energy level score is determined by the sum [ranges from 0 to 6]: 0 if sum = 0; 1 if sum = 1 or 2; 2 if sum = 3 or 4; 3 if sum = 5 or 6.)

The change from baseline to endpoint for the global PSQI score will be analyzed by the ANCOVA model as described in Section 8.2.1.

8.2.10. Subgroup Analyses (page 49)

Table HMBU.4 lists all the subgroups by which the subgroup analyses for the HAMD₁₇ total score will be conducted.

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Table HMBU.4. Definition for the Subgroups

Subgroup Variable	Categories
a. Age	a. < 55 or ≥ 55
b. Gender	b. Female or Male
c. Ethnic Origin	c. Caucasian African Descent East/Southeast Asian Western Asian Hispanic Other
d. Baseline severity of depression	d. Baseline HAM-D ₁₇ total < 40 25 or ≥ 40 25
e. Baseline severity of anxiety	e. Baseline HAMA total < 20 or ≥ 20

To analyze a specific subgroup's impact, change from baseline to endpoint will be analyzed using an ANCOVA model with all the terms described generally in Section 8.2.1- with additional terms of the subgroup and the subgroup-by-treatment interaction. The primary statistical testing will be for the treatment-by-subgroup interaction, which will be tested at the significance level of 0.10. Furthermore, treatment group differences will be evaluated within each category of a subgroup regardless of the significance level of the treatment-by-subgroup interaction.

For the subgroup of racial origin, all the categories that have less than 10% of the randomized patients in the study will be combined as Other in the analysis.

Subgroup analysis for safety variables and quality of life variables will be conducted as deemed appropriate and necessary.

8.2.12. Analysis Plan for Study Period IV: Tapering Period (page 50)

Patients who complete Study Period III have the option to enter Study Period IV, the tapering period. Patients who discontinue from the study before the last visit of Study Period III and on or after Visit 4 also have the option to enter Study Period IV.

Regardless of the last dose taken ~~at the end of the flexible dosing study period in Study Period III~~, all patients taking duloxetine or venlafaxine extended release will be grouped as duloxetine or venlafaxine extended release treatment group, and these two treatment groups will be used in all the analyses conducted for this study period.

Data from this study will be combined with data from similar designed Study F1J-MC-HMCQ according to the principle described in Section 8.2.6.

Since Study Period IV is an option for the patients, statistical inferences might not be valid if the number of patients is too small or not balanced between the two treatment

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groups. Thus, the statistical comparisons will only be made when each treatment group has at least 100 patients. Nevertheless, the statistical models will be provided in the following sections.

When performing the data analysis for this period, when the investigator is used as a factor in an analysis, it will be the one used in the analysis for Study Period II.

8.2.12.2. Concomitant Medication and Treatment Compliance (page 50)

Concomitant medication used during this study period will be summarized by treatment group. The treatment group difference in the frequency of usage for each medication will be analyzed by a Fisher's exact test. In addition, the percentage of patients who use benzodiazepines/hypnotics concomitantly will be summarized separately from other concomitant medication by visit and by at least once across the three visits in Study Period IV, and will be analyzed by a Fisher's exact test.

At each visit, the status of treatment compliance will be collected based on the percentage of capsules taken over the total capsules prescribed. A patient is considered to be compliant if the percentage is between 80% and 120%. A patient is considered to be compliant overall in this study period if he or she is compliant for each nonmissing observation in the study period. The percentage of patients who are compliant to treatment at each individual visit and overall will be summarized by treatment group and analyzed by a Fisher's exact test.

9.3.3. Final Report Signature (page 53)

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

~~The Sponsor's responsible medical officer will sign the final clinical study report for this study, confirming that to the best of his or her knowledge, the report accurately describes the conduct and results of the study.~~

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**Protocol Attachment HMBU.1.
Targeted and Suggested Visit Intervals Table (page 58)**

Protocol Attachment HMBU.1

Targeted and Suggested Intervals Between Visits Study Period I, II, & III

Study Period	Targeted Cumulative Days from Visit 2	Targeted Interval (in Days) from Prior Visit
Study Period I		
Visit 1	-3 to -9	NA
Visit 2	0	53 to 9
Study Period II		
Visit 3	5 to 9	7
Visit 4	12 to 16	7
Visit 5	19 to 23	7
Visit 6	26 to 30	7
Visit 7	40 to 44	14
Study Period III		
Visit 8	54 to 58	14
Visit 9	68 to 72	14
Visit 10	82 to 86	14

Note: If a patient's visit occurs early within the visit interval, the patient's subsequent visit should occur later in the suggested interval, if possible. For example, if the visit interval between Visit 2 and Visit 3 is 5 days, the investigator should attempt to schedule Visit 4 for 9 days after Visit 3.

Targeted and Suggested Intervals Between Visits Study Period IV

Study Period	Targeted Cumulative Days from Visit 10 or Last Visit in Study Period II or III	Targeted Interval (in Days) from Prior Visit
Study Period IV		
Visit 301	6 to 8	7
Visit 302	13 to 15	7
Visit 303	20 to 22	7

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**Protocol Attachment HMBU.2.
Study Schedule (page 60)**

Study Schedule, Protocol F1J-MC-HMBU

CRF Visit No.	1	2	3	4	5	6	7	8	9	10	301	302	303	Early D/C
Week Number	-1	0	1	2	3	4	6	8	10	12				
Procedure														
Informed Consent	X													
Demographics	X													
Psychiatric/Depression History		X												
MINI	X													
Historical Diagnosis	X													
Previous Drug/Non-Drug Therapy		X												
Height	X													
Physical Exam	X													
Weight	X									X			X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X			X	X
ECG	X						X		X	X				X
Pre-existing Conditions and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Summary										X				X
Taper Summary													X ^b	
Efficacy Measurements														
HAMD ₁₇	X	X	X	X	X	X	X	X	X	X				X
Hamilton Anxiety Rating Scale		X						X		X				X
CGI-Severity		X	X	X	X	X	X	X	X	X				X
PGI-Improvement		X	X	X	X	X	X	X	X	X				X
VAS for Pain		X	X	X	X	X	X	X	X	X				X

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Study Schedule, Protocol F1J-MC-HMBU (concluded)

GRF Visit No.	1	2	3	4	5	6	7	8	9	10	301	302	303	Early D/C
Week Number	-1	0	1	2	3	4	6	8	10	12				
Procedure														
Health Outcome Measurements														
SF-36		X					X		X					X
Quality of Life in Depression Scale		X					X		X					X
EuroQOL		X					X		X					X
Sheehan Disability Scale		X					X		X					X
Patient Health Questionnaire		X					X		X					X
Resource Use and Hospitalization Module		X					X		X					X
Cognitive Assessments														
VLRT		X					X		X				X	X
SDST		X					X		X				X	X
2DCT		X					X		X				X	X
LNST		X					X		X				X	X
Other Safety Measures														
AMDP-5		X	X	X	X	X	X	X	X	X	X	X	X	X
Change in Sexual Functioning Questionnaire-CSFQ		X					X		X					X
Pittsburgh Sleep Quality Index		X					X		X					X
Laboratory Tests														
Chemistry and Electrolytes	X						X		X					X
Hematology	X						X		X					X
Prolactin	X						X		X					X
Urinalysis ^a	X								X					
Urine Drug Screen ^a	X													
Pregnancy Test (all females) ^a	X													
Thyroid Function Test (TSH)	X													
Study Drug and Concomitant Medications														
Study Drug Dispensed		X	X	X	X	X	X	X	X	X	X			
Study Drug Compliance			X	X	X	X	X	X	X	X	X	X		X
Date of Last Dose							X		X	X	X			X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Benzodiazepine/Hypnotic Use	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: 2DCT= 2-Digit Cancellation Test; AMDP-5= Association for Methodology and Documentation in Psychiatry; CGI-Severity = Clinical Global Impressions of Severity; CSFQ = Change in Sexual Functioning Questionnaire; DESS= Discontinuation Emergent Signs and Symptoms; Early D/C = early discontinuation; ECG = electrocardiogram; EuroQOL = European Quality of Life Scale; HAMD₁₇ = 17-item Hamilton Depression Rating Scale; LNST = Letter-Number Sequencing Test; MINI = Mini International Neuropsychiatric Interview; SDST = Symbol Digit Substitution Test; SF-36 = Medical Outcomes Study Short Form 36; VAS = Visual Analog Scales; VLRT = Verbal Learning and Recall Test.

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^a To be performed at the investigator's discretion throughout the study.

^b if patient discontinues at Visit 301 or 302 complete the taper summary at the taper discontinuation visit.

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**Protocol Attachment HMBU.4.
Clinical Laboratory Tests (page 64)**

Clinical Laboratory Tests

Hematology:	Clinical Chemistry -
Hemoglobin	Serum Concentrations of:
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Total bilirubin
Mean cell hemoglobin concentration (MCHC)	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Alanine aminotransaminase (ALT/SGPT)
Monocytes	Aspartate transaminase (AST/SGOT)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Serum creatinine
Platelets	Uric acid
Prolactin	Phosphorus
	Calcium
Urinalysis ^a :	Glucose, nonfasting
Specific gravity	Total Protein
Protein	Albumin
Ketones	
Blood	Cholesterol
Nitrite	
Color	Creatine kinase (CK)
Urine Drug Screen ^a	Hepatic monitoring tests ^{a,b}
	Hepatic serology panel (A,B,C)
<u>Prolactin</u>	Thyroid Function Test:
	Thyroid-stimulating hormone (TSH)
	Pregnancy Test (all females) ^a

^a To be performed at the investigator's discretion throughout the study.

^b To be performed at sponsor request for selected patients

Protocol Attachment HMBU.5. Abbreviations and Definitions (page 66)

Abbreviations and Definitions

Study Entry Terms	<p>Screen The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial.</p> <p>Enter/Consent The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives.</p> <p>Enroll/Randomize The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.</p>
<hr/>	
2DCT	2-Digit Cancellation Test
AMDP-5	Association for Methodology and Documentation in Psychiatry
<u>AMDPAE</u>	<u>Association for Methodology and Documentation in Psychiatry collected Adverse Events</u>
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
Blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor(s), and in some cases, select sponsor personnel being unaware of the treatment assignment(s).
Compliance	Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements and the applicable regulatory requirements.
CGI-Severity	Clinical Global Impressions of Severity

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CRF	Case Report Form (sometimes referred to as Clinical Report Form). A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CSFQ	Changes in Sexual Functioning Questionnaire
DEAE	Discontinuation-emergent adverse event
ECG	Electrocardiogram
EuroQOL	European Quality of Life Scale
HAMD17	17-item Hamilton Depression Rating Scale
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IVRS	Interactive Voice Response System
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the patient's participation in the clinical trial.
LNST	Letter-Number Sequencing Test
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
MQA	Lilly Medical Quality Assurance
Patient	A subject with a defined disease.
PGI-Improvement	Patient's Global Impression of Improvement
PSQI	Pittsburgh Sleep Quality Index
QD	Once-daily
QLDS	Quality of Life in Depression Scale
SDS	Sheehan Disability Scale
SDST	Symbol Digit Substitution Test
SF-36	Medical Outcomes Study Short Form-36
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control.
TSH	Thyroid-stimulating hormone

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Treatment-Emergent Adverse Event (TEAE)	Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and which does not necessarily have to have a causal relationship with this treatment (also called treatment-emergent signs and symptoms).
VAS	Visual Analog Scale for Pain
VLRT	Verbal Learning and Recall Test

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