Protocol F1J-MC-HMBU(a)

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

Duloxetine Hydrochloride (LY248686)

Eli Lilly and Company
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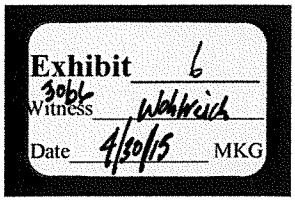


Duloxetine Versus Venlafaxine extended release in the Treatment of Major Depressive Disorder

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

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.

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 ($HAMD_{17}$). 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 discontinue 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 $HAMD_{17}$ 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:
    - $HAMD_{17}$ 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 $HAMD_{17}$ total score

- Remission rates, as defined by a $HAMD_{17}$ 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 $HAMD_{17}$ is achieved
  - Visit that the $HAMD_{17}$ 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

- 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).

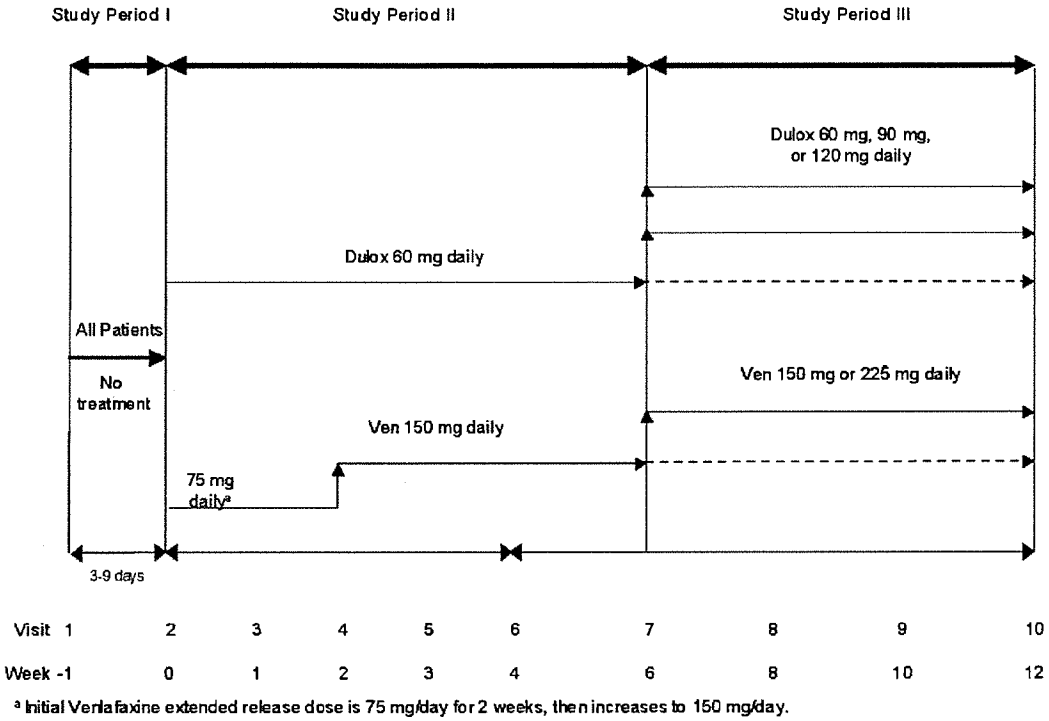
3. Investigational Plan

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).

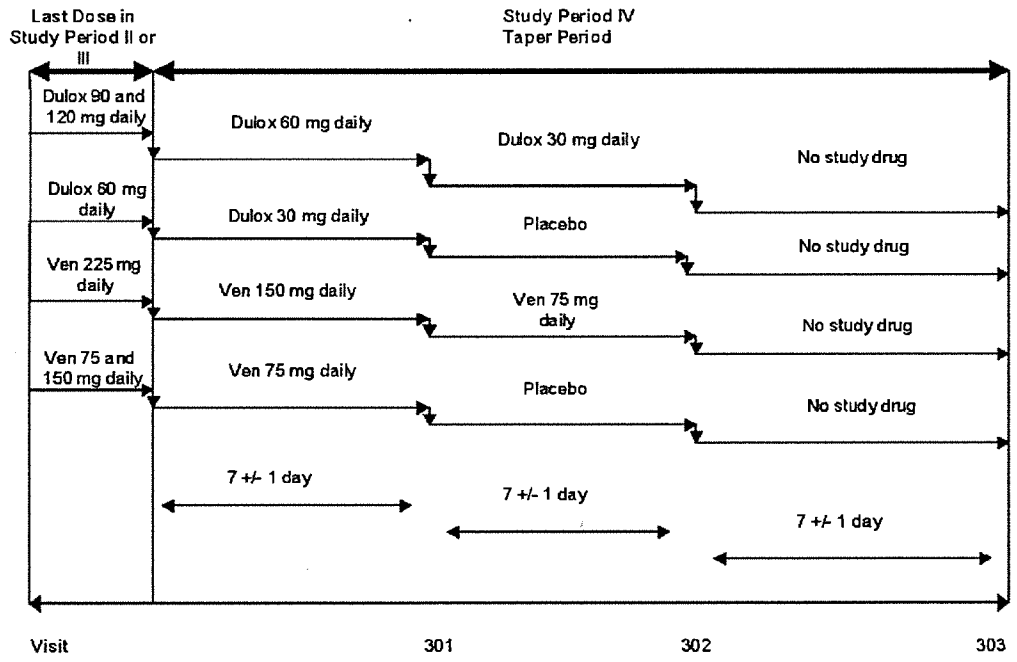
- Screening (Study Period I): Visit 1 to 2. This is a screening phase during which patients will be screened for eligibility. Visit 2 will occur 3 to 9 days after Visit 1.
- Double-Blind Fixed Dose (Study Period II): Visits 2 to 7. This is a 6-week period of double-blind treatment. Patients who meet entry criteria will be enrolled and randomised 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.



[a] 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.

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.

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.