2. LNBR Synopsis

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Clinical Study Report Synopsis: Study H9P-MC-LNBR

Title of Study: A Randomized, Placebo-Controlled, Double-Blind Study of LY2216684 Flexible-Dose 12 mg to 18 mg Once Daily as Adjunctive Treatment for Patients with Major Depressive Disorder Who Are Partial Responders to Selective Serotonin Reuptake Inhibitor Treatment

Number of Investigators: This multicenter study included 63 principal investigators.

Study Centers: This study was conducted at 64 study centers in 7 countries. Two study centers had the same principal investigator.

Publications Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 3
Date of first patient enrolled: 17 March 2011 Date of last patient completed: 30 April 2013	

Objectives: The primary objective of this study was to assess whether edivoxetine (12-18 mg flexible dose once daily [QD]) was superior to placebo QD in the adjunctive treatment of patients with major depressive disorder (MDD) (as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Text Revision® [DSM-IV-TR®]) who were identified as partial responders to an adequate course of treatment with a selective serotonin reuptake inhibitor (SSRI) during an 8-week double-blind acute adjunctive treatment phase. Superiority was defined as a statistically greater reduction in depressive symptoms from baseline to the last visit in the adjunctive treatment phase, as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) total score.

A gatekeeper strategy was used to test the following secondary objectives:

- to assess whether edivoxetine 12-18 mg QD is superior to placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in improving global functioning, as measured by change from baseline to the last visit in the adjunctive treatment phase in the Sheehan Disability Scale (SDS) global functional impairment score
- to assess whether edivoxetine 12-18 mg QD is superior to placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in achieving remission at the last visit in the adjunctive treatment phase. Remission was defined as MADRS total score $\leq$10.
- to assess whether edivoxetine 12-18 mg QD is superior to placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in achieving remission at least at the patient's last 2 consecutive visits in the adjunctive treatment phase
- to assess whether edivoxetine 12-18 mg QD is superior to placebo as an adjunctive treatment for patients with MDD who are partial responders to their SSRI treatment in improving anxiety symptoms, as measured by change from baseline to last visit in the adjunctive treatment phase in the Hospital Anxiety and Depression Scale (HADS) anxiety subscale score

The additional secondary objectives of the study were:

- to compare the efficacy of edivoxetine 12-18 mg QD with placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in improving severity of depressive illness, as measured by treatment response rates at the last visit in the adjunctive treatment phase. Response was defined as at least a 50% decrease from baseline in MADRS total score.
- to compare the efficacy of edivoxetine 12-18 mg QD with placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in improving severity of depressive illness, as measured by the change from baseline to the last visit in the adjunctive treatment phase using the following measures:
    - HADS depression subscale score
    - MADRS individual items
    - Clinical Global Impressions of Severity Scale (CGI-S)

Secondary Objectives (continued):

- to compare the efficacy of edivoxetine 12-18 mg QD with placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in improving fatigue, as measured by the change from baseline to last visit in the adjunctive treatment phase using the Fatigue Associated with Depression Questionnaire (FAsD) average score, FAsD experience subscale score, and FAsD impact subscale score
- to compare the efficacy of edivoxetine 12-18 mg QD with placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in improving health outcomes, including quality of life and role functioning, as measured by the change from baseline to the last visit in the adjunctive treatment phase using the following measures:
    - SDS work/school, social life/leisure activities, family life/home responsibilities impairment scores, number of days lost, and number of days underproductive
    - Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
    - European Quality of Life Questionnaire – 5 Dimensions (EQ-5D)
- to compare the safety and tolerability of edivoxetine 12-18 mg QD with placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment using the following measures:
    - spontaneously-reported treatment-emergent adverse events (TEAEs)
    - serious adverse events (SAEs)
    - discontinuation rates
    - discontinuation-emergent adverse events (DEAEs)
    - vital signs (pulse, blood pressure, and temperature) and weight
    - electrocardiograms (ECGs)
    - laboratory analyses
    - suicidality (ideation and behaviors) assessed by solicited questioning of suicide-related adverse events (AEs) using the Columbia-Suicide Severity Rating Scale (C-SSRS)
    - sexual functioning assessed by the Arizona Sexual Experiences (ASEX) scale
    - cognitive and physical functioning symptoms as assessed by the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)
- to assess whether edivoxetine 12-18 mg QD is superior to placebo as an adjunctive treatment for female patients with MDD, who were partial responders to their SSRI treatment and who had sexual dysfunction based on the ASEX total score at baseline, in achieving resolution of sexual dysfunction at endpoint in the adjunctive edivoxetine treatment phase. The data from this study will be combined with the data from Study H9P-MC-LNBM and Study H9P-MC-LNBQ and reported in the Summary of Clinical Safety.
- to assess whether edivoxetine 12-18 mg QD is superior to placebo as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in improving cognitive and physical functioning symptoms as assessed by the CPFQ total score and individual items. The data from this study will be combined with the data from Study H9P-MC-LNBM and Study H9P-MC-LNBQ and reported in the Summary of Clinical Safety.
- to examine the influence of cytochrome P450 (CYP) 2D6 genetic variation on edivoxetine response as adjunctive treatment with SSRIs in patients with MDD
- to evaluate the effects of abrupt discontinuation of edivoxetine compared with placebo treatment during a 1-week abrupt discontinuation phase

The exploratory objective of the study was [redacted]

Study Design: Study LNBR was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing edivoxetine 12-18 mg adjunctive to an SSRI with placebo adjunctive to an SSRI in the treatment of patients with MDD who had a partial response to their SSRI. The study included a screening phase, a 3-week double-blind adjunctive placebo lead-in confirmation phase, an 8-week double-blind adjunctive treatment phase, and a 1-week abrupt discontinuation phase. All patients were required to be taking an SSRI medication for at least 6 weeks prior to study enrollment and had to have been at an optimized stable dose for at least 4 consecutive weeks prior to Visit 2. Each patient continued on their stable SSRI dose throughout the study. The details regarding the use of a confirmation phase, the timing of randomization, and the randomization criteria were blinded to the investigators, clinical staff, and patients. At the randomization visit (Visit 5), patients were randomly assigned to adjunctive edivoxetine 12-18 mg or adjunctive placebo in a 1:1 ratio if they met blinded randomization criteria related to MADRS score at the end of the confirmation phase.

Number of Patients:

Planned to be randomized: 212 adjunctive edivoxetine 12-18 mg; 212 adjunctive placebo
Randomized: 230 adjunctive edivoxetine 12-18 mg; 219 adjunctive placebo
Completed adjunctive treatment phase: 196 adjunctive edivoxetine 12-18 mg; 189 adjunctive placebo

In addition, there were 519 patients who did not meet randomization criteria at Visit 5 but continued in the study on double-blind adjunctive placebo in order to maintain the blind. Results from the nonrandomized patients were not compared to the results from the randomized patients and are not discussed in below.

Diagnosis and Main Criteria for Inclusion: Male and female adult outpatients aged ≥18 years who met DSM-IV-TR diagnostic criteria for MDD as determined by clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) at Visit 1 with primary diagnosis confirmed by the physician. Patients had to have experienced a partial treatment response to a course of SSRI treatment for at least 6 weeks with at least the last 4 consecutive weeks at a stable, optimized dose prior to Visit 2. Patients had to meet criteria for partial response at Visit 1 and Visit 2, as defined by the investigator's opinion that the patient had experienced a minimally clinically meaningful improvement with SSRI treatment. Patients had to have a score ≥16 on the GRID 17-Item Hamilton Depression Rating Scale (GRID-$HAMD_{17}$) total score at Visit 1. Patients were also required to have a rating indicating ≤75% improvement for their current SSRI treatment using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) Modified Version at Visit 1.

Study Drug, Dose, and Mode of Administration:

Edivoxetine 12 mg/day or 18 mg/day, given orally QD as one 12-mg or 18-mg tablet.

Reference Therapy, Dose, and Mode of Administration: Placebo tablets given orally QD.

Duration of Treatment: Patients continued on their stable SSRI during all phases of the trial. All patients received 3 weeks of adjunctive placebo during the confirmation phase and no investigational product during the discontinuation phase. During the adjunctive treatment phase:

Adjunctive edivoxetine QD: 8 weeks
Adjunctive placebo QD: 8 weeks

Variables:

Efficacy: MADRS, HADS, CGI-S, FAsD
Health Outcomes: SDS (global functioning impairment score, the work/school, social life/leisure activities, and family life/home responsibilities impairment scores, number of days lost, and number of days underproductive), Q-LES-Q-SF (percent of maximum possible score and Item 15 score), EQ-5D (index and visual analog scale [VAS])
Safety: TEAEs, SAEs, discontinuation rates, DEAEs, vital signs and weight, ECGs, laboratory analyses, C-SSRS, ASEX, and CPFQ

Statistical Evaluation Methods:

Assuming an effect size of 0.30, a total of 424 patients randomized in a 1:1 ratio (212 patients per treatment group) was expected to provide approximately 85% power to detect a treatment difference between edivoxetine 12-18 mg and placebo in mean change from baseline to the last visit in the adjunctive treatment phase for the MADRS total score at a 2-sided significance level of 0.05.

Unless otherwise specified, safety and efficacy analyses for the randomized patients in the adjunctive treatment phase were conducted on an intent-to-treat (ITT) basis. When mean change from baseline was assessed, the patient was included in the analysis only if he/she had a baseline and a postbaseline measurement. Treatment effects were evaluated based on a 2-sided significance level of 0.05; 95% confidence intervals (CIs) for the difference in least-squares means (LSMeans) between treatment groups were presented. No adjustments for multiplicity were applied to comparisons of baseline characteristics or safety parameters. For efficacy, no adjustments were made for multiple comparisons; however a gatekeeper method was used to control the type I error for testing prespecified key secondary hypotheses.

The primary efficacy analysis was the contrast between edivoxetine and placebo at the last visit in the adjunctive treatment phase (Visit 11) from a repeated measures analysis of change from baseline in the MADRS total score. The model for this analysis included the fixed, categorical effects of treatment, pooled investigative site, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline MADRS total score and baseline MADRS total score-by-visit interaction. An unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

The analysis of the secondary gatekeeper objectives was to be performed only if the edivoxetine 12-18 mg versus placebo comparison was significant for the primary efficacy analysis at a 2-sided 0.05 significance level.

Continuous secondary efficacy and health outcomes measures were analyzed using the repeated measures analysis. In addition, analyses of change from baseline to last-observation-carried-forward (LOCF) endpoint in the adjunctive treatment phase were conducted using an analysis of covariance (ANCOVA) model which contained the main effects of treatment and pooled investigative site, and the appropriate baseline value was included as a covariate. For secondary efficacy variables analyzed with repeated measures methods that included data from all postbaseline visits, as well as methods that analyzed just the endpoint visit, the primary analysis method was the repeated measures method.

The percentage of patients meeting response, remission, and sustained 20% improvement criteria at each postbaseline visit during the adjunctive treatment phase was analyzed using a categorical, pseudo-likelihood-based repeated measures approach. Treatment differences in the proportions of patients meeting criteria for remission at least at the patient's last 2 consecutive visits in the adjunctive treatment phase were determined using a logistic regression model. The model for the analysis included the fixed, categorical effects of treatment and the continuous, fixed covariate of baseline MADRS total score. Response and remission at endpoint were analyzed using a logistic regression model with treatment and baseline MADRS total score as covariates. The comparisons between treatments for time to first response and time to first remission were conducted using the log-rank test and the stratified log-rank test.

Categorical safety measures (including percentages of patients with TEAEs, SAEs, AEs reported as a reason for dose reduction and discontinuation, and suicidal ideation and behavior measured using the C-SSRS and MADRS Item 10, as well as those patients who met categorical criteria for changes in vital signs and weight, ECGs, and laboratory tests) were analyzed using Fisher's exact test. Analyses of continuous laboratory data were conducted using an ANCOVA model. Analyses of other continuous safety measures (vital signs and weight, ECG, ASEX, and CPFQ) were analyzed using the repeated measures analysis and ANCOVA model.

Summary:

A total of 449 patients met randomization criteria and were randomized 1:1 to receive either edivoxetine 12-18 mg adjunctive to an SSRI or placebo adjunctive to an SSRI during the double-blind adjunctive treatment phase. The treatment groups were balanced with regard to demographics characteristics and baseline disease severity. The majority of randomized patients were White (87.3%) and female (66.8%) with a mean age of 48.4 years. On average, baseline measures indicated that the patient population in this study had moderate severity of depressive illness, as well as moderate severity for symptoms of anxiety and fatigue.

Overall in the study, edivoxetine 12-18 mg adjunctive to an SSRI was not associated with significantly greater improvements in depression severity and other efficacy and health outcomes measures compared with placebo adjunctive to an SSRI.

The primary analysis was the contrast between edivoxetine 12-18 mg adjunctive to an SSRI and placebo adjunctive to an SSRI on the mean change from baseline to the last visit in the adjunctive treatment phase (Week 8) on MADRS total score using a repeated measures analysis. There was no statistically significant difference between edivoxetine 12-18 mg adjunctive to an SSRI and placebo adjunctive to an SSRI in mean change from baseline to Week 8 in MADRS total score. In both treatment groups, statistically significant within-group mean improvements from baseline in MADRS total score were observed at Week 8. Similar results were observed for the other visits in the adjunctive treatment phase.

A gatekeeper method was to be implemented to sequentially compare edivoxetine 12-18 mg adjunctive to an SSRI and placebo adjunctive to an SSRI in improving global functioning, achieving remission at the last visit of the adjunctive treatment phase, achieving remission at least at the last 2 consecutive visits, and improving anxiety symptoms. Because the primary efficacy analysis was not statistically significant, none of the analyses in the secondary gatekeeper strategy could be considered significant. Regardless of the testing hierarchy, none of the analyses included in the gatekeeper strategy met statistical significance individually.

As with the primary efficacy analysis, other measures of improvement in depressive illness, such as probability of achieving remission or response at Week 8 or at any postbaseline visit, remission rate at the last 2 consecutive visits, probability of sustained improvement, changes on the HADS depression subscale score, and changes on the CGI-S, showed within-group improvement from baseline with both edivoxetine 12-18 mg adjunctive to an SSRI and placebo adjunctive to an SSRI, but not to an extent that was statistically significantly greater with adjunctive edivoxetine 12-18 mg compared with adjunctive placebo. The only statistically significant treatment group difference was observed on the CGI-S at Week 4, which favored edivoxetine 12-18 mg adjunctive to an SSRI. With the exception of concentration difficulties, none of the MADRS individual items were statistically significantly improved at Week 8 with edivoxetine 12-18 mg adjunctive to an SSRI treatment compared with placebo adjunctive to an SSRI.

Improvements in fatigue and anxiety were not statistically significantly different between edivoxetine 12-18 mg adjunctive to an SSRI and placebo adjunctive to an SSRI. In both treatment groups, statistically significant within-group mean improvements from baseline in fatigue and anxiety were observed throughout the 8-week adjunctive treatment phase.

Similarly, the differences in improvement in role functioning and quality of life, as measured by the SDS, Q-LES-Q-SF, and EQ-5D, were not statistically significantly greater with edivoxetine 12-18 mg adjunctive to an SSRI

compared with placebo adjunctive to an SSRI. In both treatment groups, within-group mean improvements in role functioning and quality of life were statistically significant at nearly all visits compared with baseline.

Mean duration of patient exposure to investigational product during the adjunctive treatment phase was approximately 52 days in each treatment group. The study allowed for flexible dosing of adjunctive edivoxetine 12-18 mg. At Week 3, approximately 74% of adjunctive edivoxetine-treated patients had received a dose increase to 18 mg, and a similar proportion was receiving an 18-mg dose throughout the remainder of the 8-week adjunctive treatment phase.

A statistically significantly greater percentage of patients treated with edivoxetine 12-18 mg adjunctive to an SSRI experienced at least one TEAE compared with patients treated with placebo adjunctive to an SSRI (65.4% vs. 50.5%). The most common TEAEs (reported in ≥5% of adjunctive edivoxetine-treated patients and with a greater incidence than adjunctive placebo) were hyperhidrosis, headache, nausea, dizziness, vomiting, and nasopharyngitis. Hyperhidrosis, nausea, vomiting, peripheral coldness, and vertigo occurred at a statistically significantly greater incidence with edivoxetine 12-18 mg adjunctive to an SSRI compared with placebo adjunctive to an SSRI. The majority of TEAEs were mild or moderate in severity.

Headache was the only DEAE reported in ≥5% of adjunctive edivoxetine-treated patients and with a greater incidence than adjunctive placebo based on adjunctive phase treatment assignment. In addition, headache was the only DEAE that occurred statistically significantly more frequently in patients treated with edivoxetine 12-18 mg adjunctive to an SSRI based on adjunctive phase treatment assignment compared with patients treated with placebo adjunctive to an SSRI.

There were no statistically significant differences between the edivoxetine 12-18 mg adjunctive to an SSRI treatment group and the placebo adjunctive to an SSRI treatment group in the proportion of patients who discontinued due to an AE. Depression was the only event that led to discontinuation in more than 1 patient in the edivoxetine 12-18 mg adjunctive to an SSRI treatment group. Statistically significantly more adjunctive edivoxetine-treated patients had a dose reduction requested due to an AE compared with adjunctive placebo-treated patients.

No deaths were reported in the study. SAEs were reported by 7 patients in each treatment group. A total of 16 SAEs were reported in randomized patients. Of the 7 patients in the edivoxetine 12-18 mg adjunctive to an SSRI treatment group who experienced an SAE, 2 patients experienced a total of 3 SAEs considered by the investigator to be related to study drug (myocardial infarction [actual term: unconfirmed myocardial infarction], blood creatinine increased, and blood urea increased).

Statistically significant treatment group differences were observed for numerous laboratory analytes in mean change from baseline to LOCF endpoint. No AEs of laboratory abnormalities were reported as a reason for discontinuation or dose reduction in the edivoxetine 12-18 mg adjunctive to an SSRI treatment group. There were no statistically significant differences between the edivoxetine 12-18 mg adjunctive to an SSRI treatment group and the placebo adjunctive to an SSRI treatment group in the proportion of patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3×the upper limit of normal (ULN) at any time. No patient in either treatment group had ALT or AST ≥5×ULN at any time. No patient in the adjunctive edivoxetine 12-18 mg treatment group had total bilirubin ≥2×ULN at any time compared with 3 patients (1.4%) in the adjunctive placebo treatment group.

Statistically significant mean increases in systolic blood pressure at Week 8 and in diastolic blood pressure and pulse at all visits were observed with adjunctive edivoxetine 12-18 mg compared with adjunctive placebo. The percentages of patients meeting criteria for changes in vital signs were evaluated using multiple criteria with increasing levels of clinical significance (elevation, treatment-emergent, potentially clinically significant [blood pressure only], and sustained elevation). The criteria consisted of an absolute threshold and a change from baseline amount. For each criterion, patients who did not meet the absolute threshold at baseline was the primary population. The proportions of patients with elevations in sitting pulse at any time and with treatment-emergent high sitting diastolic blood pressure at any time both occurred in significantly more adjunctive edivoxetine-treated patients compared with adjunctive placebo-treated patients. For all other vital signs parameters and categorical criteria, the proportions of patients meeting these criteria were either not statistically significantly different between treatment groups or occurred in no patient in either treatment group. Of the 8 patients in the adjunctive edivoxetine 12-18 mg treatment group who had treatment-emergent high sitting diastolic blood pressure at any time, 7 patients completed the study. Most of the patients met the criteria at a single time point. Treatment-emergent orthostatic changes in systolic blood pressure, diastolic blood pressure, and pulse at any time occurred in statistically significantly more patients in the adjunctive edivoxetine 12-18 mg treatment group compared with the adjunctive placebo treatment group. Two adjunctive edivoxetine-treated patients who had treatment-emergent orthostatic changes in blood pressure or pulse also experienced an AE of syncope/postural dizziness. Both patients completed the study.

Statistically significant mean decreases in weight were observed with edivoxetine 12-18 mg adjunctive to an SSRI compared with placebo adjunctive to an SSRI at all visits. There were no statistically significant treatment group differences in the proportion of patients with treatment-emergent decreases in weight.

Statistically significant mean decreases in PR interval and QTcF and mean increases in heart rate were observed for the edivoxetine 12-18 mg adjunctive to an SSRI treatment group compared with the placebo adjunctive to an SSRI treatment group at all visits. There were no statistically significant differences between treatment groups in change from baseline to any time point in QRS interval or QTc log-linear. The proportion of patients with treatment-emergent increases in heart rate was statistically significantly greater in the edivoxetine 12-18 mg adjunctive to an SSRI treatment group compared with the placebo adjunctive to an SSRI treatment group. For patients with a prolonged ventricular depolarization (for example, QRS $\geq$120 msec) at any time, the QTc intervals were excluded from QTc analyses. For patients who had a QRS <120 msec at any time during the study, none had a QTc interval >500 msec at any time.

There was no evidence of increased suicidal ideation or behavior in the edivoxetine 12-18 mg adjunctive to an SSRI treatment group compared with the placebo adjunctive to an SSRI treatment group.

For sexual functioning, there were no statistically significant differences between edivoxetine 12-18 mg adjunctive to an SSRI and placebo adjunctive to an SSRI in mean change from baseline to any visit in ASEX total score.

Cognitive and physical functioning symptoms that are often residual or treatment-emergent with SSRI treatment were assessed during the trial. There was a statistically significantly greater improvement in CPFQ total score at Week 4 with adjunctive edivoxetine 12-18 mg compared with adjunctive placebo but the difference was not statistically significant at Week 8.

Conclusions:

Overall, the safety profile of edivoxetine 12-18 mg was consistent with prior edivoxetine studies and with its noradrenergic mechanism of action. Edivoxetine 12-18 mg adjunctive to an SSRI did not separate from placebo in this study on measures of depressive symptoms, fatigue, anxiety, role functioning, and quality of life.