2. LNBO Synopsis

Clinical Study Report Synopsis: Study H9P-MC-LNBO

Title of Study: Long-Term, Open-Label, Safety Study of LY2216684 12 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 56 principal investigators.	
Study Centers: This study was conducted at 56 study centers in 7 countries.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 28 September 2010 Date of last patient visit: 27 December 2012	**Phase of Development:** 3

Objectives:

The primary objective of this study was to evaluate the long-term safety and tolerability of edivoxetine administered once daily (QD) in the adjunctive treatment with a selective serotonin reuptake inhibitor (SSRI) for up to approximately 1 year in patients with major depressive disorder (MDD) who were partial responders to their SSRI treatment. The safety measures included the collection and reporting of discontinuation rates, treatment-emergent adverse events (TEAEs), vital signs, weight, electrocardiograms (ECGs), and laboratory analysis.

The secondary objectives of the study were as follows:

- To evaluate the safety and tolerability of edivoxetine as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment using the following measures:
  - Serious adverse events (SAEs)
  - Discontinuation-emergent adverse events (DEAEs)
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Arizona Sexual Experiences (ASEX) scale
  - Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)
- To evaluate the effect of edivoxetine on depressive symptoms as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment using the following measures:
  - Montgomery-Asberg Depression Rating Scale (MADRS) total score and individual items
  - Hospital Anxiety and Depression Scale (HADS) depression subscale score
  - Clinical Global Impression - Severity (CGI-S)
  - Response rate, remission rate, time to response, and time to remission
- To evaluate the effect of edivoxetine as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in reducing fatigue symptoms associated with depression, using the Fatigue Associated with Depression (FAsD) average score, the Fatigue Experience subscale score, and the Fatigue Impact subscale score.
- To evaluate the effect of edivoxetine as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment in reducing anxiety symptoms associated with depression, using the HADS anxiety subscale score.

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Secondary Objectives (continued):

- To evaluate the effects of edivoxetine as an adjunctive treatment for patients with MDD who were partial responders to their SSRI treatment on quality of life and health outcomes using the following measures:
  - Sheehan Disability Scale (SDS) global functional impairment, work/school, social life/leisure activities, family life/home responsibilities impairment scores, number of days lost, and number of days underproductive
  - EuroQol Questionnaire – 5 Dimension (EQ-5D)
  - Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)
  - Resource Utilization (RU)
- To examine the influence of cytochrome P450 (CYP) 2D6 genetic variation on edivoxetine response in patients with MDD who were partial responders to their SSRI treatment
- To assess the plasma concentrations of edivoxetine during adjunctive treatment with SSRIs in patients with MDD who were partial responders to their SSRI treatment

The exploratory objectives of the study were as follows:

- [redacted]
- [redacted]

Study Design: Study LNBO was an open-label assessment of safety and tolerability over 1 year treatment of edivoxetine as an adjunctive therapy in patients with MDD who were partial responders to their SSRI treatment. The study included a Screening Period (Period I), a 1-year open-label treatment phase for adjunctive treatment (Period II), and a 1 week discontinuation phase (Period III).

Number of Patients:
Planned: 600 patients
Enrolled: 608 patients
Treated (at least 1 dose): 608 patients
Completed: 323 patients

Diagnosis and Main Criteria for Inclusion: Male and female adult outpatients aged ≥18 years who met *Diagnostic and Statistical Manual for Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR) diagnostic criteria for MDD as determined by clinical assessment by the Mini-International Neuropsychiatric Interview (MINI) and 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 have a score ≥16 on the GRID 17-Item Hamilton Rating Scale for Depression (GRID-$HAMD_{17}$) total score at Visit 1 and Visit 2. Patients were determined to be partial responders by history and by the opinion of the investigator. Patients were required to have a rating which indicated ≤75% improvement for their current SSRI treatment using the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) at Visit 1. Patients were excluded if they had any of the following criteria: any additional DSM-IV-TR Axis I condition other than major depression that was considered the primary diagnosis within 1 year of Visit 1; other primary Axis I anxiety diagnosis within the past year (including panic disorder, obsessive-compulsive disorder [OCD], posttraumatic stress disorder [PTSD], generalized anxiety disorder [GAD], and social phobia, but excluding specific phobias); current or previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; a serious or unstable medical condition; any diagnosed medical condition that could be exacerbated by noradrenergic agents, including unstable hypertension, unstable heart disease, tachycardia or tachyarrhythmia, narrow-angle glaucoma, or history of urinary hesitation or retention; used excluded concomitant medications; serious ideation/risk for harm to self or others; and pregnancy or breastfeeding status.

Study Drug, Dose, and Mode of Administration:
Edivoxetine (LY2216684), 12 or 18 mg, given orally, once a day in tablet form.

Reference Therapy, Dose, and Mode of Administration: Not applicable.

Duration of Treatment:
Screening period: from 3 days to 30 days
Treatment period: 54 weeks
Discontinuation period: 1 week

Variables:

Efficacy: Secondary efficacy measures included:

- Change from baseline to LOCF endpoint and change from baseline to each postbaseline visit in Study Period II for:
  - MADRS
  - HADS
  - CGI-S
  - FAsD
- Percent change from baseline to LOCF endpoint in Study Period II for MADRS total score
- Categorical variables at each visit and at LOCF endpoint in the Adjunctive Treatment Phase for MADRS total score (response rate and remission rate)
- Time to event variable (time to first response, time to first remission, time to loss of response, time to loss of remission, time to remission for patients with response but not remission at Week 8)

Safety: Primary safety measures included the collection and reporting of discontinuation rates, TEAEs, vital signs, weight, ECGs, and laboratory analysis. Other safety measures included C-SSRS, ASEX, and CPFQ.

Bioanalytical and Pharmacokinetic: Blood samples collected to measure edivoxetine plasma concentrations. Plasma samples were analyzed for edivoxetine by liquid chromatography and mass spectrometry.

Health Outcomes:

- Mean change from baseline to each postbaseline visit and mean change from baseline to last observation carried forward (LOCF) endpoint in Study Period II for:
  - 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)
  - EQ-5D index
  - EQ-5D visual analog scale (VAS)
  - RU measures

Statistical Evaluation Methods:
The sample size for this study was not based on statistical or power considerations. There were 608 patients enrolled in this study to provide 6-month safety exposure data for at least 300 patients and 1 year safety exposure data for at least 100 patients in order to meet International Conference on Harmonisation (ICH) regulatory guidelines; both safety exposure guidelines were met.

Safety and efficacy analyses were conducted on the enrolled population, defined as all entered patients who were assigned and dispensed edivoxetine. Unless otherwise specified, safety and efficacy analyses were conducted on an intent-to-treat (ITT) basis, meaning that data were analyzed by the treatment to which patients were assigned, even if the patient did not take the assigned treatment, did not receive the correct treatment, or did not comply with the protocol.

The primary objectives of this study were to evaluate the safety and tolerability of edivoxetine administered QD in the adjunctive treatment of patients on SSRI by evaluating discontinuation rates, TEAEs, vital signs, ECGs, and laboratory measurements. For each TEAE, the level of severity of the event (mild, moderate, or severe) was determined by patient or physician opinion. Treatment-emergent adverse events were also summarized by maximum severity as reported while on treatment.

The incidence rates of treatment-emergent abnormal, high, or low laboratory values at all postbaseline visits were assessed. Patients meeting criteria for elevations in blood pressure and pulse, treatment-emergent and potentially clinically significant (PCS) changes in vital signs, and sustained elevations in blood pressure and pulse were analyzed. Patients who experienced clinically significant changes in weight were characterized. The incidence of patients meeting criteria for treatment-emergent changes in ECG intervals and pulse was calculated.
The incidence of treatment-emergent overall abnormal qualitative ECGs was summarized.

The mean change from baseline to each postbaseline visit during Study Period II for vital signs, ECG intervals, and laboratory values, was primarily estimated from repeated-measures analyses. A repeated-measures analysis refers to a restricted maximum likelihood (REML)-based, mixed-effects model using all the postbaseline observations. Each model included the fixed, categorical effects of pooled investigative site and visit, as well as the continuous, fixed covariates of baseline and the baseline-by-visit interaction. An unstructured covariance matrix was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The mean change from baseline to LOCF endpoint was also assessed using analysis of covariance (ANCOVA) models with the main effect of pooled investigative site and baseline score as covariate.

The secondary objectives of the study were to evaluate efficacy and health outcomes, using the following continuous measures: MADRS, HADS, CGI-S, FAsD, SDS, QLES-Q-SF, and EQ-5D. For each measure, the mean change from baseline to each postbaseline visit during Study Period II was estimated from a repeated-measures analysis as described. The mean change from baseline to LOCF endpoint was also determined using ANCOVA models.

The percentage of patients meeting remission and response criteria at each postbaseline visit during the adjunctive treatment phase were estimated from a categorical, pseudo-likelihood-based repeated-measures analysis of visitwise binary outcomes which indicated whether patients met remission (response) criteria. The analyses included the fixed, categorical effect of visit, as well as the continuous, fixed covariate of baseline MADRS total score.

Secondary safety data from the C-SSRS, CPFQ, ASEX, and RU were also analyzed, as well as DEAEs.
Subgroup analyses were conducted for some of the efficacy and safety measures.

Summary and Conclusions:

Study LNBO was a multicenter, open-label investigation of the long-term safety and tolerability of edivoxetine, administered for up to approximately 1 year as adjunctive treatment to patients with MDD who had a partial response to SSRI treatment.

Patients enrolled in this study had experienced a partial response to therapy with an SSRI, meaning that they had experienced clinically meaningful improvement to their current SSRI and their baseline scores indicated that they were still experiencing moderate impairment in depressive symptoms and role functioning. They also reported moderate levels of anxiety and fatigue symptoms and were low in life satisfaction and quality of life ratings. The median duration of the patient SSRI treatment was approximately 5 months and the SSRI treatment therapies were approximately equally distributed across patients, with the exception of fluvoxamine which was taken only by 3 patients. In general, the demographics of the sample are consistent with the broader MDD population, with the majority of patients being female and a mean onset of MDD in the fourth decade.

Both edivoxetine doses of 12 mg and 18 mg were utilized in the study, with no clear preference for dose although the study design (open-label study with a single treatment) prevents direct dose comparisons. Approximately 54% of patients completed the study duration of 1 year.

The assessment of safety and tolerability of long-term adjunctive edivoxetine was made through a number of clinically relevant analyses of safety measures, including the collection and reporting of discontinuation rates, TEAEs, vital signs, weight, ECGs, and laboratory analysis. Approximately 75% of patients reported at least one TEAE during the open-label adjunctive edivoxetine treatment phase. The most common TEAEs (reported by ≥10% of patients) were nausea, hyperhidrosis, constipation, and headache. One (1) death, due to a probable myocardial infarction, was reported during the study and it was not judged by the investigator to be related to the SSRI, investigational product, or study procedures. Headache was the only symptom reported by ≥5% of patients during the abrupt discontinuation phase.

Increases in blood pressure and pulse were observed across visits during the open-label adjunctive edivoxetine treatment phase. The magnitude of these increases was consistent with previous edivoxetine data and was expected given the mechanism of action of edivoxetine as a norepinephrine reuptake inhibitor (NRI).

The majority of patients who had some suicidal ideation at baseline experienced a decrease in suicidal ideation when given edivoxetine as adjunctive treatment with a SSRI.

On both clinician-rated and patient-rated measures of depression, including MADRS, HADS, CGI-S, and FAsD, patients experienced improvement in depression symptoms and severity from their baseline. Not only did patients improve in their depression illness with an increased probability of remission, patients also had improvements from baseline in their role functioning and quality of life, as measured by SDS, EQ-5D, and Q-LES-Q-SF.

A summary of the edivoxetine plasma concentrations following coadministration of edivoxetine with various SSRIs was provided. The edivoxetine exposure in this study was consistent with previous clinical pharmacology evaluations including drug interaction studies of edivoxetine with SSRIs and in Phase 2 trials examining edivoxetine as a monotherapy MDD treatment. In study LNBO, the edivoxetine plasma concentrations were comparable across the SSRI treatments at each edivoxetine dose. Functional CYP2D6 status based on concomitant SSRI resulted in few differences in TEAE frequency between poor metabolizers and non-poor metabolizers. Similarly, TEAE frequencies based on CYP2D6 and CYP2C19 genotype did not show overall differences between poor metabolizer

and non-poor metabolizers; however, the low frequency of poor metabolizer genotypes prevent reliable comparisons between groups.

Overall, the observed safety findings (TEAEs, blood pressure, and pulse increases) are consistent with the profile of a drug with a norepinephrine mechanism of action. There were no differences in safety and efficacy outcomes based on SSRI treatment. Further well-controlled studies are needed to better characterize the safety, efficacy, and risk/benefit of edivoxetine.