2. LNBI Synopsis

Clinical Study Report Synopsis: Study H9P-MC-LNBI

Title of Study: A Randomized, Double-Blind Comparison of LY2216684 and Placebo and Long Term Treatment with LY2216684 in Adult Patients with Major Depressive Disorder	
Number of Investigator(s): This multicenter study included 43 principal investigator(s), all psychiatrists.	
Study Center(s): This study was conducted at 43 study centers in 5 countries (United States, Finland, Poland, Argentina, and Russia).	
Publication Based on the Study: Pangallo B, Dellva MA, D'Souza D, Essink B, Iyengar S, Russell J, Goldberger C. A randomized, double-blind study comparing LY2216684, a selective norepinephrine reuptake inhibitor and placebo in the treatment of major depressive disorder. *Neuropsychopharmacol* 2010;35:S211.	
Length of Study: Date of first patient enrolled: 24 November 2008 Date of last patient completed acute phase: 17 February 2010	**Phase of Development:** II/III

Objectives: The primary objective of Study LNBI was to assess whether LY2216684 was superior to placebo in the treatment of patients with MDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision® (DSM-IV-TR; APA 2004), during a 10-week, double-blind, acute treatment phase. Superiority was defined as a statistically greater reduction in depressive symptoms from baseline to endpoint as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) total score.

A gatekeeper strategy was used to test the following secondary hypothesis to be eligible for possible inclusion in the label:

- To assess whether LY2216684 was superior to placebo in the acute treatment of patients with MDD in improving global function as measured by change from baseline to endpoint in the Sheehan Disability Scale (SDS) Global Functional Impairment score (Sheehan 1983).

The additional secondary objectives were as follows:

- To compare the efficacy of LY2216684 with placebo in the acute treatment of patients with MDD as measured by the change from baseline to endpoint using the following measures:
  - Clinical Global Impression of Severity (CGI-Severity)
  - 16-Item Quick Inventory of Depressive Symptomatology-Self Rated ($QIDS\text{-}SR_{16}$)
- To compare the efficacy of LY2216684 with placebo in the acute treatment of patients with MDD as measured by response and remission rates defined using the MADRS and $QIDS\text{-}SR_{16}$.
- To compare the efficacy of LY2216684 with placebo in the acute treatment of patients with MDD in reducing cognitive impairment as measured by change from baseline to endpoint in the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ).
- To compare the effects of LY2216684 with placebo in the acute treatment of patients with MDD on quality of life and health outcomes using the following measures:

- SDS work/school, social life/leisure activities, and family life/home responsibilities impairment scores
- Euro-Qol Questionnaire – 5 Dimension (EQ-5D)

- To compare the efficacy of LY2216684 with placebo in the acute treatment of patients with MDD in reducing fatigue symptoms using the following measures:
  - Fatigue Associated with Depression (FAsD) Patient Reported Outcome (PRO)
  - Item C of the CPFQ
  - Brief Fatigue Inventory (BFI)
  - Visual Analog Scale for Fatigue (VAS-F)
- To evaluate the effects of LY2216684 in the long-term treatment of patients with MDD in improving depression and related symptoms using the following measures:
  - MADRS
  - CGI-Severity
  - QIDS-SR_{16}
  - FAsD PRO
  - CPFQ
  - BFI
  - VAS-F
- To evaluate the effects of LY2216684 in the long-term treatment of patients with MDD as measured by response and remission rates defined using the MADRS and QIDS-SR_{16}.
- To evaluate the effects of LY2216684 in the long-term treatment of patients with MDD on quality of life, health outcomes, and resource utilization using the following measures:
  - SDS work/school, social life/leisure activities, family life/home responsibilities, and global functional impairment scores
  - EQ-5D
  - Resource Utilization form
- To compare the safety and tolerability of LY2216684 with placebo in the acute treatment of patients with MDD using spontaneously reported treatment-emergent adverse events (TEAEs), taper-emergent adverse events (AEs), discontinuation rates, vital signs, electrocardiograms (ECGs), laboratory analyses, and solicited questioning of suicide-related AEs (behavior and ideations), using the Colombia-Suicide Severity Rating Scale (C-SSRS).
- To evaluate the safety and tolerability of LY2216684 for up to approximately 1 year in patients with MDD. The safety evaluation will be based on information from TEAEs, taper-emergent AEs, discontinuation rates, vital signs, ECGs, laboratory analyses, and solicited questioning of suicide-related AEs (behavior and

ideations) using the C-SSRS.

- To characterize LY2216684 pharmacokinetics in an adult population, its variability and potential influence of patient factors such as age, weight, gender, and cytochrome P450 (CYP)2D6 genotype on LY2216684 pharmacokinetics.
- To assess the impact of CYP2D6 genotype that may influence efficacy and safety in a population of adult patients with MDD.

The exploratory secondary objectives of the study were as follows:

- [redacted].
- [redacted].

Study Design: H9P-MC-LNBI is a 62 week Phase II/III multicenter study with a 10-week randomized, double-blind, placebo-controlled, flexible-dose, parallel-arm acute treatment phase comparing LY2216684 (6 to 18 mg once daily) and placebo followed by a 1-year blinded extension phase of LY2216684 in patients with major depressive disorder.

Number of Patients:

Planned: 478
Actual: 495
Randomized: 250 LY2216684, 245 placebo
Treated: 250 LY2216684, 245 placebo
Completed Acute Treatment Phase: 194 LY2216684, 214 placebo

Diagnosis and Main Criteria for Inclusion: Patients were eligible to be included in this study if they were adult men or women 18 to 65 years old at informed consent, met criteria for MDD as defined by DSM-IV-TR criteria without psychotic features, as determined by clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (MINI) at Visit 1, and had a Grid Hamilton Rating Scale for Depression (GRID-$HAMD_{17}$) total score $\geq$18 and CGI-Severity $\geq$4 at Visits 1 and 2.

Study Drug, Dose, and Mode of Administration:
LY2216684: 6, 9, 12, or 18 mg/day, given QD as 6-, 9-, or 12-mg tablets

Reference Therapy, Dose, and Mode of Administration: placebo tablets were identical in appearance, color, taste, and smell to LY2218864 tablets

Duration of Treatment:

This study consisted of 4 study periods:

Study Period I: screening phase of not less than 3 days and not more than 30 days

Study Period II: 10-week acute treatment phase

Study Period III: 1-year blinded long-term extension phase

Study Period IV: 2-week taper phase

Variables:

Efficacy: MADRS, Clinical Global Impressions of Severity (CGI-Severity), 16-Item Quick Inventory of Depression Symptomatology Self-Rated ($QIDS\text{-}SR_{16}$), Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), Brief Fatigue Inventory (BFI), Visual Analog Scale for Fatigue (VAS-F), and Fatigue Associated with Depression Patient Reported Outcome (FAsD PRO)

Health Outcomes: Sheehan Disability Scale (SDS), EuroQol Questionnaire-5 Dimension (EQ-5D), Resource Utilization form

Safety: Adverse events (AEs), concomitant therapies, laboratory measurements, vital signs, electrocardiograms (ECGs), and Columbia Suicide Severity Rating Scale (C-SSRS)

Evaluation Methods:

The analyses of the primary efficacy measure (MADRS total score), all secondary efficacy measures, health outcome/quality of life measures, and all safety measures were conducted on an intent-to-treat (ITT) basis. Treatment effects were evaluated based on a two-sided significance level of 0.05.

The primary efficacy analysis was the contrast between LY2216684 and placebo at the last visit in the acute treatment phase (Week 10 [Visit 7]) from a repeated measures analysis on change from baseline in the MADRS total score. The model for this analysis included the fixed class 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. The SDS global functional impairment score was a key secondary endpoint. A sequential gatekeeper strategy was used to control the experiment-wise Type I error rate.

Continuous secondary measures were analyzed using the repeated measures methods if at least 3 post-baseline assessments were scheduled. Other secondary measures were analyzed using analysis of covariance (ANCOVA) on change from baseline to last observation carried forward (LOCF) endpoint. The ANCOVA model contained the main effects of treatment and pooled investigative site, and baseline score as a continuous covariate. The visitwise percentages of patients meeting response and remission criteria were analyzed using a categorical, pseudo-likelihood-based repeated measures approach. The percentages of patients meeting response and remission criteria at endpoint were analyzed using Fisher's exact tests. The comparisons between treatments of time to first response and time to first remission were conducted using the log-rank test and the stratified log-rank test.

Continuous health outcome/quality of life measures were analyzed using repeated measures and ANCOVA models.

Fisher's exact tests were used to evaluate treatment differences for categorical safety variables, including percentages of patients with treatment-emergent adverse events (TEAEs), serious adverse events, and adverse events reported as a reason for dose reduction and discontinuation, as well as those of patients who met categorical criteria for changes in vital signs, electrocardiograms, and laboratory tests. Repeated measures analyses and analysis of variance were used to evaluate treatment differences in continuous safety measures.

Summary:

A total of 495 patients were enrolled in the acute treatment phase of the study (250 LY2216684; 245 placebo). Statistically significantly more patient from the placebo group completed the acute treatment phase compared to the LY2216684 group (87.3% vs 77.6%). The majority of the patients were female (61.2%), White (77.0%), and mean age was 44.8 years.

LY2216684 showed statistically significant improvement on the primary analysis, the contrast between LY2216684 and placebo at the last visit (Week 10) from a repeated measures analysis on change from baseline in the MADRS total score, as well as at Week 5 and Week 7. Repeated measures analyses of the probability of MADRS response and remission at each visit also showed statistically significant treatment differences in the LY2216684-treated patients compared with placebo-treated patients at Week 5 (response only), Week 7, and Week 10. In addition, patients in the LY2216684 treatment group also had a statistically significantly higher MADRS response rate and MADRS remission rate at endpoint (LOCF) when compared with the placebo treatment group. Kaplan-Meier estimates showed a statistically significantly shorter time to first response for LY2216684-treated patients when compared with placebo-treated patients, but no statistically significant difference between the groups in the time to first MADRS remission.

A sequential gatekeeper strategy was used to control the experiment-wise Type I error rate for the secondary objective of whether LY2216684 was superior to placebo in improving global function as measured by change from baseline to endpoint in the SDS global functional impairment score. LY2216684-treated patients demonstrated a statistically significant decrease (improvement) from baseline to Week 10 in the SDS global functional impairment score compared to placebo-treated patients. The effect of treatment on the severity of depression was also assessed using the CGI-Severity scale and the QIDS-SR_{16}. Patients in the LY2216684 treatment group had a statistically significant decrease (improvement) compared with the patients in the placebo treatment group in the change from baseline to Week 10 in both the CGI-Severity scale and the QIDS-SR_{16}. Overall, these results demonstrate an improvement in the severity of depression for the LY2216684 treatment group compared with the placebo-treated patients.

Patients in the LY2216684 treatment group had reductions in fatigue symptoms as evidenced by statistically significant decreases (improvement) in the FAsD PRO average, fatigue experience average, and fatigue impact average scores from baseline to Week 10 compared with patients in the placebo group. In the analysis of VAS-F, patients treated with LY2216684 demonstrated statistically significant decreases (improvement) in change from baseline to Week 10 on the severity of overall fatigue during the past week score and the fatigue interference with daily activities during the past week score. Similarly, there was a statistically significant improvement in fatigue symptoms as assessed by the BFI for patients in the LY2216684 treatment group compared with the placebo group.

Patients in the LY2216684 treatment group also had greater reductions in cognitive impairment relative to patients in the placebo group, as evidenced by a statistically significant decrease (improvement) in change from baseline to LOCF endpoint in the CPFQ total score and in 6 of 7 CPFQ individual items.

Additional secondary measures included quality of life and health outcome measures. LY2216684-treated patients showed statistically significant decreases in quality of life measures such as the SDS work/school, social life/leisure activities, and family life/home responsibilities impairment scores and a statistically significant decrease in the number of days lost and number of days underproductive at Week 10. These results demonstrate an improvement in functionality for LY2216684-treated patients compared with placebo-treated patients. In the analysis of EQ-5D, acute treatment with LY2216684 compared with placebo was associated with a numerically higher mean change from baseline in both UK and US population-based index scores, and a statistically significantly higher mean change in the VAS health state score. For resource utilization, the analysis of mean change from baseline to endpoint in resource utilization during the acute treatment phase showed no statistically significant differences between treatment groups.

The safety and tolerability of LY2216684 compared with placebo were assessed by adverse events, laboratory measurements, vital signs, ECGs, and the C-SSRS, used to capture the occurrence, severity, and frequency of suicide-related thoughts and behaviors.

During the acute treatment phase, 1 LY2216684 patient experienced a ruptured cerebral aneurysm and died due to a subarachnoid haemorrhage. This was the only patient in the LY2216684 group who had an SAE. Two placebo-treated patients each reported 1 SAE: lumbar radiculopathy and major depression. A total of 23 (9.2%) patients in the LY2216684 treatment group reported AEs as reason for discontinuation, compared with 4 (1.6%) patients in the placebo treatment group; the difference between groups was statistically significant. In addition, statistically significantly more LY2216684-treated patients had dose reductions requested by the investigator due to AEs.

Statistically significantly more LY2216684-treated patients (68.8%) reported at least 1 TEAE compared with placebo-treated patients (53.9%). Statistically significantly more patients in the LY2216684 treatment group reported the following TEAEs compared with placebo-treated patients: nausea, erectile dysfunction, constipation, dizziness, heart rate increased, hyperhidrosis, tachycardia, vomiting, and libido decreased.

Statistically significant differences between the placebo-treated and LY2216684-treated patients for mean change from baseline to endpoint were observed for some chemistry and hematology laboratory tests during the acute treatment phase; however, the differences were small and unlikely clinically significant. No statistically significant differences between the placebo and LY2216684 treatment groups were observed for mean change from baseline to endpoint for urinalysis laboratory tests. There was a statistically significant difference between treatment groups at any time during the acute treatment phase for the following treatment-emergent abnormal laboratory values: high calcium and abnormal urine ketones.

Statistically significant greater mean increases over placebo in supine and standing pulse for LY2216684 (approximately 4 to 10 bpm) were observed at every visit. Statistically significant greater mean increases from baseline for LY2216684 over placebo were observed in supine systolic blood pressure at all visits (1.8 to 3.0 mm Hg), in supine diastolic blood pressure at all visits (1.6 to 4.2 mm Hg), and standing diastolic blood pressure at most visits (1.1 to 3.3 mm Hg).

Statistically significantly greater percentages of patients meeting criteria for sustained elevations in supine systolic or diastolic blood pressure at 2 and 3 consecutive visits (≥10 mm Hg change from baseline) were observed for LY2216684 compared with placebo. When an absolute threshold was included with the increase criteria, there was no significant difference between treatment groups in the percentages of patients with sustained blood pressure elevations. Statistically significantly more LY2216684-treated patients met criteria for treatment-emergent orthostatic changes in systolic blood pressure at anytime compared with placebo-treated patients.

Statistically significant greater mean decreases in PR interval, QRS interval, uncorrected QT interval, and Fridericia-corrected QT interval (QTcF) and greater mean increases in Bazett-corrected QT interval (QTcB) were observed for LY2216684 compared with placebo at most visits. These changes may be accounted for by the observed statistically significant greater mean increase in heart rate for LY2216684 compared with placebo at all visits.

There were no statistically significant differences in treatment emergent suicidal ideation between treatment groups. No patients experienced suicidal behavior during the acute treatment phase.

Conclusions: The results of this study provide evidence that LY2216684 6-18 mg QD is effective and generally well tolerated for up to 10 weeks when used in the treatment of patients with MDD.