2. HBBR Synopsis

Approval Date: 30-Aug-2011 GMT

Clinical Study Report Synopsis: Study H8Y-MC-HBBR

Title of Study: A Long-Term, Phase 2, Multicenter, Randomized, Open-Label, Comparative Safety Study of LY2140023 Versus Atypical Antipsychotic Standard of Care in Patients with DSM-IV-TR Schizophrenia

Number of Investigators: This multicenter study included 29 principal investigators.

Study Centers: This study was conducted at 29 study centers in 4 countries.

Publications Based on the Study: None at this time.

Length of Study:
Date of first patient enrolled: 03 April 2009
Date of final database lock: 10 February 2011

Phase of Development: 2

Objectives: The primary objective of this study was to assess time to discontinuation due to lack of tolerability among patients with schizophrenia receiving LY2140023, given orally twice daily for 24 weeks, versus those on atypical antipsychotic standard-of-care (SOC) treatment. Lack of tolerability was defined as discontinuation due to adverse events (AEs).

The secondary objectives of the study were as follows (unless otherwise noted, all objectives were to be assessed during both Study Period III [Active Treatment Phase] and Study Period IV [Active Treatment Extension Phase]):

- to further evaluate the safety and tolerability of LY2140023 compared with SOC treatment, as assessed by the following measures: treatment-emergent adverse events (TEAEs), extrapyramidal symptoms (EPS), electroencephalograms (EEGs), electrocardiograms (ECGs) (analysis for Study Period III only), neurological examination, changes in vital signs, weight, and laboratory values, and solicited questioning of suicide-related AEs (behavior and ideations) using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- to determine the pharmacokinetics (PK) and exposure variability of LY2140023 and LY404039 (Study Period III only) in patients with schizophrenia
- to examine the long-term efficacy of LY2140023 compared with SOC treatment, as measured by the following scales: Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity Scale (CGI-S), 16-item Negative Symptoms Assessment (NSA-16), MATRICS Consensus Cognitive Battery (MCCB), and the Montgomery-Asberg Depression Rating Scale (MADRS)
- to assess if LY2140023 demonstrated improvement in health-outcome measures, including quality of life, functioning, resource utilization, and patient-reported outcomes compared to SOC treatment
- To evaluate rates of response, remission, and relapse among patients treated with LY2140023 compared to those on SOC treatment.

Study Design: A Phase 2, multicenter, randomized, parallel, open-label study comparing the long-term safety and tolerability of LY2140023 with atypical antipsychotic agents considered to be the current SOC for patients with schizophrenia. The study included a 24-week active treatment phase and an optional 28-week active treatment extension phase.

Number of Patients:
Planned randomized: Approximately 260 (130 LY2140023, 130 SOC)
Actual randomized: 261 (130 LY2140023, 131 SOC comparator)
Treated (at least 1 dose): 130 active drug, 131 comparator
Completed Visit 13: 35 active drug, 59 comparator
Completed Visit 20: 12 active drug, 46 comparator

Diagnosis and Main Criteria for Inclusion: Patients were male or female, 18 to 65 years of age (inclusive), with a diagnosis of schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (Disorganized, 295.10; Catatonic, 295.20; Paranoid 295.30; Residual, 295.60; or Undifferentiated, 295.90) and confirmed by the Structured Clinical Interview for DSM-IV (SCID). Patients had moderate symptomatology, with prominent negative symptoms of schizophrenia and evidence of functional impairment. Eligible patients were those for whom, in the opinion of the investigator, a switch to another antipsychotic medication or initiation of antipsychotic medication was indicated. Patients were excluded if they had a CGI-S score >4 at the time of study entry, or if they had a history of inadequate response to 2 or more antipsychotic medication trials of at least 8 weeks duration in the 12 months prior to Visit 1 of Study H8Y-MC-HBBR (HBBR). Patients also were not eligible to participate in Study HBBR if they had a history of seizures or additional specified criteria that may indicate decreased seizure threshold.

Test Product, Dose, and Mode of Administration:
LY2140023 (80 mg/day), given orally twice daily as two 40-mg tablets

Reference Therapy, Dose, and Mode of Administration: Oral doses of SOC treatments at the following doses: olanzapine (15 mg/day), aripiprazole (20 mg/day), or risperidone (4 mg/day).

Duration of Treatment:
Screening/antipsychotic taper period: Up to 7 days
Single-blind placebo lead in: 3 days
Active treatment phase (open label): 24 weeks
Optional active-treatment extension phase (open label): 28 weeks

Variables (Active Treatment Phase):
Efficacy: Efficacy variables used in the analysis of secondary endpoints include the CGI-S, PANSS, NSA-16, MCCB, and MADRS.
Safety: AEs, Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), and Abnormal Involuntary Movement Scale (AIMS), ECGs, EEGs, vital signs, weight, laboratory values, neurological examination, and C-SSRS.
Health Outcomes: UCSD Performance-based Skills Assessment-Brief Version (UPSA-B), Personal and Social Performance (PSP) scale, EuroQol: 5 Dimensions (EQ-5D) Questionnaire, resource utilization, and the Subjective Well-Being Under Neuroleptic Treatment Scale (SWN-S).
Pharmacokinetic/Pharmacodynamic: Sparse plasma samples were collected to measure the concentrations of the prodrug LY2140023 and the active moiety LY404039.

Statistical Evaluation Methods:
All analyses were conducted on an intent-to-treat (ITT) basis. All treatment comparisons were evaluated based on a 2-sided significant level of .05. Repeated measure analyses (MMRM) contained fixed class effects for gender, investigator, visit, treatment, and treatment-by-visit interaction as well as the continuous, fixed covariates-of-baseline measurement and baseline-by visit interaction. Unless otherwise specified, when an analysis of variance (ANOVA) model was used to analyze a continuous efficacy variable, the model contained the main effects of treatment and investigator. Similar logic was applied to an analysis of covariance (ANCOVA) model, which, in general, refers to the ANOVA model with baseline values added as a covariate. Type III sums of squares for the least square means (LSMeans) were used for the statistical comparison from ANOVA or ANCOVA models. Unless otherwise specified, baseline was defined as the last nonmissing observation at or before randomization (Visit 3), and endpoint was defined as the last nonmissing observation obtained from Visit 4 through Visit 13.

Primary Outcome and Statistical Methodology**:** The time to discontinuation due to AEs during Study Period III was compared between LY2140023 and standard of care using the log-rank test from the Kaplan-Meier survival analysis. Patients who completed Study Period III or who discontinued for a reason other than AEs were considered as censored observations.

Efficacy: Change from baseline during Study Period III in PANSS, MADRS total score, CGI-S, NSA-16 total score, and the 7 cognitive function domains of the MCCB were analyzed via MMRM using the longitudinal observations at each postbaseline visit. Significance tests were based on the LSMeans and Type III sum of squares. The treatment-group differences in response, remission, and relapse rates were analyzed by using a Fisher's exact test. For time to first response, time to first remission, and time to first relapse, the Kaplan-Meier survival curves of time to event were calculated by treatment groups. The comparison of the survival curves between treatment groups was conducted by a log-rank test.

Safety: Categorical Safety Measures: The incidence rates of TEAEs were analyzed by Fisher's exact test. TEAEs were also summarized by maximum severity as reported while on treatment. Solicited AEs from the neurological examination were analyzed similar to TEAEs. For each symptom of the neurological examination, the degree of severity was used to determine whether there was a treatment-emergent increase during the active treatment period. The numbers of patients with suicide-related thoughts, behaviors, and acts based on the C-SSRS were compared across LY2140023 and SOC using Fisher's exact test. Treatment-group comparisons of the categorical changes (potentially clinically significant [PCS] changes and treatment-emergent abnormal, high, and low values) in laboratory analytes at endpoint and any time during the active treatment phase were assessed using Fisher's exact test. Changes in vital signs and weight were summarized using shift tables. The incidence of patients meeting criteria for PCS changes in vital signs, weight, ECG intervals, and heart rate were compared between LY2140023 and SOC treatment groups using Fisher's exact test. Categorical changes in the SAS, BAS, and the AIMS were summarized. For the BAS, the incidence of patients with a global score of 2 or greater at any postbaseline visit and a baseline score <2 at all visits were compared across treatment groups using Fisher's exact test. A similar categorical analysis on the incidence of patients with a SAS total score >3 at any postbaseline visit and baseline score ≤3 at all visits was conducted. For the AIMS, the incidence of patients with a score of 3 or greater in any of the items 1 to 7 or a score of 2 or greater in any 2 of the items 1 to 7 that was not present at baseline was compared across treatment groups.

Continuous Safety Measures: Mean changes from baseline to postbaseline values in vital signs, weight, SAS total score, AIMS total score, BAS Global score, and ECG intervals were assessed using the MMRM. The treatment difference in rank-transformed mean change from baseline to last observation for laboratory analytes was assessed using an ANOVA model.

Health Outcomes: The changes from baseline to postbaseline values in the UPSA-B, PSP, EQ-5D index, VAS global health rating, and SWN-S were analyzed using MMRM. Summary statistics were also provided for these measurements.

Rate of hospitalization (defined as a stay in a hospital or other inpatient setting) and time to hospitalization were compared between the 2 treatment groups.

Pharmacokinetic/Pharmacodynamic: A series of pharmacostatistical models were evaluated using Nonlinear Mixed Effect Modeling program (NONMEM, version 7) to identify the model that best described the LY2140023 and LY404039 data.

Summary:
Study HBBR was designed to evaluate the long-term safety and tolerability of LY2140023 monohydrate (LY2140023) for up to 1 year in moderately ill patients with prominent negative symptoms of schizophrenia. A total of 402 patients entered the study; 261 were randomized to BID doses of LY2140023 (n=130 patients) or to standard-of-care (SOC) therapy (n=131 patients). A significantly greater number of patients in the SOC group (n=46) completed the full 52-week study than did those on LY2140023 (n=12). The most common reasons for early study discontinuation were AEs, perceived lack of efficacy, and withdrawn consent. Patients in the 2 treatment groups did not differ with respect to baseline characteristics such as gender, ethnicity, and age. The groups also were comparable with respect to baseline measures of psychiatric symptoms, psychiatric history, and extrapyramidal symptoms (EPS). The mean PANSS total score at baseline was 85.38, reflecting moderately severe overall symptomatology; the mean PANSS Negative score was greater than the mean PANSS Positive score, reflecting prominent negative symptoms, as specified in the protocol.

The primary analysis showed LY2140023 to be comparable to SOC in time to discontinuation due to AEs through 24 weeks of treatment. However, the higher incidence of LY-treated patients discontinuing due to psychosis-related AEs during the extension phase led to a statistically significant difference between groups at 52 weeks. Throughout the study, the most frequently reported AEs leading to discontinuation in both groups were those related to patients' underlying psychosis (LY2140023, n=17; SOC, n=13). At the 52-week endpoint, all-cause discontinuation and discontinuation due to perceived lack of efficacy were significantly greater among LY-treated patients than among those in the SOC group. There were no significant differences between treatment groups in the incidence of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), or AEs that led to study discontinuation.

Patients in the LY2140023 group were significantly more likely to report TEAEs of insomnia, vomiting, agitation, dyspepsia, bronchitis, and weight decrease, while SOC-treated patients experienced significantly more treatment-emergent akathisia and weight gain. Serious adverse events included 3 deaths (none of the 3 deaths was considered by investigators to be related to treatment with study drug or to protocol procedures). Serious adverse events of convulsion were reported in 2 patients (1 patient experienced 2 convulsion events 1 day after discontinuing LY2140023 and beginning treatment with another antipsychotic agent, and another patient had a convulsion prior to randomization). Extensive repeat EEG assessments of all study patients did not demonstrate any abnormal epileptiform-like changes that were frequent or remarkably different between treatment arms.

In general, patients in the LY2140023 treatment group had a more favorable metabolic profile, with fewer treatment-emergent increases in total cholesterol, low-density lipoprotein (LDL) cholesterol or triglycerides; a mean increase in high-density lipoprotein (HDL) cholesterol; and significant decreases in weight, body mass index, and waist circumference compared to those on SOC. A significantly greater percentage of SOC patients had treatment-emergent abnormal elevations in liver enzymes, creatinine phosphokinase (CPK), prolactin, as well as a significantly greater percentage of patients with treatment-emergent abnormal low urine analysis-specific gravity and mean cell hemoglobin concentration compared to LY2140023 at any time. While both treatment groups were associated with elevated CPK, these increases generally appeared to be transient and were not correlated with any clinical symptoms. In addition, between-group comparisons of changes in ECG intervals (as measured by QTc Fridericia) did not generally show significant differences between groups; none of the changes in QT intervals was deemed to be clinically relevant. The overall incidence of treatment-emergent Parkinsonism and akathisia was significantly higher among SOC-treated patients than among patients on LY2140023.

These data provide further evidence that the potential antipsychotic LY2140023, with its glutamatergic mechanism of action, may have a unique tolerability profile characterized by a low incidence of the AEs (and a decrease in mean weight compared to an increase in mean weight with SOC therapies) that are typically observed with currently available, dopaminergic antipsychotic treatments.

Efficacy was a secondary endpoint in Study HBBR. Certain design elements of the trial (open-label, lack of placebo arm, investigator choice of SOC treatment) prevent definitive conclusions regarding efficacy. In addition, the rate of all-cause discontinuation and discontinuation for lack of efficacy was significantly higher for the LY2140023 arm than it was for the SOC arm, further influencing the efficacy data. Furthermore, due to the small number of LY2140023 patients in the active treatment extension phase (28 LY2140023-treated patients entered the extension phase, of whom 14 had Visit 20 efficacy assessments), efficacy comparisons between LY2140023 and standard of care should not be overinterpreted. Patients in the LY2140023 treatment group demonstrated statistically significant (within-group) mean improvements in the PANSS total score at each visit of the acute treatment period and through the first 12 weeks of the extension phase (through Week 36). The magnitude of the improvement for LY2140023-treated patients was considerably smaller and more variable at the final assessment (Week 52). Patients in the SOC group had significant, and consistently strong, mean improvements throughout the study; improvement for SOC patients achieved statistically significant separation from the LY2140023 group, beginning at Week 16 and continuing through Week 52. Both treatment groups were associated with significant improvements in their negative symptoms throughout the 52-week study, as measured by the change from baseline to each postbaseline visit in both the PANSS Negative score and the NSA-16 scale.

A parent-metabolite model with first-order oral absorption was developed to simultaneously describe LY2140023 and LY404039 concentration-time data. The model adequately described the PK profile of LY2140023 and LY404039. Further investigation of the influence of patient characteristics (covariates) on the PK behavior of LY2140023 and LY404039 is warranted, and will be explored in future analyses with larger databases. Since covariate analyses were not conducted, the final model in this report is termed a 'base model,' which indicates no covariates were incorporated. The data from this study may be utilized for a pooled analysis across studies HBBR and HBBM, to provide a larger sample size for analysis.

The base model population estimates of CL/F for LY2140023 and LY4040239 were 71.4 L/h and 18.9 L/h respectively, and are comparable to the population analysis results from Study H8Y-MC-HBBI (71.1 L/h and 24.6 L/h) and noncompartmental analysis results from Study H8Y-EW-HBCP (94.5 L/h and 32.7 L/h). Between- and within-patient variability were moderate to high in this analysis, and tended to be slightly higher than has been seen in previous studies. The majority of concentration data (95%) in the current study was associated with 40-mg and 80-mg BID dosing, therefore the proportionality of exposure across dose levels was not evaluated.

Although, no formal PK/PD modeling was performed, the concentrations and PK parameter estimates were examined from the patient who had reported 2 convulsion events viewed as potentially related to LY2140023 treatment. The LY2140023 and LY404039 concentrations and PK parameters for this patient were consistent with observations from other study patients. Furthermore, the onset of the convulsive episodes was recorded approximately 24 hours after the last dose of LY2140023, which corresponds to modest plasma concentrations of LY2140023 and LY404039, given the short half-life of both analytes. This suggests the convulsion events might not have been related to plasma drug exposure.

The primary pharmacogenetic analysis in non-Hispanic Caucasians treated with LY2140023 suggests a genetic effect exists in this population. Specifically, patients in the T/A or T/T groups responded better than did patients in the A/A group, especially for the change in PANSS total and negative scores; at earlier time points (prior to Week 6), patients in the T/T group responded the best. Response rate analysis showed that, at Week 4, patients in the T/T group had a higher response rate than the overall non-Hispanic Caucasian group treated with LY2140023. These results suggest that in non-Hispanic Caucasians treated with LY2140023, the A/A group is the least responsive group. This finding is directionally consistent with results from the HBBD pharmacogenetic analysis. The genetic effect of rs7330461 was also examined in African Americans treated with LY2140023. Plots of LSMean change in PANSS total, positive, negative, and NSA-16 total scores suggested that, at earlier time points, the T/T group was the most responsive group in this population, although the differences between the T/A and A/A groups were not clear. The genetic effect is not clear at later time points. The plasma exposure of LY2140023 and LY404039 in the T/A and T/T groups, within the non-Hispanic Caucasians, appeared to be comparable to the exposure in other groups.

To examine the specificity of rs7330461, the genetic effect was examined in patients treated with SOC. Interestingly, in non-Hispanic Caucasians, the T/T group was the least responsive group, which is consistent with the findings from the HBBD pharmacogenetic analysis for the olanzapine-treated patients. This treatment response profile is the opposite of what was observed in non-Hispanic Caucasians treated with LY2140023. No genetic effect was observed in African Americans treated with SOC.

Conclusions:

- LY2140023 was comparable to atypical SOC medications in the time to discontinuation due to AEs through the first 24 weeks of treatment; this reflects the study's primary outcome. However, the higher incidence of LY-treated patients discontinuing due to psychosis-related AEs during the extension phase led to a statistically significant difference between groups at 52 weeks. In general, safety and tolerability findings from 52-week LY2140023 data were consistent with observations from 2 previous 4-week acute trials.
- LY2140023 was generally well tolerated, with a distinct safety profile characterized by a low incidence of dopamine-related AEs compared to SOC and a decrease in mean weight (compared to an increase in mean weight with SOC therapies). There were no significant differences between treatment groups in the overall incidence of SAEs, TEAEs, or AEs that led to study discontinuation. Lilly will continue to monitor for the identified risks of convulsion and gastrointestinal-related events.
- The efficacy of LY2140023, as measured by PANSS total and NSA-16 at 6 weeks and 6 months, is consistent with the profile of an active antipsychotic drug.
- A significant difference in favor of the SOC group was observed in terms of time to discontinuation for lack of efficacy across the active treatment and active treatment extension phases. There also was a significant difference in favor of SOC in the mean change in several efficacy measures at both 24 and 52 weeks. LY2140023 demonstrated similar improvement in negative symptoms compared to SOC throughout the study. However, the design of the trial prevents definitive conclusions regarding efficacy.
- The population pharmacokinetics in patients with schizophrenia were characterized with a simultaneous parent-metabolite model with first-order oral absorption, and the estimated population clearance value was similar to previous studies.
- Pharmacogenetic analysis indicated that the HTR2A SNP rs7330461 was associated with differential response to antipsychotic treatment: non-Hispanic Caucasian patients with the T/T or T/A genotype showed a better response to LY2140023 than Caucasians with the A/A genotype, whereas those with the T/T genotype showed a lesser response to SOC.