2. HBDE Synopsis

Clinical Study Report Synopsis: Study H8Y-MC-HBDE

Title of Study: A Phase 3, Multicenter, Double-Blind Comparison of LY2140023 and Aripiprazole in Patients with DSM-IV-TR Schizophrenia Followed by Open-Label Treatment with LY2140023	
Number of Investigator(s): This multicenter study included 57 principal investigators.	
Study Centers: This study was conducted at 57 study centers in 10 countries.	
Publication Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 11 April 2011 Date of last patient completed: 12 October 2012	**Phase of Development:** 3

Approval Date: 05-Apr-2013 GMT

Objectives:

The primary objective of this study was to test the hypothesis that mean weight gain, as assessed by change from baseline, would be statistically significantly less for flexibly dosed LY2140023 (20, 40, or 80 mg twice daily [BID]) than for flexibly dosed aripiprazole (10, 15, or 30 mg/day) in patients with schizophrenia after 24 weeks of double-blind treatment.

The secondary objectives of this study are listed below:

- To test the hypothesis that the proportion of patients with potentially clinically significant (PCS) weight gain (weight gain from baseline of ≥7%), would be statistically significantly less for LY2140023 than for aripiprazole after 24 weeks of double-blind treatment.
- To evaluate the safety and tolerability of LY2140023 compared with aripiprazole, based on rates of and time to discontinuation due to lack of tolerability during 24 weeks of double-blind treatment, where lack of tolerability was defined as discontinuation due to adverse events (AEs).
- To evaluate the safety and tolerability of LY2140023 compared with aripiprazole after 24 weeks of double-blind treatment with respect to assessment of changes from baseline in extrapyramidal symptoms (EPS), as evaluated using the Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), and Abnormal Involuntary Movement Scale (AIMS); laboratory tests including prolactin; vital signs; treatment-emergent adverse events (TEAEs); neurological examination; and solicited questioning about suicide-related AEs (behavior and ideations) using the Columbia-Suicide Severity Rating Scale (C-SSRS).
- To evaluate the efficacy of LY2140023 compared with aripiprazole, based on the following measurements after 24 weeks of double-blind treatment:
  - Change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score, PANSS positive subscale; PANSS negative subscale; PANSS general psychopathology subscale; Personal and Social Performance Scale (PSP) score; Clinical Global Impression-Severity Scale (CGI-S); and the 16-item Negative Symptom Assessment (NSA-16).
  - Incidence of response, where response was defined as a 30% decrease from baseline for PANSS total scores (1-7 scale for each item).
- To evaluate the efficacy of LY2140023 compared with aripiprazole within a prospectively defined subpopulation, as measured by the change from baseline on the PANSS and other efficacy measures after 24 weeks of double-blind treatment.
- To assess whether LY2140023 demonstrates improvement compared with aripiprazole on health outcomes, including quality of life and functioning, based on the following measurements after 24 weeks of double-blind treatment:
  - Change from baseline on the EuroQol Questionnaire - 5 Dimension (EQ-5D)
  - Resource utilization, as measured by the Schizophrenia Resource Utilization Module (S-RUM)
  - Change from baseline on the Subjective Well-Being Under Neuroleptic Treatment Scale-Short Form (SWN-S).
- To further evaluate efficacy, safety, and tolerability of LY2140023 through assessment of all efficacy and safety measures at the end of the 28-week open-label period.

The exploratory objective of the study was to examine the effect of genetic variation on response to treatment. Further exploratory analyses were presented in the statistical analysis plan.

Study Design: Study H8Y-MC-HBDE was a multicenter, randomized, double-blind, Phase 3 study to assess the safety and efficacy of LY2140023 (flexibly dosed between 20 and 80 mg BID) in patients with schizophrenia. An active control, aripiprazole (flexibly dosed between 10 and 30 mg/day), was included for comparison. Study H8Y-MC-HBDE consisted of 3 study periods: a screening and antipsychotic taper phase (up to 10 days, from Visit 1 to Visit 2); a double-blind active treatment phase (Visit 2 to Visit 12); and an open-label active treatment phase (Visit 12 to Visit 20) during which all patients were treated with LY2140023. Patients who qualified for enrollment were randomized in a 3:1 ratio to LY2140023 or aripiprazole. To allow for a thorough assessment of LY2140023 as a tailored therapy, as well as for use in a broad schizophrenic population, a comparison of efficacy between LY2140023 and aripiprazole within a prospectively defined subpopulation was incorporated as a secondary objective of this trial. The subpopulation was determined by genotyping used to exclude all non-Hispanic White patients (by self-report of race/ethnicity) who had the A/A genotype at the HTR2A SNP, rs7330461.

Number of Patients:

Planned: 670 entered, 600 randomized
Randomized to double-blind phase: 516 LY2140023, 162 aripiprazole
Treated during double-blind phase (at least 1 dose): 675
Completed double-blind phase: 231 LY2140023, 84 aripiprazole
Treated during open-label phase (at least 1 dose): 198 LY2140023, 73 aripiprazole
Completed open-label phase: 83

Diagnosis and Main Criteria for Inclusion: Patients were 18 to 65 years of age (inclusive) at study entry, with a diagnosis of schizophrenia as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV-TR) and confirmed by the Structured Clinical Interview for DSM-IV-TR. Patients were not eligible to participate in the study if they had received treatment with aripiprazole in the past 2 months or had been hospitalized for an exacerbation in symptoms of schizophrenia in the past 2 months, or had had a history of seizure unless it was a single simple febrile seizure meeting specified criteria or a single seizure with an identifiable etiology that had been completely resolved.

LY2140023, Dose, and Mode of Administration:

LY2140023 40 mg, given orally BID as a 40-mg tablet. LY2140023 dosage was adjustable from 40 mg BID to 20 mg BID or 80 mg BID.

Aripiprazole, Dose, and Mode of Administration:

Aripiprazole 15 mg/day, given orally once daily (QD) as a 15-mg capsule. Aripiprazole dosage was adjustable from 15 mg QD to 10 mg QD or 30 mg QD.

Duration of Treatment:

The double-blind phase of the study, during which patients received either LY2140023 or aripiprazole, was 24 weeks in duration. The open-label treatment phase of the study, during which all patients received LY2140023 monotherapy was 28 weeks in duration.

LY2140023 cumulative study exposure during the double-blind phase: 152.5 patient years
LY2140023 cumulative study exposure during the open-label phase: 96.0 patient years
LY2140023 cumulative study exposure (across double-blind and open-label phases): 248.5 patient years

Variables:

Efficacy: Secondary: PANSS (total, positive, negative, and general psychopathology scores), CGI-S, and NSA-16 during the double-blind phase of the study.

Safety: Primary: change from baseline in body weight during the double-blind phase.

Supportive: the earliest time point at which treatments separated in terms of weight change, PCS weight gain at endpoint, weight change analysis (ANCOVA) from baseline to endpoint of the double-blind phase and monthly postbaseline visits, PCS weight loss at endpoint, PCS weight gain or loss at any time and at each visit, and time to first PCS weight gain or loss.

Other safety variables: adverse events, clinical laboratory tests (including prolactin levels), vital signs, body mass index (BMI) and waist circumference, electrocardiograms (ECGs), EPS and abnormal movements (BAS, SAS, AIMS), neurological examinations, and suicidality (C-SSRS).

Health Outcomes: Secondary: PSP, EQ-5D (mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and visual analogue scale scores), SWN-S (total, self-control, emotional regulation, social integration, and mental functioning scores), and S-RUM during the double-blind phase of the study.

Statistical Evaluation Methods:

Efficacy: Efficacy variables were evaluated using a mixed-model repeated measures (MMRM) analysis for the double-blind treatment phase. The model included the fixed, categorical effects of treatment, gender, pooled study site, visit, treatment-by-visit interaction, predefined subpopulation (yes/no), as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. The primary contrast was the LY2140023 versus aripiprazole comparison at Visit 12. The MMRM analysis, without the fixed effect of predefined subpopulation, was applied to the predefined subpopulation.

Safety: An MMRM model was used to analyze the primary outcome, changes from baseline in weight during the double-blind treatment phase. The model included the fixed, categorical effects of treatment, gender, pooled study site, visit, treatment-by-visit interaction, and prior olanzapine use (yes or no, where "yes" was defined as usage of olanzapine for more than 7 cumulative days during the 6 weeks prior to screening), as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. The within-patient errors were modeled using an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The primary contrast was the LY2140023 versus aripiprazole comparison at Visit 12.

Secondary analyses of the primary outcome, body weight, were conducted. Based on the visit-wise treatment contrasts from the primary analysis, a sequential testing procedure was used to determine (with appropriate Type I error control) the earliest time point at which the treatments separated in terms of weight change. The incidence of patients meeting criteria for PCS weight gain (ie, ≥7% increase from baseline) or weight loss (ie, ≥7% decrease from baseline) at endpoint and at any time during the double-blind phase was compared between treatment groups using the Cochran-Mantel-Haenszel test, controlling for baseline BMI and prior olanzapine use. Analysis of covariance (ANCOVA) models were also applied to weight change from baseline to Visit 12 (6-month) and to monthly visits during the double-blind treatment phase. The last-observation-carried-forward was used to impute missing data.

Safety analyses were done for the double-blind and the open-label treatment phases. This included summaries of incidence of TEAEs, serious AEs (SAEs), and AEs resulting in discontinuation; neurological examination; treatment-emergent abnormal, high, and low values in laboratory analytes at endpoint and any time; PCS changes in vital signs, ECG intervals, and heart rate; and treatment-emergent changes on EPS rating scales. Incidence rates of categorical variables were compared between the LY2140023 and aripiprazole treatment groups using Fisher's exact test. The C-SSRS was summarized by treatment. The change from baseline in vital signs, ECG, SAS total score, AIMS items 1-7 total score, and BAS global score was assessed using a repeated-measures analysis with a model similar to that used for the efficacy analysis. The change from baseline to the last observed measure in the laboratory analytes was rank transformed prior to analysis and was assessed using an analysis of variance model with treatment as a fixed effect. Abnormalities of selected labs, including glucose and lipids, liver function, prolactin, creatine phosphokinase (CK), and eosinophil count were analyzed.

Health Outcomes: Changes from baseline in PSP score, EQ-5D dimension scores, EQ-5D VAS, SWN-S domain scores, and SWN-S total score for the double-blind treatment phase were assessed by using the MMRM model as described for efficacy variables.

General considerations: Unless otherwise specified, all analyses were done on an intent-to-treat (ITT) basis, that is, all patients were included in the groups to which the patients were assigned and received at least 1 dose, even if the patient did not receive the correct treatment, or otherwise did not strictly adhere to the protocol. Type III tests for the least-squares (LS) means were used for the statistical comparison based on generalized linear models. All treatment comparisons were evaluated at a two-sided significance level of 0.05. No adjustments for multiple comparisons were made, unless otherwise specified. For change-from-baseline analysis, only patients with baseline and at least 1 postbaseline measure were included.

Summary:

Patient Characteristics and Exposure: Of the 962 patients who entered the study, 678 patients were assigned to treatment in the 24-week double-blind treatment phase, and 273 patients enrolled in the 28-week open-label phase. There were 675 patients who received at least 1 dose of study drug during the double-blind phase. There were 315 patients who completed the double-blind phase of the study, including 42 patients who completed Visit 12 procedures, but discontinued prior to enrolling in the open-label phase. Eighty-three patients completed the open-label phase of the study.

Based on failure of a pivotal registration trial, Study H8Y-MC-HBBM, to meet its primary efficacy endpoint, and an independent futility analysis of a second registration trial, Study H8Y-MC-HBBN, that indicated that the study was unlikely to achieve its primary efficacy endpoint if enrollment were allowed to complete, the LY2140023 schizophrenia development program was terminated and Study H8Y-MC-HBDE was stopped early. Enrollment was complete before the study was stopped. The impact of early study termination on the double-blind phase results was minimal since 97% of patients had completed or had already discontinued from the double-blind phase of the study.

Of 672 patients in the ITT population, the mean (standard deviation [SD]) age was 42.45 (10.88) years, and the majority of patients were male (64.3%). The majority of patients were white (52.4%) or black/African-American (44.9%). The mean (SD) weight was 89.90 (22.21) kg, and the mean (SD) BMI was 30.44 (7.39) kg/m^2. There were no statistically significant differences between treatment groups with respect to baseline characteristics, including age, gender, ethnicity, weight, and BMI. Baseline characteristics for the predefined subpopulation and the open-label ITT population were similar to those for the overall ITT population. In the overall ITT population, the mean (SD) age at first treatment of schizophrenia was 27.22 (9.42) years, and the mean duration of lifetime illness was 17.67 (11.32) years. The mean (SD) number of past psychiatric hospitalizations was 3.67 (8.31). The majority of patients did not have a first or second degree relative with a history of schizophrenia. Patient and family psychiatric history for the open-label ITT population were similar to that of the overall ITT population.

There were no statistically significant differences in baseline score between the LY2140023 and aripiprazole groups for the efficacy measures of PANSS total, positive, negative, and general psychopathology scores, CGI-S, and NSA-16, and for the health outcome measures of PSP, EQ-5D, SWN-S and S-RUM in the overall ITT population, as well as the predefined subpopulation.

The rate of study completion between the LY2140023 and aripiprazole treatment groups was not statistically significantly different. During the double-blind phase of the study, the most common reasons for discontinuation were AEs–subject decision (56 patients, 8.3%), subject decision–consent withdrawn (55 patients, 8.2%), lost to follow-up (52 patients, 7.7%), protocol violation (40 patients, 6.0%), AEs–physician decision (36 patients, 5.4%), and perceived lack of efficacy–physician decision (36 patients, 5.4%). There were no statistically significant differences between the LY2140023 and aripiprazole groups with respect to reason for discontinuation, with the exception of AE–physician decision (LY2140023: 34 patients, 6.7%; aripiprazole: 2 patients, 1.2%; p=.005). During the open-label phase, the most common reason for discontinuation was sponsor decision (132 patients, 48.9%), which primarily reflects the early termination of the study.

Among patients in the overall ITT population during the double-blind phase, there were no statistically significant differences between treatment groups in time to discontinuation for any reason and in time to discontinuation due to lack of efficacy. Patients in the LY2140023 group had a statistically significantly shorter time to discontinuation due to AEs compared to patients in the aripiprazole group (p=.043).

In the LY2140023 group of the overall ITT population, there were 161 patients (31.5%) with >168 days of exposure to LY2140023 for a cumulative study exposure of 152.5 patient-years. Among patients in the open-label ITT population, there were 95 patients (35.2%) with >168 days of exposure to LY2140023 for a cumulative study exposure of 96.0 patient-years. Across the double-blind and open-label phases of the study, 189 patients (32.4%) had >168 to ≤364 days of exposure and 44 patients (7.5%) had >364 days of exposure to LY2140023 for a cumulative study exposure of 248.5 patient-years.

Efficacy: The LY2140023 group of the overall ITT population was associated with statistically significantly less improvement in PANSS total scores compared with the aripiprazole group at Week 4 (treatment difference in LS mean change, standard error, p-value; 2.42 [1.40], p=.045), Week 16 (4.98 [1.59], p=.002), Week 20 (4.36 [1.77], p=.014), and Week 24 (3.55 [1.77], p=.045). The LY2140023 group of the predefined subpopulation was associated with statistically significantly less improvement in PANSS total scores compared with the aripiprazole group at Week 16 and Week 20. For the overall ITT population, there were no statistically significant differences in response rate by PANSS total score between treatment groups across all weeks (Weeks 1 to 24). At Week 24, however, there was a statistically significant difference between treatment groups (p=.017) with 9.1% of patients in the LY2140023 group and 16.1% of patients in the aripiprazole group showing response. In the predefined subpopulation, there were no statistically significant differences in response rate between treatment groups across all weeks (Weeks 1 to 24) or at Week 24. There were no statistically significant differences between treatment groups in remission rate at endpoint, time to first response, time to onset of remission, symptomatic remission rate at any time, and time to symptomatic remission measured by PANSS scores during the double-blind phase of the study.

The LY2140023 group was associated with statistically significantly less improvement in CGI-S score compared with the aripiprazole group at Week 20 (0.20 [0.09], p=.032) in the overall ITT population and at Week 20 and Week 24 in the predefined subpopulation.

The NSA-16, PSP, EQ-5D, SWN-S, and S-RUM were analyzed in accordance with the statistical analysis plan. The only statistically significant differences for LY2140023 versus aripiprazole were in the mean change of SWN-S physical functioning scores at Week 6 (0.8 [0.4], p=.026) and Week 12 (1.2 [0.4], p=.004; higher in LY2140023) and S-RUM number of outpatient group sessions participated in since baseline, not as part of a partial care program (Week 24, .056 [0.22], p=.014; lower in LY2140023).

Safety: For the primary outcome measure, the change from baseline in body weight during the double-blind phase of the study, the LY2140023 group was associated with a statistically significantly greater weight decrease from baseline at Week 24 (-3.2 [0.7] kg, p<.001) compared with the aripiprazole group.

Secondary assessments of the primary outcome measure revealed the earliest time point at which treatments differed statistically in mean weight change was Week 2. There were no statistically significant differences between treatment groups in the overall ITT population in weight increase ≥7% from baseline at any time or at endpoint. A secondary ANCOVA analysis demonstrated the LY2140023 group had a statistically significantly greater weight decrease from baseline compared with the aripiprazole group at Week 24 and at the monthly postbaseline visits (Weeks 4, 8, 12, 16, and 20). There were no statistically significant differences between treatment groups in time to first PCS weight gain. Patients in the LY2140023 group had a statistically significantly shorter time to first PCS weight loss (≥7% decrease from baseline; p<.001) compared with patients in the aripiprazole group.

There were no confirmed seizure events in the study.

In the overall ITT population, 47 patients (7.0%) reported at least 1 SAE; 42 patients (8.2%) were in the LY2140023 group and 5 patients (3.1%) were in the aripiprazole group. The incidence of SAEs occurring in the LY2140023 group was statistically significantly higher than in the aripiprazole group (p=.032), which is attributed to a higher incidence of schizophrenia-related SAEs in the LY2140023 group. Serious AEs that occurred in more than 1 patient in any treatment group were schizophrenia, psychotic disorder, suicide attempt, and dystonia. There were no statistically significant differences between groups in incidence of any of these SAEs. There was 1 death, an SAE of completed suicide, in a patient in the LY2140023 group. In the open-label ITT population, 12 patients (4.4%) reported at least 1 SAE. The SAEs that occurred in more than 1 patient were delusion, anxiety, and schizophrenia.

There were 97 patients (14.4%) in the overall ITT population who discontinued due to AEs; 83 patients (16.2%) were in the LY2140023 group and 14 patients (8.7%) were in the aripiprazole group. The rate of discontinuations due to AEs in the LY2140023 group was statistically significantly higher than in the aripiprazole group (=.020). The majority of discontinuations due to AEs in both treatment groups were due to psychiatric and gastrointestinal-related AEs. There were no statistically significant differences between groups in incidence of any of these AEs. The overall significant treatment difference in discontinuation due to AEs appeared to be partially explained by schizophrenia-related SAEs; discontinuations due to schizophrenia, psychotic disorder, and auditory hallucination occurred in 25 patients (4.9%) in the LY2140023 group compared with 2 patients (1.2%) in the aripiprazole group. There were 3 patients in the overall ITT population (1 randomized to LY2140023 and 2 randomized to aripiprazole) who were excluded from this analysis, since the AEs leading to discontinuation were not present/flagged at the summary visit. In the open-label ITT population, there were 14 patients (5.2%) who discontinued due to AEs. The AE leading to discontinuation that occurred in ≥1% of patients was schizophrenia.
In the overall ITT population, 479 patients (71.3%) experienced at least 1 TEAE; 370 patients (72.4%) were in the LY2140023 group, and 109 patients (67.7%) were in the aripiprazole group. There was no statistically significant difference in TEAE incidence rate between treatment groups. The TEAEs reported in ≥3% of patients in the LY2140023 group were nausea, insomnia, headache, vomiting, nasopharyngitis, blood CK increased, anxiety, decreased appetite, diarrhoea, schizophrenia, and dizziness. Among TEAEs reported in ≥3% of patients in the LY2140023 and aripiprazole groups, there was a statistically significantly higher incidence of nausea (p=.023) and statistically significantly lower incidences of akathisia (p=.007) and dyspepsia (p=.027) in the LY2140023 group. In the open-label ITT population, 114 patients (42.2%) experienced at least 1 TEAE. The TEAEs reported in ≥3% of patients were headache, nausea, and insomnia.
There were no clinically relevant laboratory findings in patients receiving LY2140023 during the double-blind and open-label phases of the study.
There were no clinically significant findings on vital signs or ECGs for the LY2140023 group compared with the aripiprazole group.
There were no categorical differences from aripiprazole compared with LY2140023 on the SAS, BAS, and AIMS.
In addition to the 1 LY2140023 patient who died due to an SAE of completed suicide, there were 6 suicide attempts reported on the C-SSRS, all occurring in the LY2140023 group, but there were no statistically significant treatment differences in suicidal ideation and behavior on the C-SSRS during the double-blind phase. No patients had an increase in suicidal ideation compared to lifetime/lead-in baseline or suicidal behavior during the open-label phase of the study.

Conclusions:

- Study H8Y-MC-HBDE met the primary objective of the study, as LY2140023 showed statistically significantly less weight gain compared with aripiprazole.
- Patients treated with LY2140023 had a mean decrease in weight.
- Significantly more patients met the criteria for PCS weight loss (≥7% decrease from baseline) with LY2140023 compared with aripiprazole.
- There was no significant difference between the proportions of LY2140023 and aripiprazole patients with PCS weight gain.
- Patients in both treatment groups demonstrated improvement in schizophrenia symptoms from baseline. The LY2140023 group demonstrated significantly less efficacy compared with the aripiprazole group in the overall ITT population, as measured by PANSS total score and PANSS positive and general psychopathology subscores.
- No new safety findings were identified; however, inferior efficacy in this longer-term study led to clinically significant differences in important outcomes such as schizophrenia-related SAEs.
- There was 1 death during the study in the LY2140023 group due to a completed suicide.

- There was a statistically significantly greater incidence of discontinuation due to AEs and in the overall number patients with at least 1 SAE in the LY2140023 group compared with the aripiprazole group. These differences appeared to be the consequence of worsening of schizophrenia and may be attributed to inferior efficacy of LY2140023 compared with aripiprazole.
- Nausea was the only TEAE that occurred with a statistically significantly higher incidence in the LY2140023 group compared with the aripiprazole group.
- There were no clinically relevant laboratory changes associated with LY2140023.
- There were no clinically significant findings on vital signs or ECGs for the LY2140023 group compared with the aripiprazole group.
- There were no categorical differences between the aripiprazole and LY2140023 groups on the SAS, BAS, and AIMS.