2. HBBM Synopsis

Clinical Study Report Synopsis: Study H8Y-MC-HBBM

Title of Study: A Phase 2, Multicenter, Double-Blind, Placebo-Controlled Comparator Study of 2 Doses of LY2140023 versus Placebo in Patients with DSM-IV-TR Schizophrenia	
Number of Investigators: This multicenter study included 46 principal investigators.	
Study Centers: This study was conducted at 42 study centers in 4 countries and in Puerto Rico. For the HBBM study, 4 of the study centers experienced a change in investigator during the life of the trial, which accounts for the difference in the numbers of investigators and study sites.	
Publication(s) Based on the Study: None at this time.	
Length of Study: Date of first patient enrolled: 29 March 2010 Date of last patient completed: 25 May 2012	**Phase of Development:** 2

Approval Date: 19-Dec-2012 GMT

Objectives: The primary objective of this study was to test the hypothesis that at least 1 dose level of LY2140023, given orally to patients with schizophrenia at 80 mg BID (twice daily) or 40 mg BID, would demonstrate significantly greater efficacy than placebo at Visit 9, as measured by the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score, in 1 or more of the following populations: overall schizophrenia population, predefined subpopulation: subpopulation of patients that excluded all non-Hispanic white patients (by self-report of race/ethnicity) who had the A/A genotype at the serotonin 2A receptor (HTR2A) single nucleotide polymorphism (SNP), rs7330461.

Gated Secondary Objectives:

Key secondary objectives tested for possible inclusion in the label included:

- That LY2140023, at 80 mg BID or 40 mg BID doses, demonstrates significantly greater improvement than placebo at Visit 9 in the overall schizophrenia population, as assessed by the change from baseline in the Personal and Social Performance Scale (PSP) score;
- That LY2140023, at 80 mg BID or 40 mg BID doses, demonstrates significantly greater improvement than placebo at Visit 9 in the predefined subpopulation, as assessed by the change from baseline in the PSP score.

Additional Secondary Objectives:

- To assess if LY2140023 demonstrated significantly greater efficacy than placebo at Visit 9, as measured by the change from baseline in the following scales: PANSS positive subscale, PANSS negative subscale, PANSS general psychopathology subscale, Clinical Global Impression-Severity (CGI-S) Scale; 16-item Negative Symptom Assessment (NSA-16), and Montgomery-Åsberg Depression Rating Scale (MADRS).
- To examine the response rates for LY2140023 compared with placebo at Visit 9, as measured by the change from baseline in the PANSS total score. Response was defined as a 30% decrease from baseline for PANSS total scores (1-7 scale for each item).
- To examine if LY2140023 demonstrated significantly greater efficacy in females than placebo at Visit 9, as measured by the change from baseline in the PANSS total score.
- To compare the rates of discontinuation and time to discontinuation between LY2140023 and placebo.
- To assess if LY2140023 demonstrated greater improvement than placebo on health outcomes, including quality of life and functioning, as measured by the EuroQol Questionnaire – 5 Dimensions (EQ-5D); resource utilization, as measured by the Schizophrenia Resource Utilization Module (S-RUM); and the Subjective Well-Being Under Neuroleptic Treatment Scale – Short Form (SWN-S).
- To characterize the pharmacokinetics (PK) of LY2140023 and LY404039 in patients with schizophrenia.
- To compare LY2140023 and placebo in terms of extrapyramidal symptoms (EPS) at Visit 9, as measured by the change from baseline on the Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), and Abnormal Involuntary Movement Scale (AIMS).
- To examine the effect of LY2140023 on prolactin compared with placebo as measured by the mean change in prolactin levels.
- To examine the effect of LY2140023 on weight change compared with placebo.
- To further evaluate the safety and tolerability of LY2140023 compared with placebo, as assessed by treatment-emergent adverse events (TEAEs), electrocardiograms (ECGs), neurological examination, vital signs and laboratory tests, and solicited questioning of suicide-related adverse events (AEs) (behavior and ideations) using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Study Design: Study H8Y-MC-HBBM was a multicenter, randomized, double-blind, parallel, fixed-dose, Phase 2 study to assess the efficacy and safety of 2 dose levels of LY2140023 (80 mg BID or 40 mg BID) compared to placebo in patients with schizophrenia, with a risperidone treatment arm to ensure assay sensitivity in patients with schizophrenia. The unblinded study design consisted of 3 periods: a screening and antipsychotic taper phase, a 7-day placebo lead-in phase that was blinded to investigators and patients, and a 6-week active treatment phase. Patients were hospitalized beginning at Visit 2 and may have been discharged from the hospital after 3 weeks (beginning after Visit 5) if they met protocol defined criteria. To control for potential rating bias, improve reliability, and decrease variation, centralized ratings via video conference conducted by an approved vendor were utilized in all countries except Germany and Croatia, where this technology was not available and local blinded raters were used. In both cases, the raters were blind to the study design, entrance criteria, and treatment assignment.

Number of Patients:
Planned: N = 875; n = 250: LY2140023 (40 mg), n = 250: LY2140023 (80 mg), n = 250: placebo, n = 125: risperidone
Randomized: N = 1013; n = 293: LY2140023 (40 mg), n = 282: LY2140023 (80 mg), n = 295: placebo, n = 143: risperidone
Treated (at least 1 dose): N = 1009; n = 292: LY2140023 (40 mg), n = 280: LY2140023 (80 mg), n = 295: placebo, n = 142: risperidone
Completed: N = 539; n = 143: LY2140023 (40 mg), n = 129: LY2140023 (80 mg), n = 171: placebo, n = 96: risperidone

Diagnosis and Main Criteria for Inclusion: Male or female, 18 to 65 years of age, with a diagnosis of schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; APA2000) (Disorganized, 295.10; Catatonic, 295.20; Paranoid 295.30; or Undifferentiated, 295.90) and confirmed by the Structured Clinical Interview for DSM-IV-TR (SCID). Patients must have been suffering from schizophrenia for at least 1 year prior to visit 1, as determined from onset of illness. Eligible patients were those for whom a modification of antipsychotic medication was acutely indicated, in the opinion of the investigator. To be included in the study, patients must have experienced an exacerbation of their illness within the 2 weeks prior to study entry, requiring a need for intensification of the level of psychiatric care.

LY2140023 Dose and Mode of Administration:
LY2140023 40 mg, given orally twice a day (BID) as one 40-mg tablet at each dose; 80 mg, given orally BID as one 80-mg tablet at each dose.

Placebo Dose and Mode of Administration: Placebo given orally BID as a matching tablet.

Risperidone Dose and Mode of Administration: Risperidone 2 mg given orally BID as one 2-mg over-encapsulated tablet at each dose..

Duration of Treatment: Blinded placebo lead-in for all patients: 1 week; LY2140023 40 mg BID or 80 mg BID, Risperidone 2 mg BID, placebo: 6 weeks

Variables:
Efficacy: Primary: PANSS total score; Gated Secondary: Personal and Social Performance (PSP) scale. Secondary: PANSS positive subscore, PANSS negative subscore, PANSS general psychopathology subscore, NSA-16 total score, CGI-S score, and MADRS total score.
Safety: EPS (as measured by the BAS, SAS, and AIMS) and prolactin, ECGs, vital signs, weight, laboratory values, neurological examination, and suicidal ideation/behavior (based on the patient's score in the Columbia-Suicide Severity Rating Scale [C-SSRS]).
Pharmacokinetic/Pharmacodynamic: Plasma concentrations of LY2140023 and LY404039.
Pharmacogenomics: A 23-mL blood sample (3 mL for a genetic assay conducted as a part of the protocol and a 20-mL sample for additional genetic testing) for pharmacogenomics evaluation.
Health Outcomes: PSP, EuroQoL Questionnaire – 5 Dimension (EQ-5D), Schizophrenia Resource Utilization Model (S-RUM), Subjective Well-Being Under Neuroleptic Treatment – Short Form (SWN-S), MATRICS Consensus Cognitive Battery (MCCB), Performance-Based Skills Assessment-Brief Version (UPSA-B).

Statistical Evaluation Methods:
Primary Analysis Methodology and Model: The primary outcome measure (efficacy) was the change from baseline in the PANSS total score. To assess the efficacy of the given doses of LY2140023 for the two indicated populations (overall schizophrenia population and predefined subpopulation), while controlling the type 1 error

probability (α), a sequential testing procedure was implemented as outlined in the statistical analysis plan. The resulting procedure was an application of fallback testing methodology and provided strong control of the type 1 error rate for the primary objective at the 1-sided 0.025 level.

A mixed-effects repeated measures model (MMRM) was used to model changes from baseline in PANSS total for the overall population and the predefined subpopulation, respectively. For the overall population, the model included the fixed, categorical effects of treatment, investigative site, visit, treatment-by-visit interaction, gender, and predefined subpopulation, as well as the continuous, fixed covariates of baseline and baseline score-by-visit interaction. A similar MMRM model, excluding the categorical term of predefined subpopulation, was used for the predefined subpopulation. The primary comparisons were the LY2140023 doses versus placebo at Visit 9. Significance tests for each population (overall population and predefined subpopulation) were based on least-squares means and Type III tests, using one-sided significance tests as defined by the multiple testing strategy.

Gated Secondary Efficacy Analyses: The gated secondary outcome was the change from baseline in the PSP score. The change from baseline in PSP score was analyzed similarly to the PANSS total score by using the MMRM model for the overall population and the predefined subpopulation. The gated secondary hypotheses were tested using a parametric gatekeeping procedure as defined in the statistical analysis plan.

Secondary Analyses for Primary Outcome: An analysis of covariance (ANCOVA) model was applied on change from baseline to the last postbaseline measure for PANSS total score among doses of LY2140023, risperidone, and placebo. The last-observation-carried-forward (LOCF) method was used to impute any subsequent missing data. The model had baseline as a covariate and investigative site, gender, predefined subpopulation, and treatment as fixed effects. Response was defined as a 30% decrease from baseline for PANSS total score. The Fisher exact test was used to compare responder rates among treatment groups.

Other Secondary Efficacy Variables: The changes from baseline in PANSS Subscales, NSA-16 total score, CGI-S score, and MADRS total score were analyzed by using the MMRM model.

Safety:
Categorical Safety Measures: The incidence rates of TEAEs and treatment-emergent neurological examination were analyzed using the Fisher exact test. Treatment group comparisons of the categorical changes (treatment-emergent abnormal, high, and low values) in laboratory analytes and treatment-emergent significant changes in fasting glucose and lipids were also assessed using the Fisher exact test. The incidence of patients with treatment-emergent EPS changes and patients with potentially clinically significant changes in ECG intervals, heart rate, vital signs, weight, and criteria for sustained blood pressure elevations and orthostatic changes in blood pressure and pulse were assessed using the Fisher exact test as well.
Continuous Safety Measures: The safety measures, including EPS scores, vital signs, body weight, BMI, and ECG intervals were analyzed using an MMRM model similar to that used for the primary analysis. The changes from baseline to last observed measure in the laboratory tests were rank-transformed and assessed using an ANOVA model with treatment as fixed effect.

Health Outcome/Quality of Life Analyses: The changes from baseline in the EQ-5D profile domain score and EQ-5D visual analog scale were assessed using an ANCOVA model. The change from baseline in SWN-S domain scores and SWN-S total score were analyzed using the MMRM model.

Pharmacokinetics: A parent-metabolite model was developed in which parameters for both LY2140023 and LY404039 were determined simultaneously. The effect of patient factors on LY404039 PK was explored. LY2140023 and LY404039 concentration data were summarized in a standalone population PK report.

Pharmacogenomics: The effect size for each dose of LY2140023, in terms of changes in efficacy measures, was estimated for the predefined subpopulation, the complementary subpopulation, and the overall population.

Summary:
Patient Characteristics and Exposure: Of the 1571 patients who entered the study, 1013 were randomly assigned to treatment, 1009 received at least 1 dose of study drug, 539 completed the study, and 470 did not complete the study. The most common reasons for early discontinuation across treatment arms were perceived lack of efficacy-physician

decision (159 patients, 15.8%), subject decision–consent withdrawn (107 patients, 10.6%), and AEs-physician decision (81 patients, 8.0%).

Of the 1009 ITT patients, the mean (standard deviation [SD]) age was 40.0 (11.52) years and majority of patients were male (64.1%). The majority of patients were white (63.5%) or black or African American (34.0%). The mean (SD) weight was 82.10 (20.43) kg and the mean (SD) BMI was 27.68 (6.55) kg/m^2. Patients' mean age (SD) at first treatment of schizophrenia was 25.73 (8.97) years, the mean duration of lifetime illness was 14.93 (10.73) years, and the mean number of previous psychiatric hospitalizations was 7.77 (8.23). The overall mean (SD) PANSS total score was 84.1 (14.7). There were no statistically significant differences between treatment groups in baseline PANSS total score, PANSS positive score, PANSS negative score, PANSS general psychopathology score, CGI-Severity score, NSA-16 total score, or MADRS total score. Baseline EPS was similar across the treatment groups on the SAS Total Score and the BAS Global Score, however, overall statistically significant differences were seen among groups at baseline on the AIMS 1-7 Total Score (p=.027).

There were 215 (37.6%) patients with >42 days of exposure to LY2140023 with a mean (SD) exposure to LY2140023 of 29.3 (14.9) days, and total patient exposure of 45.9 patient-years.

For the primary efficacy analysis, neither of the LY2140023 doses showed a statistically significant improvement on the PANSS total score compared with placebo in either the overall population or the predefined subpopulation. Risperidone, the active control, statistically separated from placebo on improvement in PANSS total score at Visit 9 in both populations ($p \leq .001$). As the relevant primary null hypotheses were not rejected, no testing of gated secondary objectives occurred. For the secondary analysis of the primary outcome, ANCOVA analyses confirmed the primary analysis, no efficacy of LY2140023 as measured by PANSS total score was demonstrated in either the 40-mg or 80-mg BID groups compared to placebo. A statistically significant difference from placebo was seen in the LY2140023 80-mg group with fewer patients on LY2140023 80 mg achieving responder status (defined as having a 30% or more decrease in PANSS total score) than patients on placebo (Visits 4-9: responder rate LY2140023 80 mg, 15.2%; responder rate placebo, 24.9%; p=.009). For all secondary efficacy variables except PANSS general psychopathology subscore in the LY2140023 40-mg group (p=.045), there was no statistically significant improvement at Visit 9 compared with placebo for either LY2140023 doses in the MMRM analyses in the overall population.

The PSP, EQ-5D, S-RUM, and SWN-S were analyzed in accordance with the SAP. The only statistically significant difference for LY2140023 vs placebo was on the SWN-S. In MMRM analysis of SWN-S in the overall population, there were significant differences from placebo in the LY2140023 40-mg group in change from baseline on the self-control score (1.2 for LY2140023 40 mg vs 0.5 for placebo; p=.043) and emotional regulations score (1.8 for LY2140023 40 mg vs 0.9 for placebo; p=.038); significant differences from placebo in the LY2140023 80-mg group in change from baseline in SWN total score (7.7 for LY2140023 80 mg vs 4.4 for placebo; p=.024); and significant differences from placebo in the risperidone group in change from baseline on the self-control score (1.8 for risperidone vs 0.5 for placebo; p=.001), social integration score (2.6 for risperidone vs 0.9 for placebo; $p \leq .001$), and SWN total score (8.9 for risperidone vs 4.4 for placebo; p=.002).

Details of the pharmacokinetic analyses and results will be reported in the standalone population pharmacokinetic and pharmacodynamic report for studies HBBM and HBBN.

In addition to testing of the predefined subpopulation, prespecified genetic association analyses were also conducted. In non-Hispanic white patients treated with 40 mg BID of LY2140023, suggestive evidence was observed for a genetic association at rs7330461 on the primary efficacy outcome of PANSS total score at Visit 9, in which the T/T patients showed improved response compared to the A/T or A/A patients; this association was not observed for patients treated with 80 mg BID of LY2140023. In non-Hispanic white patients treated with 40 mg BID of LY2140023, the genetic association at rs7330461 was also observed for secondary efficacy outcomes of PANSS positive score and PANSS general score, suggesting the observation on PANSS total is being driven by these subscales in HBBM. In patients with T-carrier genotype of rs7330461, statistically significant improvement over placebo was seen at Visit 9 for LY2140023 40-mg BID and risperidone groups for PANSS total score, positive score, and general score at unadjusted 2-sided alpha of 0.05. In patients with T/T genotype of rs7330461, statistically significant improvement over placebo was seen at Visit 9 for LY2140023 40-mg group for PANSS total

score at an unadjusted 2-sided alpha of 0.05. Statistically significant improvement over placebo was seen at Visit 9 for LY2140023 40-mg BID and risperidone groups for PANSS positive score.

A total of 44 (4.4%) patients experienced at least 1 SAE during the study. The most frequently occurring SAEs were schizophrenia-related events; schizophrenia was reported in 19 (1.9%) patients, and psychotic disorder was reported in 5 (0.5%) patients. All other SAEs were reported in <1% of patients. An additional 11 SAEs were reported within 30 days after patient discontinuation or completion; 10 of the 11 events were related to the primary disease state.

There was 1 death during the study in the LY2140023 80-mg treatment group secondary to cocaine intoxication. Two additional deaths occurred in patients who signed informed consent to participate but prior to receiving randomized treatment. One patient died of acute cardiac arrest during the screening period, and 1 patient committed suicide during the placebo lead-in period.

The overall incidence of AEs leading to study discontinuation was not significantly different between treatment groups (p=.208). Overall, 104 (10.3%) patients discontinued due to AEs. The most frequently reported AE leading to discontinuation in all treatment groups was schizophrenia (3.7%) and psychotic disorder (1.1%).

A total of 594 ITT patients in the overall population (58.9%) reported at least 1 TEAE. The most frequently reported TEAEs were headache (7.8%), schizophrenia-related events (schizophrenia and psychotic disorder: 5.7% and 2.5%, respectively), nausea (5.6%), insomnia (5.6%), and increased blood creatine phosphokinase (4.8%). The incidence of dysmenorrhoea and sinusitis was significantly greater for the LY2140023 40-mg group than the placebo group; the incidence of agitation was significantly greater for the LY2140023 80 group than the placebo group, and the incidence of dyspepsia and weight increase was significantly greater for the risperidone group than the placebo group.

Statistically significant differences for change from baseline in laboratory results for LY2140023 compared to placebo were as follows: LY2140023 40-mg group, statistically significant increase compared to placebo in basophils and eosinophils; LY2140023 80-mg group, statistically significant increase compared to placebo in uric acid, prolactin, eosinophils, and atypical lymphocytes and statistically significant decrease compared to placebo in platelet count and UA-PH; risperidone group, statistically significant increase compared to placebo in estimated creatinine clearance and prolactin and statistically significant decrease compared to placebo in total and direct bilirubin, magnesium, erythrocyte count, hematocrit, hemoglobin, and platelet count.

Statistically significant overall differences for incidences of treatment-emergent high and low laboratory values between treatment groups at any time included incidence of treatment-emergent high alkaline phosphatase (p=.027; LY2140023 80 mg < placebo), alanine aminotransferase/serum glutamic pyruvic transaminase (p=.038; risperidone > placebo), prolactin (p<.001; LY2140023 40 mg < placebo; risperidone > placebo), eosinophils (p<.001; LY2140023 40 mg > placebo; LY2140023 80 mg > placebo), mean cell volume (p=.023), and incidence of treatment-emergent low albumin (p=.041), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (p=.019), total bilirubin (p=.018; risperidone > placebo), calcium (p=.019), erythrocytes (p=.015; risperidone > placebo), and platelet count (p=.042).

In the analyses of potentially clinically significant or treatment-emergent orthostatic changes at any time, in vital signs and weight the LY2140023 80-mg group showed a potentially clinically significant increase in standing diastolic blood pressure compared to placebo (p=.028). No other statistically significant changes in blood pressure were noted for either LY2140023 40 mg or LY2140023 80 mg. Compared with placebo, the risperidone group showed a potentially clinically significant increase in weight in the overall population (p<.001). There were no statistically significant differences in sustained elevations in blood pressure between the treatment groups overall or compared to placebo.

ECGs: Four (4) patients (1.5%) in the LY2140023 80-mg group had a change in QTcF >30 msec versus 13 patients (4.6%) in the placebo group (p=.048). Overall, of the 28 patients who experienced a QTcF change from baseline >30 msec, one male patient randomized to risperidone had a >60 msec change at Visit 4 and was discontinued from the study.

C-SSRS: One statistically significant value in favor of risperidone (p=.016) was noted for treatment-emergent suicidal ideation compared to lead-in baseline for patients randomized to risperidone. No other statistically significant differences were noted for treatment-emergent suicidal ideation or behavior compared to lead-in and lifetime baseline. There were no statistically significant differences from placebo in either of the LY2140023 treatment groups for any of the events during treatment.

Extrapyramidal Symptoms: On the AIMS total score the LY2140023 80-mg group had a statistically significant decrease compared to placebo at Visit 9 (p=.049). There was no statistically significant difference from placebo in any of the treatment groups in BAS global score or SAS total score. There were no statistically significant differences from placebo in akathisia on the BAS, parkinsonism on the SAS, or dyskinesias on the AIMS.

Conclusions:

- Treatment with LY2140023 methionil (LY2140023 monohydrate) was not effective in improving PANSS total score compared to placebo in patients with schizophrenia.
- There was lack of efficacy of LY2140023 therapy compared to placebo therapy on the PANSS subscales (with the exception of general psychopathology), PSP, CGI-S, NSA-16, and MADRS results in patients with schizophrenia.
- The all-cause discontinuation rate was higher on both doses of LY2140023 than on placebo.
    - Discontinuations due to AEs were comparable between LY2140023 and placebo.
    - Discontinuations due to lack of efficacy were more frequent on both doses of LY2140023 than on placebo and risperidone
- Patients in the LY2140023 groups had a significantly shorter time to study discontinuation for any reason compared to placebo and a significantly shorter time to discontinuation due to lack of efficacy.
- Overall, LY2140023 was generally well tolerated with no new significant safety findings compared to previous trials.
- There were no clinically relevant mean laboratory changes compared to placebo on LY2140023.
- There was 1 death during the study in the LY2140023 80-mg treatment group due to cocaine intoxication. Two additional deaths occurred in patients who signed informed consent to participate but prior to receiving randomized treatment. One patient died of acute cardiac arrest during the screening period, and 1 patient committed suicide during the placebo lead-in period.
- The most frequently reported TEAEs were headache, schizophrenia related-events (schizophrenia and psychotic disorder), nausea, insomnia, and increased blood creatine phosphokinase.
- TEAEs on LY2140023 that were statistically significant either overall or compared to placebo were extrapyramidal disorder (80 mg), agitation (80 mg), dysmenorrhea (40 mg), and sinusitis (40 mg). These events on LY2140023 40 mg were not considered to be of clinical significance, and the association of LY2140023 80 mg with EPS or agitation should be examined in further trials.
- LY2140023 was not associated with weight changes compared to placebo.
- There were no clinically significant findings on vital signs or ECGs for LY2140023 compared to placebo.
- No statistically significant categorical differences from placebo existed for any treatment group on either SAS, BAS or AIMS.
- There were no statistically significant differences on the C-SSRS in LY2140023 treatment groups compared to placebo for any of the events during treatment.
- There is suggestive evidence that there was an improved response to LY2140023 40 mg BID in non-Hispanic white patients with the T/T genotype at the HTR2A SNP rs7330461 compared to the patients with A/T and A/A genotypes.
- There was a greater improvement for non-Hispanic white patients with rs7330461 T-carrier or T/T genotype treated with LY2140023 40 mg BID compared to placebo, as measured by the change from baseline in PANSS total score.