# 2. HBCO Synopsis

# Clinical Study Report Synopsis: Study H8Y-MC-HBCO

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| **Title of Study:** A 17-Week, Phase 2, Multicenter, Randomized, Double-Blind Study of Treatment with LY2140023 Combined with Standard of Care Compared to Placebo Combined with Standard of Care in the Treatment of Patients with Prominent Negative Symptoms of Schizophrenia | |
| **Number of Investigators:** This multicenter study included 21 principal investigators. | |
| **Study Centers:** This study was conducted at 21 study centers in 4 countries. | |
| **Publication(s) Based on the Study:** None at this time. | |
| **Length of Study:**<br>Date of patient enrolled (Visit3): 27Jan2010<br>Date of last patient completed: 28Jun2012 | **Phase of Development:** 2 |

Approval Date: 05-Nov-2012 GMT

**Objectives:**

The primary objective of this study was to test the hypothesis that treatment with LY2140023 compared to placebo, when added to a fixed dose of a standard of care (SOC) antipsychotic, would demonstrate significantly greater reduction of negative symptoms, as assessed by the 16-item Negative Symptom Assessment scale (NSA-16), in patients with schizophrenia. Patients included in this study were concurrently receiving 1 of 4 second generation antipsychotics (SGAs): aripiprazole, olanzapine, risperidone, or quetiapine.

The secondary objectives of the study were as follows:

- to determine whether LY2140023 in combination with a fixed dose of SOC (LY2140023 + SOC) demonstrates superior symptom improvement compared to placebo when combined with a fixed dose of SOC (PBO + SOC), as measured by the Positive and Negative Syndrome Scale (PANSS) total score.
- to determine whether LY2140023 + SOC demonstrates superior symptom improvement compared to PBO + SOC, as measured by the PANSS Positive subscale and the Clinical Global Impression-Severity Scale (CGI-S).
- to determine whether LY2140023 + SOC demonstrates improvement in cognition and subsequent improvement in functioning compared to PBO + SOC, as measured by the MATRICS Consensus Cognitive Battery (MCCB) and the UCSD Performance-Based Skills Assessment-Brief Version (UPSA-B).
- to evaluate the safety and tolerability of LY2140023 + SOC compared to PBO + SOC as assessed by the following measures:
    - treatment-emergent adverse events (TEAEs),
    - extrapyramidal symptoms (EPS),
    - electroencephalograms (EEGs), electrocardiograms (ECGs),
    - neurological examination,
    - vital signs and body weight,
    - laboratory values, and
    - solicited questioning of suicide-related adverse events (behavior and ideations) using the Columbia-Suicide Severity Rating Scale (C-SSRS).
- to assess overall treatment effectiveness of LY2140023 + SOC compared to PBO + SOC, as measured by all-cause discontinuation, discontinuation due to lack of efficacy, and discontinuation due to adverse events (AEs).
- to determine whether LY2140023 + SOC demonstrates superior improvement in health outcome measures compared to PBO + SOC, as assessed by the following:
    - Personal and Social Performance Scale (PSP),
    - Schizophrenia Resource Utilization Module (S-RUM),
    - Subjective Well-Being Under Neuroleptic Treatment-Short Form (SWN-S), and
    - EuroQoL Questionnaire-5 Dimension (EQ-5D).

The following exploratory objectives were characterized in the comprehensive study statistical analysis plan (SAP):

- to evaluate rates of response, remission, and relapse among patients treated with LY2140023 + SOC compared to PBO + SOC.
- to assess LY2140023 + SOC compared to PBO + SOC, as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS), and the PANSS Negative, PANSS General Psychopathology, and NSA-16 subscales.
- to examine the effect of genetic variation on response to treatment.
- to explore appropriate doses of LY2140023 in combination with an SOC antipsychotic.

Further exploratory analyses were presented in the SAP.

**Study Design:** Study H8Y-MC-HBCO was a multicenter, randomized, double-blind, parallel, placebo-controlled, Phase 2, proof-of-concept trial to assess the safety and efficacy of LY2140023 as combination therapy with widely used SGAs considered to be the SOC in treating patients with schizophrenia. Patients may have entered the study (at Visit 1) either as inpatients or as outpatients.

**Number of Patients**:
Planned: 280 randomized
Randomized: 167 patients: 84 LY2140023 + SOC, 83 PBO + SOC
Treated (at least 1 dose): 164 patients: 82 LY2140023 + SOC, 82 PBO + SOC
Completed: 110 patients: 50 LY2140023 + SOC, 60 PBO + SOC

**Diagnosis and Main Criteria for Inclusion:** Patients were males or females, 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, Text Revision (DSM-IV-TR) and confirmed by the Structured Clinical Interview for DSM-IV (SCID-RV). Patients must have been on the SOC antipsychotic (aripiprazole, risperidone, olanzapine, or quetiapine) for at least 3 months prior to study entry and must have been on a fixed dose of the medication for at least 2 weeks prior to study entry.

**LY2140023, Dose, and Mode of Administration:**
LY2140023 40 mg/day, given orally twice daily (BID) as a 20-mg tablet. LY2140023 dosage was adjustable from 10 mg to 40 mg BID.

**Placebo, Dose, and Mode of Administration:** Placebo tablets to match LY2140023 tablets.

**SOC, Dose, and Mode of Administration:** Oral administration of SOC therapies (aripiprazole, risperidone, olanzapine, or quetiapine) were based on U.S. labeling.

**Duration of Treatment:** 16 weeks
LY2140023 Total Patient Exposure: 19.8 years Placebo Total Patient Exposure: 21.3 years

**Variables:**
Efficacy: Primary: NSA-16 total score (change from baseline).
Secondary: PANSS (total and positive score), CGI-S, and MCCB. Exploratory: NSA-16 (items, subscores, subgroups, other comparisons), PANSS (negative, general psychopathology, PANSS-8 subscores, and response, remission, and relapse rates), and MADRS.
Safety: Adverse events, vital signs, physical examinations, clinical laboratories (including prolactin levels), ECGs, EEGs, neurological examinations, extrapyramidal symptoms, and suicidality.
Health Outcomes: UPSA-B, PSP, EQ-5D, S-RUM, SWN-S, and hospitalizations.

**Statistical Evaluation Methods:**

Efficacy: The primary efficacy outcome was change from baseline in the NSA-16 total score. Changes from baseline to all postbaseline visits in the active treatment period were analyzed using a restricted maximum likelihood-based MMRM. Model terms included fixed class effects for visit, investigative site, treatment, SOC type, baseline positive symptom stratum, and treatment-by-visit interaction as well as the continuous, fixed covariates of baseline measurement and baseline-by-visit interaction. Kenward-Roger (KR) approximation was used to estimate denominator degrees of freedom. The primary contrast of interest from this model was model-based mean changes between LY2140023 with SOC versus placebo with SOC at Visit 13. Significance tests were based on LSMeans and Type III tests at a 1-sided 0.05 level. SAS PROC MIXED was used to perform the analysis. The significance of within-group changes from baseline were evaluated at a 2-sided 0.05 level by testing whether the treatment group changes were different from 0 using a t-test at each visit that the efficacy measure was collected. Changes from baseline to all postbaseline visits in PANSS total positive subscore, CGI-S score, and MCCB cognitive function domains raw score and T-score and MCCB overall composite score were analyzed similar to the primary efficacy variable by using a MMRM model.

Unless otherwise specified, all analyses were conducted on an intent-to-treat (ITT) basis. The ITT population included all patients who were randomized to treatment (Visit 4) and received at least 1 dose, even if the patient did not receive the correct treatment or did not strictly adhere to the protocol. Comparisons of efficacy parameters between LY2140023 with SOC and placebo with SOC were evaluated at the 1-sided 0.05 significance level.

Health Outcomes: The change from baseline to all postbaseline visits in the UPSA-B, PSP, EQ-5D index (including Visual Analog Scale global health score), and SWN-S was assessed using a MMRM model similar to the analysis of the primary efficacy outcome. Fisher's exact test was used to compare incidence of hospitalization and number of unique type of hospitalizations between treatment groups. S-RUM between treatment groups comparisons were done using an ANCOVA.

Safety: Unless otherwise specified, all categorical and continuous safety analyses were performed on the ITT population. Unless otherwise stated, comparisons of safety parameters between LY2140023 + SOC and PBO + SOC were evaluated at the 2-sided significance level of 0.05.

Treatment-emergent AEs were summarized in tables using the MedDRA Preferred Term, sorted by decreasing frequency within each treatment group by each visit and for entire active treatment period. Treatment-emergent AEs were summarized by Preferred Term sorted by decreasing frequency within System Organ Class for all TEAEs, TEAEs by maximum severity, and TEAEs considered possibly related to study drug. The number and proportion of patients with at least 1 event for each type of event were summarized and compared between treatment groups. Incidence rates were compared between LY2140023 + SOC and placebo + SOC using Fisher's exact test.

**Summary:**

Patient Characteristics and Exposure: Of the 187 patients who entered the study (Visit 3), 167 were randomly assigned to treatment (Visit 4), 164 received at least 1 dose of study drug, 110 completed the study, and 57 did not complete the study. The most common reasons for early discontinuation were AEs (n=16), protocol violation (n=14), subject decision – consent withdrawn (n=9), and lost to follow-up (n=8).

Of the 164 ITT patients, the mean (standard deviation [SD]) age was 43.3 (10.71) years and majority of patients were male (77.44%). The majority of patients were Black or African American (51.22%) or White (46.34%). The mean (SD) weight was 90.2 (20.49) kg and the mean (SD) BMI was 30.3 (7.18) $kg/m^2$. Patients' mean age (SD) at first treatment of schizophrenia was 26.0 (9.73) years and the mean duration of life illness was 18.3 (11.25) years. Most patients had moderate schizophrenia (n=105, 64.0%) with severe schizophrenia occurring in 37 (22.6%) of patients. The overall mean (SD) NSA-16 total score was 59.9 (9.41) and the overall PANSS total score was 77.8 (13.51). There were no statistically significant differences between treatment groups in baseline NSA-16 total score, PANSS total score, PANSS positive score, PANSS negative score, PANSS general psychopathology, CGI-severity score, MADRS total score, MCCB overall composite T-score, and UPSA total score.

There were 54 (65.9%) patients with >98 days of exposure to LY2140023 with a mean (SD) exposure to LY2140023 of 88.4 (36.61) days and a total patient exposure of 19.8 patient-years.
Efficacy: For treatment comparisons, the LY2140023 + SOC group was not associated with a statistically significant change in least squares mean (LS Mean) (standard error) NSA-16 total score compared with the PBO + SOC group at Week 16 (1.0 [1.6], p=0.723) or at any other timepoint. Secondary efficacy results also did not have statistically significant treatment differences between LY2140023 + SOC group and PBO + SOC group in PANSS (total and positive score), CGI-S, and MCCB. Health outcome parameters did not have statistically significant treatment differences between LY2140023 + SOC group and PBO + SOC group.
The only SAEs that occurred in more than 1 patient in any treatment group were psychotic disorder (PBO + SOC, n=1 and LY2140023 + SOC, n=3) and schizophrenia (PBO + SOC, n=1 and LY2140023 + SOC, n=3). There were no SAEs in PBO + SOC group that were reported in ≥3% of patients and also were ≥2 times the LY2140023 +SOC group's incidence rate. Serious AEs in LY2140023 + SOC group that were reported in ≥3% of patients and also were ≥2 times the PBO +SOC group's incidence rate were: psychotic disorder and schizophrenia.
There were no deaths during the study.
There were 16 (9.8%) patients overall who discontinued due to AEs during the treatment period. The only AEs leading to discontinuation that occurred in more than 1 patient were nausea, vomiting, psychotic disorder, and schizophrenia.
Of the 164 randomized patients who received at least 1 dose of study medication, 108 (65.9%) experienced at least 1 TEAE. Treatment-emergent AEs in PBO + SOC group that were reported in ≥3% of patients and also were ≥2 times the LY2140023 +SOC group's incidence rate were: arthralgia, dry mouth, akathisia, fatigue, toothache, upper respiratory tract infection, cough, and somnolence. Treatment-emergent AEs in the LY2140023 + SOC group that were reported in ≥3% of patients and also were ≥2 times the PBO + SOC group's incidence rate were: nausea, vomiting, diarrhoea, vulvovaginal mycotic infection, abdominal discomfort, pain, worsening of schizophrenia (psychotic disorder and schizophrenia), and weight increased. A statistically significant increase in the occurrence of vomiting was observed in LY2140023 + SOC treated patients compared to PBO + SOC treated patients (p=0.032).
Most of the 108 (65.9%) patients who reported at least 1 TEAE during the study had mild or moderate AEs (n=99 [60.4%]).
Adverse events considered treatment-related by the investigator in the LY2140023 + SOC group that were reported in ≥2% of patients and also were ≥2 times the PBO + SOC group's incidence rate were: nausea, vomiting, abdominal discomfort, diarrhoea, dyskinesia, and salivary hypersecretion. Adverse events considered treatment-related by the investigator in the PBO + SOC group that were reported in ≥2% of patients and also were ≥2 times the LY2140023 +SOC group's incidence rate were: headache, akathisia, blood creatine phosphokinase increased, dry mouth, insomnia, fatigue, and somnolence.
There were no statistically significant differences in changes in laboratory values among treatment groups in the ITT population. There were 14 patients (PBO + SOC group, n=8 and LY2140023 + SOC group, n=6) with >5 times the upper limit of normal for creatine phosphokinase. There were no statistically significant differences between treatment groups in the incidence of patients who had treatment-emergent abnormal aspartate aminotransferase, alanine aminotransferase, or total bilirubin laboratory values.
While statistically significant differences between treatment groups were observed in changes in vital signs and physical characteristics, these changes were not considered to be clinically relevant. There were no statistically significant differences between groups in terms of potentially clinically significant changes at endpoint in ECG intervals or HR. There were no statistically significant differences between treatment groups or clinical correlates of any abnormal EEGs. There were no statistically significant differences in changes in neurological examination, EPS, or C-SSRS between treatment groups.

**Conclusions:**

- Treatment with pomaglumetad methionil (LY2140023 monohydrate) when added to a fixed dose of SOC antipsychotic was not effective in reducing negative symptoms as assessed by the NSA-16 in patients with schizophrenia.

- There was lack of efficacy of LY2140023 + SOC therapy compared to PBO + SOC therapy in the PANSS total and subscales, CGI-S, and MCCB results in patients with schizophrenia.
- LY2140023 + SOC was generally well tolerated.
- SAEs in LY2140023 + SOC group that were reported in ≥3% of patients and also were ≥2 times the PBO +SOC group's incidence rate were worsening of schizophrenia.
- TEAEs in the LY2140023 + SOC group that were reported in ≥3% of patients and also were ≥2 times the PBO + SOC group's incidence rate were: nausea, vomiting, diarrhoea, vulvovaginal mycotic infection, abdominal discomfort, pain, worsening of schizophrenia, and weight increased.
- LY2140023 + SOC was not associated with development of EPS or prolactin elevation compared to PBO + SOC.
- No clinically significant weight changes were observed with LY2140023 + SOC compared to PBO + SOC.
- There were no clinically significant findings on vital signs or ECGs for LY2140023 + SOC compared to PBO + SOC.
- There were no deaths or seizure events reported during the study.