# 2. HBDF Synopsis

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

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| **Title of Study:** A Phase 3, Short-Term, Multicenter, Placebo-Controlled, Randomized Withdrawal Study of LY2140023 Monohydrate in Patients with DSM-IV-TR Schizophrenia | |
| **Number of Investigators:** This multicenter study included 13 principal investigators. | |
| **Study Centers:** This study was conducted at 13 study centers in 2 countries. | |
| **Publications Based on the Study:** None at this time. | |
| **Length of Study:**<br>Date of first patient enrolled: 31 October 2011<br>Date of last patient completed: 18 September 2012 | **Phase of Development:** 3 |

**Objectives:**

The primary objective of this study was to assess whether LY2140023, when administered in an acute treatment trial with flexible doses (40 mg or 80 mg) twice daily (BID), was associated with physical dependence, as measured by the occurrence of withdrawal symptoms during a randomized withdrawal phase in patients diagnosed with schizophrenia. Assessment was to be based on a comparison of randomized LY2140023-treated patients with those on placebo, as measured by the maximum of the 3-day moving average of the patient's total score on the Discontinuation Symptom Checklist-Modified Rickels (DSCMR).

The secondary objectives of the study were as follows:

- To characterize the symptoms observed in randomized patients treated with LY2140023 compared with those on placebo during the withdrawal phase, as measured by the area under the curve (AUC) for the total score and on each item of the DSCMR over time
- To evaluate symptoms in randomized patients treated with LY2140023 compared with those on placebo during the withdrawal phase, as measured by the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar)
- To evaluate the safety and tolerability of randomized LY2140023 compared with placebo during the withdrawal phase, as measured by the following: treatment-emergent adverse events (TEAEs); 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; electrocardiograms (ECGs); neurological examination; and solicited questioning regarding suicide-related adverse events (AEs; behavior and ideation) using the Columbia-Suicide Severity Rating Scale (C-SSRS)
- To assess the safety and tolerability of randomized LY2140023 during the open-label treatment phase, as measured by the following: TEAEs; EPS, as evaluated using the BAS, SAS, and AIMS scales; laboratory tests, including prolactin; vital signs; ECGs; neurological examination; and solicited questioning regarding suicide-related AEs (behavior and ideation) using the C-SSRS
- To assess the efficacy of randomized LY2140023 compared with placebo during the withdrawal phase, as measured by the Clinical Global Improvement-Severity (CGI-S) and Brief Psychiatric Rating Scale (BPRS) scales
- To assess whether LY2140023, when administered in flexible doses (40 mg or 80 mg BID), is associated with physical dependence within a prospectively defined subpopulation, as measured by the occurrence of withdrawal symptoms during a randomized withdrawal phase in patients diagnosed with schizophrenia

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-HBDF was a short-term, multicenter, placebo-controlled, randomized withdrawal study comparing LY2140023 with placebo in the treatment of outpatients with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) schizophrenia. The study included 3 phases: a screening and antipsychotic drug taper phase (7 day window; from Visit 1 to Visit 2); an open-label treatment phase (4 weeks; Visit 2 to Visit 8) during which all patients received LY2140023 monotherapy; and a 2 week, double-blind, randomized withdrawal phase (Visit 8 to Visit 12) during which patients who had completed the open-label phase and met prespecified, blinded criteria were to be randomized in a 1:1 fashion to receive either LY2140023 or placebo. The duration of the open-label treatment phase would enable sufficient time to bring patients' plasma LY2140023 to "steady state" (given the molecule's short half-life) and was an adequate period of time to assess response to treatment. Although Study HBDF was intended to be conducted as an outpatient study, if a patient's clinical status changed so that more intensive supervision or monitoring was required, the investigator was permitted to hospitalize the patient, as clinically warranted.

**Number of Patients**:

Planned: 150 entered, 80 randomized

Treated during open-label phase (at least 1 dose): 123

Randomized to double-blind randomized withdrawal phase: 103 patients: 53 LY2140023, 50 placebo

Treated during double-blind randomized withdrawal phase (at least 1 dose): 103 patients: 53 LY2140023, 50 placebo

Completed the double-blind randomized withdrawal phase: 98 patients: 51 LY2140023, 47 placebo

**Diagnosis and Main Criteria for Inclusion:** Patients were male or female outpatients, 18 to 65 years of age (inclusive) at study entry, with a diagnosis of schizophrenia as defined in the DSM-IV-TR and confirmed by the Structured Clinical Interview for DSM-IV-TR Disorders. At Visit 1, the patient must have required a modification of antipsychotic medication or the initiation of antipsychotic medication, as indicated by their present clinical psychiatric status and/or treatment tolerability as an outpatient. Patients were not eligible to participate in the study if they had been hospitalized for an exacerbation of symptoms of schizophrenia with a discharge date in the 2 months preceding Visit 1, or if they had a CGI-S score >4 at Visit 1. Patients must not have had any other current Axis I psychiatric diagnoses in addition to schizophrenia.

**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 80 mg BID.

**Placebo, Dose, and Mode of Administration:** Placebo tablets to match LY2140023 tablets. Placebo tablets were given orally BID.

**Duration of Treatment:** The open-label treatment phase of the study, during which all patients received LY2140023 monotherapy was 4 weeks in duration. The double-blind randomized withdrawal phase of the study, during which patients who had completed the open-label phase and met prespecified, blinded criteria received either LY2140023 or placebo, was 2 weeks in duration.

LY2140023 Mean Patient Exposure (across open-label and double-blind randomized withdrawal phases): 32.2 days

Placebo Mean Patient Exposure: 15.9 days

**Variables:**

Efficacy: Secondary: BPRS (total, positive, negative, and anti-depression scores) and CGI-S during the double-blind randomized withdrawal phase (hereafter referred to as the randomized withdrawal phase) of the study; Exploratory: dosage, hospitalizations during the open-label and randomized withdrawal phases of the study.

Safety: Primary: DSCMR (maximum of the 3-day moving average of total score) during the randomized withdrawal phase of the study.

Supportive: DSCMR (total score, peak total score, time to peak total score) and CIWA-Ar during the randomized withdrawal phase of the study.

Other safety variables: adverse events; clinical laboratories (including prolactin levels); vital signs, weight, body mass index, and waist circumference; ECGs; neurological examinations; extrapyramidal symptoms and abnormal movements (BAS, SAS, AIMS); and suicidality (C-SSRS).

**Statistical Evaluation Methods:**

Efficacy: For the open-label phase, the efficacy variables and the changes from baseline at each visit were summarized. For the randomized withdrawal phase, the efficacy variables were evaluated using a mixed-model repeated measures (MMRM) analysis. The model included the fixed, categorical effects of randomized treatment, gender, investigative site, visit, randomized treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. Unless otherwise specified, all analyses were to be done on an intent-to-treat basis. All patients were included in the groups to which the patients were randomized 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. Unless otherwise stated, all statistical analyses conducted for the randomized withdrawal phase were to compare only the randomized placebo and randomized LY2140023 groups. Type III tests for the least-squares (LS) means were to be used for the statistical comparison using generalized linear models (MMRM, analysis of variance [ANOVA], or analysis of covariance [ANCOVA]). Significance tests were to be based on LS means and Type III tests at a 1-sided 0.025 alpha level (equivalent to a 2-sided 0.05 alpha level).

Safety: The primary outcome measure was the maximum of the 3-day moving averages of the patient's total score on the DSCMR during the randomized withdrawal phase. A comparison between LY2140023 and placebo was to be performed using an ANCOVA model, with baseline as a covariate, and investigative site, gender, and treatment as fixed effects. The analysis was to include data from randomized patients in the LY2140023 and placebo groups.

Analysis variables for the secondary objective related to the DSCMR were AUC (as defined by the total score of the DSCMR over time during the randomized withdrawal phase normalized for 14 days), peak total score (maximum observed total score), and time to peak total score (the number of days until the highest value on the DSCMR). Area under the curve and the peak total score were to be log transformed and analyzed using an ANCOVA model with baseline total score as a covariate, and investigative site, gender, and treatment as fixed effects. The LS means for each treatment, the difference in means between the randomized LY2140023 and placebo groups, and the 95% confidence intervals (CIs) for the difference in means were to be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means, ratio of geometric means, and 95% CIs for the ratio of geometric means, ratio of geometric means, and 95% CIs for the ratio of geometric means. Time to peak total score was to be summarized for the placebo group. If there were 2 or more time points with the same value, only the first time point was to be used. Medians and range (minimum and maximum) of the time to peak total score for the placebo group were to be presented. These analyses for time to peak total score were to be repeated for each individual items of the DSCMR.

Symptoms of withdrawal, as measured by the CIWA-Ar total score were to be calculated by adding the individual items. The change from baseline in the total score and the individual items was to be summarized by randomized and non-randomized treatment groups separately at each visit during the randomized withdrawal phase. The change from baseline was to be assessed comparing the randomized treatment groups using an MMRM analysis similar to that used for the efficacy variables. The baseline CIWA-Ar total score and the individual items were to be presented and analyzed with a single factor ANOVA model with fixed effect of treatment.

Treatment-emergent AEs were summarized by preferred term, sorted by decreasing frequency within system organ class for all TEAEs, and TEAEs considered possibly related to study drug. Treatment-emergent AEs occurring during the open-label treatment phase were also summarized by maximum severity, as reported while on treatment. Treatment-emergent AEs occurring during the randomized withdrawal phase were also summarized by randomized treatment group, nonrandomized treatment group, and combined LY2140023. Treatment-emergent AEs occurring during the open-label and randomized withdrawal phases were summarized by maximum severity, as reported while on treatment.

Unless otherwise specified, safety analyses were done for the open-label and randomized withdrawal phases of the study. Unless otherwise stated, comparisons of safety parameters between the LY2140023 and placebo groups during the randomized withdrawal phase were evaluated using Fisher's exact test. All tests of safety were conducted at a 0.05 2-sided alpha level. No adjustments for multiple comparisons were made for safety analyses, unless otherwise stated.

**Summary:**

Patient Characteristics and Exposure: Of the 174 patients who entered the study and participated in the antipsychotic drug taper phase, 123 entered the open-label treatment phase and 103 were assigned to treatment in the 2-week randomized withdrawal phase. No nonrandomized patients entered into the randomized withdrawal phase, as none had a CGI-S score >4. There were 123 patients who received at least 1 dose of study drug. There were 98 patients who completed the randomized withdrawal phase of the study and 5 patients who were randomized to the withdrawal phase, but did not complete the study. During the antipsychotic drug taper phase, reasons for early discontinuation were entry criteria not met (n=45), schedule/conflict preventing continuation (n=4), and sponsor decision (n=2). The most common reasons for early discontinuation during the open-label phase of the study were AEs (n=5), lost to follow-up (n=4), protocol violation (n=4), perceived lack of efficacy (n=3), and subject decision-consent withdrawn (n=2). During the randomized withdrawal phase, reasons for early discontinuation among patients in the LY2140023 and placebo groups were sponsor decision (n=1), subject decision-consent withdrawn (n=1), subject is moving or has moved (n=1), and AEs (n=2).

Of the 123 enrolled patients, the mean (standard deviation [SD]) age was 42.86 (11.45) years and the majority of patients were male (75.6%). The majority of patients were Black or African American (66.7%), followed by White (28.5%). The mean (SD) weight was 91.97 (21.88) kg and the mean (SD) body mass index (BMI) was 30.81 (7.18) kg/m$^2$. Of the 103 randomized patients, the mean (SD) age was 42.74 (11.44) years and the majority of patients were male (72.8%). The majority of patients were Black or African American (66.0%), followed by White (29.1%). The mean (SD) weight was 92.67 (21.45) kg, and the mean (SD) BMI was 31.09 (7.06) kg/m$^2$. Among all enrolled patients, the mean age (SD) at first treatment of schizophrenia was 27.4 (9.9) years, and the mean duration of lifetime illness was 17.64 (11.17) years. For randomized patients, the mean age at first treatment of schizophrenia was 27.9 (10.9) years for patients in the placebo group and 27.5 (9.6) years for patients in the LY2140023 group. The mean duration of lifetime illness was 17.34 (11.11) years for patients in the placebo group and 16.76 (10.96) years and for patients in the LY2140023 group. The majority of all enrolled patients and randomized patients had paranoid-type schizophrenia (n=110, 89.4% and n=91, 88.3%, respectively). The mean (SD) baseline CGI-S score was 3.0 (0.8). Mean (SD) BPRS total score, positive score, negative score, and anxiety-depression score at baseline were 29.8 (8.3), 7.9 (3.5), 5.2 (2.1), and 7.0 (3.3), respectively. There were no statistically significant differences between the placebo and LY2140023 groups in baseline score for either efficacy measure. There were no statistically significant differences between treatment groups in baseline DSCMR or CIWA-Ar measures.

Mean (SD) days of exposure to LY2140023 during the open-label phase was 25.8 (6.0) days. During the randomized withdrawal phase, mean days of exposure was 15.9 (8.7) days and 14.7 (2.1) days in the placebo and LY2140023 groups, respectively. The mean (SD) days of exposure to LY2140023 across the open-label and randomized withdrawal phases of the study was 32.2 (10.9) days.

Efficacy: There were no statistically significant differences between the LY2140023 and placebo treatment groups in mean BPRS total score, positive score, negative score, and anxiety-depression score at Visit 10 or Visit 12. The LY2140023 group was not associated with a statistically significant mean CGI-S score compared with the placebo group at any visit during the randomized withdrawal phase.

Safety: For the primary outcome measure, the maximum of the 3-day moving average of total score on the DSCMR, there was no difference between treatment groups with respect to worsening of withdrawal symptoms.

Secondary analyses of the primary outcome measure revealed a smaller AUC and peak total score associated with the placebo treatment group. Although time to peak total DSCMR score was 4.0 days, this was not considered to be a significant sign for symptom withdrawal due to the fact the primary objective showed no withdrawal symptoms, as defined in the study, and also the placebo peak was significantly smaller than any peak seen on LY2140023. Therefore, the peak seen on placebo was not considered reflective of withdrawal symptoms. Except for happiness, no differences were seen between treatment groups in other individual items of the DSCMR. No differences were seen between treatment groups in peak score of the individual items of the DSCMR.

There were no statistically significant differences between treatment groups in change in CIWA-Ar total score at any postbaseline visit.

There were no serious AEs (SAEs) or deaths during the study.

There were 5 patients (4.1%) who discontinued due to AEs during the open-label treatment phase. Adverse events leading to discontinuation were anxiety, fatigue, headache, insomnia, and schizophrenia. None of the AEs occurred in more than 1 patient. There were no patients in the placebo group and 2 patients (3.8%) in the LY2140023 group who discontinued due to AEs during the randomized withdrawal phase. Adverse events leading to discontinuation in the LY2140023 group were ECG QT interval (actual term: QTc>500) and hepatic enzyme increased. The patient with the AE of ECG QT interval had an abnormal QTc value resulting from a machine over-read. Two ECGs read by the cardiologist showed the corrected QT intervals below 500 milliseconds, and these values were included in the safety database, rather than the machine-read ECG interpretation. Since the patient was anxious about the initial over-read, it was decided to discontinue the patient from the study at Visit 8, prior to randomization. There were no statistically significant differences between treatment groups in incidence of AEs leading to discontinuation.

Of the 123 patients in the open-label phase who received at least 1 dose of study medication, 83 (67.5%) experienced at least 1 TEAE. The TEAEs reported in ≥3% of patients were nausea, headache, anxiety, tremor, vomiting, blood creatine phosphokinase (CK) increased, agitation, hyperhidrosis, insomnia, somnolence, constipation, dizziness, diarrhea, fatigue, and irritability. Of the 103 randomized patients, 13 (26.0%) in the placebo group and 21 (39.6%) in the LY2140023 group experienced at least 1 TEAE. Treatment-emergent AEs in the placebo group that were reported in ≥3% of patients and also were ≥2 times the LY2140023 group's incidence rate were headache, visual impairment, and hearing impaired. Treatment-emergent AEs in the LY2140023 group that were reported in ≥3% of patients and also were ≥2 times the placebo group's incidence rate were agitation, nausea, and blood CK increased.

Most of the 83 patients (67.5%) who reported at least 1 TEAE during the open-label phase had mild AEs (n=52, 42.3%). Thirty-one patients (25.2%) had moderate AEs. There were no severe AEs during the open-label phase. During the randomized withdrawal phase, no patients in the placebo group had severe TEAEs. Among patients in the LY2140023 group, most patients had mild (n=15, 28.3%) and moderate AEs (n=5, 9.4%). There was 1 patient (1.9%) with a severe AE of blood CK increased.

Adverse events considered study drug related by the investigator and reported in ≥3% of patients during the open-label phase were nausea, headache, anxiety, vomiting, agitation, and tremor. Adverse events considered study drug related by the investigator in the placebo group that were reported in ≥3% of patients and also were ≥2 times the LY2140023 group's incidence rate were headache, visual impairment, and hearing impaired. Adverse events considered study drug related by the investigator in the LY2140023 group that were reported in ≥3% of patients and also were ≥2 times the placebo group's incidence rate were agitation, nausea, blood CK increased, hyperhidrosis, and vomiting.

There were no noted clinical consequences in patients with CK and eosinophil abnormalities during the open-label phase of the study.

While statistically significant differences between treatment groups were observed in changes in vital signs at Visit 11, these changes were not considered clinically relevant, as the findings were not consistent with heart rate as measured by ECG. There were no statistically significant differences between treatment groups in neurological examination findings during the randomized withdrawal phase of the study. Although there were statistically significant changes in the SAS at Visit 9, these changes were very small, and were not considered clinically relevant. No statistically or clinically significant findings were reported on the C-SSRS, BAS, and AIMS.

**Conclusions:**

- In Study HBDF, the primary analysis found no statistically significant evidence of withdrawal symptoms (measured by DSCMR) associated with LY2140023.
- No new safety findings were identified.
- There were no discontinuations due to worsening of schizophrenia during the randomized withdrawal phase, which further supports the reliability of the findings.
- No SAEs, deaths, or seizures were reported during the study.