2. HBBV Synopsis

Clinical Study Report Synopsis: Study H8Y-MC-HBBV

Title of Study: Long-Term Open-Label Safety Study of Pomaglumetad Methionil in Patients with Schizophrenia

Number of Investigators: This multicenter study included 37 principal investigators.

Study Centers: This study was conducted at 36 study centers in 8 countries.

Publications Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 3
Date of first patient enrolled: 13 December 2011 Date of last patient visit: 12 October 2012 Note: This study was terminated on 28 August 2012 based on a global decision by Lilly to close the LY2140023 schizophrenia development program. This decision was made after pivotal registration trial data failed to meet the primary study endpoint (failed to demonstrate efficacy).	

Objectives:

Primary Objective: The primary objective of this study was to evaluate the long-term safety of pomaglumetad methionil (LY2140023) in patients with schizophrenia by monitoring extrapyramidal symptoms (EPS), as evaluated by the Barnes Akathisia Scale (BAS), the Simpson-Angus Scale (SAS), and the Abnormal Involuntary Movement Scale (AIMS); weight; prolactin; and the following metabolic parameters: fasting glucose, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein (HDL) cholesterol, and total triglycerides.

Secondary Objectives:

- To evaluate the safety and tolerability of LY2140023 as measured by the following: 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).
- To evaluate the long-term efficacy of LY2140023 in patients diagnosed with schizophrenia as measured by the Clinical Global Impressions-Severity (CGI-S), Brief Psychiatric Rating Scale (BPRS), and time to discontinuation due to lack of efficacy or initiation of an adjunctive antipsychotic treatment.
- To evaluate the long-term safety of LY2140023 in a prospectively defined subpopulation.

Exploratory objective: [redacted].

[redacted]

Study Design: A multicenter, open-label, Phase 3, single-arm study assessing the long-term safety and tolerability of LY2140023 given orally in flexible doses (20 mg, 40 mg, and 80 mg twice daily [BID]) in outpatients with schizophrenia, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). The study enrolled patients who completed 1 of 2 previous LY2140023 trials: Study H8Y-MC-HBDE (HBDE) or Study H8Y-MC-HBDF (HBDF). The original study design H8Y-MC-HBBV (HBBV) planned for the enrollment of new patients (that is, patients who had not previously participated in an LY2140023 study) to fulfill the regulatory requirement of long-term exposures; however, due to early study closure, new patients were not enrolled.

Regarding the prior feeder studies, patients who completed Study HBDE received double-blind treatment (pomaglumetad methionil or aripiprazole) for 24 weeks, followed by a 28 week open-label phase where all patients received LY2140023. Patients who completed HBDF received LY2140023 for 4 weeks, followed by an additional 2 weeks of either pomaglumetad methionil or placebo. Patients who experienced symptom worsening, as defined by the protocol, were eligible to receive adjunctive antipsychotic treatment, which included risperidone, olanzapine, quetiapine, or aripiprazole, after the LY2140023 dose was maximized.

Number of Patients:

Planned: 280 patients LY2140023 (flexible dose)

Randomized: Not applicable. This was an open-label, single-arm trial without a comparator treatment.

Treated (at least 1 dose): 129 active drug

Note: The study ended early due to Lilly's decision to close the LY2140023 development program for schizophrenia. Therefore, Study HBBV enrollment was lower than the initially planned 280 patients.

Diagnosis and Main Criteria for Inclusion: Eligible patients who completed an LY2140023 feeder study (HBDE or HBDF) and were males or females, 18 to 65 years of age (inclusive, at feeder study entry), with schizophrenia. Additional inclusion criteria included:

- Diagnosis of schizophrenia as defined in the DSM-IV-TR (APA 2000; Disorganized, 295.10; Catatonic, 295.20; Paranoid, 295.30; Residual, 295.60; or Undifferentiated, 295.90) and confirmed by the Structured Clinical Interview for DSM-IV-TR (SCID).
- Patients must be considered reliable and have a level of understanding sufficient to perform all tests and examinations required by the protocol.
- Patients had to provide their own informed consent.

Test Product, Dose, and Mode of Administration:

LY2140023 flexible dose of 20 mg, 40 mg, or 80 mg tablets (tablet administered orally BID). Rollover patients from Study HBDE (Phase 3 open-label feeder study) continued to receive feeder study LY2140023 dose at Visit 1 (20 mg, 40 mg, or 80 mg). Rollover patients from Study HBDF (Phase 3 double-blind feeder study) received 40 mg LY2140023 at Visit 1. Investigators were permitted to make dose adjustments at their discretion based on clinical response and patient safety/tolerability starting at Visit 1.

Reference Therapy Dose, and Mode of Administration: Not applicable.

Duration of Treatment: Treatment was planned for up to 2 years. Due to study termination, duration of treatment was up to 10 months.

Variables:

Safety: Safety assessments included TEAEs, serious adverse events (SAEs), AEs, ECGs, suicidality (based on patient C-SSRS score), EPS scales (as measured by the BAS, SAS, and AIMS), standard laboratory tests (blood, urine), vital signs, weight, and waist circumference.

Efficacy: Efficacy variables included the CGI-S and BPRS.

Pharmacogenetic: A 10 mL blood sample for pharmacogenomics testing was collected where Investigator Review Board (IRB) policy and local regulations allowed; however, sample testing had not yet been conducted when the study was ended. Therefore, no pharmacogenomics results are presented in this synopsis report.

Statistical Evaluation Methods:

General Considerations: Analyses are presented for all intent-to-treat (ITT) patients but only for visits where study drug treatment was pomaglumetad methionil monotherapy (PMM) only. Baseline was defined as the Visit 1 assessment, and endpoint was defined as the last post-baseline measurement in the study or last measurement prior to receiving adjunctive therapy, whichever came first. Categorical variables were summarized using incidence rates, and continuous variables were summarized using descriptive statistics. For change-from-baseline analysis, only patients with baseline and at least 1 post-baseline measure were included. All total and subscale scores were derived from individual items. In cases of missing items, total and subscale scores were calculated using the average of the available items, as long as 80% or more of the individual items were available.

Safety: For primary safety outcome measures, categorical changes were summarized for BAS, SAS, and AIMS.

- For the BAS, the incidence of patients with a global score ≥2 at any postbaseline visit and a baseline score <2
- A similar categorical analysis on the incidence of patients with a SAS total score >3 at any postbaseline visit and baseline score ≤3
- For the AIMS, the incidence of patients with a score ≥3 in any of the Items 1 to 7 or a score ≥2 in any 2 of the Items 1 to 7, that was not present at baseline

Treatment-emergent changes in fasting glucose and lipid levels (including total cholesterol, LDL cholesterol, HDL cholesterol, and total triglycerides) were analyzed using the American Diabetes Association (ADA, 2001) guidelines and National Cholesterol Education Program (NCEP ATP III) guidelines at endpoint and at any time during study. Categorical changes in prolactin levels were summarized at each post-baseline visit and at endpoint using shift tables in terms of low, normal, and high values as defined by the lab reference ranges. Potentially clinically significant (PCS) changes in body weight (kg), either increases or decreases of ≥7% from baseline, were summarized at endpoint and at any time during the study.

For secondary safety outcome measures, the proportion of patients experiencing SAEs, AEs resulting in discontinuation, TEAEs, and AEs reported as reasons for dose reduction were summarized. C-SSRS scores were also summarized. Treatment-emergent low, high, and abnormal lab values, which included both scheduled and unscheduled laboratory test data, at endpoint and any time during the study were summarized. Change from baseline to the last observed measure in lab values were summarized, and Wilcoxon signed-rank tests assessed mean change. Baseline lab data from patients were excluded from magnesium (n = 38) and creatinine clearance analyses (n = 3) due to inaccuracies during data reconciliation with the feeder studies. Separate analyses were conducted on the incidence rates of liver function, eosinophils, and creatinine phosphokinase (CK) abnormalities. Summaries were provided for PCS changes in vitals and ECG, as well as change from baseline in EPS, vitals, and ECG. Mean change from baseline to each post-baseline visit in EPS, vitals, and ECG was analyzed using a mixed-model repeated measure (MMRM) analysis, including terms for baseline, visit, investigator site, and baseline-by-visit interaction for the Overall Group.

Efficacy: Positive and Negative Syndrome Scale (PANSS) scores were collected in HBDE, and BPRS scores were collected in HBDF. For PANSS score collection, the BPRS total score and BPRS domains were extracted from the PANSS in the feeder study as the baseline assessment in this study. BPRS total score, BPRS positive score, BPRS negative score, BPRS anxiety-depression score, and CGI-S score were summarized by visit and at endpoint. Mean change from baseline to each post-baseline visit was analyzed using an MMRM analysis, including terms for baseline, visit, investigator site, and baseline-by-visit interaction for the Overall Group.

Due to study closure, the following analyses were not performed:

- Neurological examination
- Time to discontinuation due to lack of efficacy or initiation of an adjunctive antipsychotic treatment
- Long-term safety of pomaglumetad methionil in the predefined subpopulation
- Effect of genetic variation on response to treatment

Summary:

Due to exposure differences in prior feeder studies, Table 1 presents all patient exposure to LY2140023 by feeder studies, HBDE and HBDF. The Overall patient column in the table includes all enrolled patients given monotherapy and/or adjunctive antipsychotic treatment. To fully understand patient safety and tolerability for LY2140023 without potential confounds from adjunctive treatment, the presented results and conclusions in this synopsis includes all patients, but only for visits where study drug treatment was PMM only. Therefore, data after the start of adjunctive antipsychotic treatment were excluded from these analyses. It should be noted that although safety outcomes of patients in the adjunctive treatment group (n=11) were not formally analyzed, none of these patients experienced an SAE. One of the 11 patients discontinued from the study due to an AE (nausea). The remaining 10 patients discontinued from the study due to sponsor decision, which was based on program termination.

Table 1. Patient Exposure to Study Treatment

Production Data - Production Mode
Summary of Patient Study Treatment Exposure
By Patient Analysis Group
All Pomaglumetad Methionil Patients
H8Y-MC-HBBV

Variable	HBDE (N=55)	HBDF (N=74)	Overall (N=129)
Total Patient Exposure (days)	3731	8641	12372
Total Patient Exposure (years)	10.2	23.7	33.9
Exposure Duration in subsets of weeks n (%)			
<= 2	3 (5.5)	2 (2.7)	5 (3.9)
> 2 to <=4	8 (14.5)	7 (9.5)	15 (11.6)
> 4 to <=8	15 (27.3)	11 (14.9)	26 (20.2)
> 8 to <=12	9 (16.4)	4 (5.4)	13 (10.1)
> 12 to <=16	9 (16.4)	11 (14.9)	20 (15.5)
> 16 to <=20	8 (14.5)	11 (14.9)	19 (14.7)
> 20 to <=24	2 (3.6)	13 (17.6)	15 (11.6)
> 24 to <=36	1 (1.8)	9 (12.2)	10 (7.8)
> 36 to <=48	0 (0.0)	6 (8.1)	6 (4.7)
Total	55 (100.0)	74 (100.0)	129 (100.0)
Mean weeks exposure	9.7	16.7	13.7
SD	6.1	10.7	9.7
Minimum	1	1	1
Median	8	16	12
Maximum	25	40	40
25th Percentile	4	7	6
75th Percentile	14	22	20

Abbreviations: N = number of enrolled patients by patient analysis group; n/(%) = number/percentage of patients for each category per patient analysis group; SD = standard deviation.

[redacted]

Disposition

Of the 129 enrolled patients, 107 (82.9%) discontinued due to sponsor decision, and 10 patients (7.8%) withdrew their consent. Additional reasons for study discontinuation were adverse events (2.4%), lost to follow-up (2.3%), protocol violation (1.6%), perceived lack of efficacy based on subject decision (1.6%), and scheduling conflicts (1.6%).

Baseline characteristics

The greatest percentage of patients came from the United States (107; 82.9%), followed by Greece (12; 9.3%). The majority of patients were African American (58.9%), and patients had a mean age of 43.5 years. Approximately 65% of patients were male. The mean body mass index (BMI) of patients was 31.2.

Safety

Primary HBBV safety results for EPS, weight, prolactin levels, and metabolic parameters are summarized in Table 2. Based on BAS, SAS, and AIMS scores, treatment-emergent EPS was low, and no patient met the treatment-emergent Parkinsonism criteria. Three patients developed treatment-emergent akathisia during the trial; however, akathisia did not persist throughout study continuation, and BAS scores for these patients returned to baseline. One patient met the criteria for treatment-emergent dyskinesia, which was defined as an AIMS score ≥3 in any of the 1−7 items or a score of ≥2 in any two of the 1−7 items, which was not present at baseline. However, this patient did not consistently meet these criteria at any post-baseline visit during the study. Approximately 10% of patients had PCS changes in body weight, defined as an increase or decrease ≥7% from baseline weight, and the incidence for PCS weight gain and weight loss were similar. A majority of patients (84.6%) reported normal prolactin levels. Based on ADA and NCEP guidelines, few patients met criteria for treatment-emergent impaired or high range levels of metabolic changes in fasting glucose, cholesterol, or triglycerides. No patients reported triglyceride values greater than 500 mg/dL. Regarding secondary safety objectives, 52 patients (40.3%) reported experiencing TEAEs. The most commonly reported TEAEs were nausea (10; 7.8%), tremor (4; 3.1%), and vomiting (4; 3.1%). It should be noted that of the 10 patients who experienced nausea, 6 of these patients were on placebo at the time of HBBV study entry and were being reintroduced to LY2140023 treatment. One patient experienced an SAE (exacerbation of schizophrenia symptoms), which occurred 24 hours after the patient was discontinued from LY2140023 treatment. There were no clinically significant findings for C-SSRS, vital signs, or ECG measures. There were no deaths reported in this study.

Efficacy

Non-clinically relevant changes on BPRS total, positive, and negative scores were recorded on some visits; however, efficacy analyses were hindered by the decreasing number of patients across visits and by early study termination. Repeated measures of analysis of change from baseline BPRS scores showed that, in general, patients remained clinically stable with LY2140023 treatment. Similarly, no clinically relevant changes were observed in CGI-S scores.

Table 2. Summary of Study HBBV Primary Safety Objectives

Categorical Changes in Extrapyramidal Symptom Measures at Any time during Study	n (%)	
SAS (N = 126)[a]	0 (0.0)	
BAS (N = 126)[b]	3 (2.4)	
AIMS (N = 129)[c]	1 (0.8)	
Potentially Clinically Significant Weight Changes at Endpoint (kg) (N = 129)[d]	n (%)	
≥7% Decrease from Baseline	7 (5.4)	
≥7% Increase from Baseline	6 (4.7)	
Shift from Baseline to Endpoint Prolactin* (µg/L) (N = 123)[d]	n (%)	
Normal to Low	4 (3.3)	
Normal to Normal	98 (79.7)	
Normal to High	7 (5.7)	
Shift from Baseline to Endpoint Metabolic parameters** (mg/dL)	N[e]	n (%)
Fasting Glucose (Normal to High)	80	1 (1.3)
Cholesterol (Normal to High)	88	2 (2.3)
LDL Cholesterol (Normal to High)	45	0 (0.0)
HDL Cholesterol (Normal to Low)	100	6 (6.0)
Triglycerides (Normal to High)	102	2 (2.0)

Abbreviations: AIMS = Abnormal Involuntary Movement Scale; BAS = Barnes Akathisia Scale; HDL = high density lipoprotein; LDL = low density lipoprotein; PPM = pomaglumetad methionil monotherapy; SAS = Simpson-Angus Scale

Notes: Included data highlight clinical relevance of the safety outcomes; consequently, table columns may not equal 100% All data are taken from the PMM analysis set Baseline is defined as the Visit 1 assessment, and endpoint is defined as the last post-baseline measurement in the study, or last measurement prior to receiving adjunctive therapy, whichever comes first; [a] number of patients with SAS total score ≤3 during baseline period and at least one post-baseline measurement; [b] number of patients with BAS global score <2 during baseline period and at least one post-baseline measurement; [c] number of patients not satisfying the treatment-emergent dyskinesia criteria during baseline period and having at least one post-baseline measurement; [d] number of patients with a baseline and at least one post-baseline value; [e] number of patients in each patient analysis group meeting the baseline criteria at all baseline records and having at least one non-missing post-baseline measurement for each lab test

*Normal prolactin range for males: 2 64-13 33 µg/L; normal prolactin range for females: 2 74-26 72 µg/L **Normal metabolic values for the Normal to High shift (baseline/endpoint, mg/dL) for fasting glucose: <100 / ≥126; cholesterol: <200 / ≥240: LDL: <100 / ≥160; HDL ≥40/<40; triglycerides <150/≥200

Source: [redacted]

Conclusions:

Study HBBV was a multicenter, open-label, Phase 3, single-arm study assessing the long-term safety and tolerability of LY2140023 given orally in flexible doses (20 mg, 40 mg, and 80 mg BID) in patients diagnosed with schizophrenia. This study was terminated based on a global decision by Lilly to close the LY2140023 schizophrenia development program. This decision was made after pivotal registration trial data failed to meet the primary study endpoint (failed to demonstrate efficacy). HBBV primary and secondary results showed that:

- Few patients developed treatment-emergent EPS, and it did not appear to be sustained.
- Approximately 5% of patients displayed PCS weight decreases ≥7% and 5% displayed weight increases ≥7%.

- Approximately 90% of patients had prolactin levels within, or below, the normal range (µg/L).
- In general, clinically relevant or consistent effects on metabolic parameters were not observed with LY2140023 treatment.
- Approximately 40% of patients experienced TEAEs. The most commonly reported TEAEs were nausea (7.8%), tremor (3.1%), and vomiting (3.1%). One patient experienced an SAE after trial discontinuation.
- Clinically relevant changes in suicidality, vital signs, and ECG measures were not observed in patients treated with LY2140023.
- Regarding efficacy, in general patients remained clinically stable.