1. HBBO Clinical Study Report Synopsis

A Long-Term, Open-Label, Multicenter Study of LY2140023 Compared to Atypical Antipsychotic Standard of Care in Patients with DSM-IV-TR Schizophrenia

Pomaglumetad methionil (LY2140023 monohydrate)
Schizophrenia

An open-label study to assess the long-term safety and tolerability of LY2140023, given orally twice daily in flexible doses, compared with atypical standard of care antipsychotic therapy (aripiprazole, olanzapine, quetiapine, or risperidone) in patients with schizophrenia.

Eli Lilly and Company
Protocol H8Y-MC-HBBO(c)
Phase 2/3
First patient enrolled (assigned to therapy): 02 June 2010
Last patient visit: 10 October 2012
Study Report Electronically Approved by Lilly.

Approval date provided below.

Coordinating/Principal Investigator: [redacted], USA

Responsible Medical Officer: [redacted]
Eli Lilly and Company

Approval Date: 24-Apr-2013 GMT

2. HBBO Synopsis

Clinical Study Report Synopsis: Study H8Y-MC-HBBO

Title of Study:
A Long-Term, Open-Label, Multicenter Study of LY2140023 Compared to Atypical Antipsychotic Standard of Care in Patients with DSM-IV-TR Schizophrenia

Number of Investigator(s):
This multicenter study included 88 principal investigator(s).

Study Center(s):
This study was conducted at 80 study centers in 9 countries and Puerto Rico.

Publication(s) Based on the Study:
None at this time

Length of Study:
Date of first patient visit: 2 June 2010
Date of last patient visit: 10 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 (due to lack of efficacy).

Phase of Development: 2/3

Objectives:

The primary objective of this study was to assess time to discontinuation due to lack of tolerability among patients with schizophrenia receiving up to 52 weeks of LY2140023, given orally twice daily, compared with those on atypical antipsychotic standard of care (SOC) treatment. Lack of tolerability was defined as discontinuation due to adverse events (AEs).

The secondary objectives of the study were:

- to evaluate the safety and tolerability of LY2140023 compared with SOC treatment up to 52 weeks, as assessed by the following measures: treatment-emergent adverse events (TEAEs); extrapyramidal symptoms (EPS); neurological examination; changes in vital signs, weight, and laboratory tests; and solicited questioning of suicide-related AEs (behavior and ideations) using the Columbia-Suicide Severity Rating Scale (C-SSRS).
- to examine the long-term efficacy and outcomes of LY2140023 compared with SOC treatment up to 52 weeks, as measured by the following scales: Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S) scale, 16-item Negative Symptoms Assessment (NSA-16), Personal and Social Performance (PSP) Scale, and the Subjective Well-Being Under Neuroleptic Treatment (SWN-S) scale.
- to further evaluate the safety and tolerability of LY2140023 compared with SOC treatment over an additional 52 weeks in patients who have completed the first 52 weeks of Study Period I.
- to further evaluate the maintenance of efficacy of LY2140023 compared with SOC treatment over an additional 52 weeks in patients who have completed the first 52 weeks of Study Period I.
- to assess whether LY2140023 demonstrates improvement compared with SOC treatment in health outcome measures, including the Schizophrenia Resource Use Model (S-RUM) and EuroQol: 5 Dimension (EQ-5D) for Study Period I.
- to assess the continued safety and tolerability of LY2140023 in Study Period II.
- to evaluate the long-term safety and efficacy of LY2140023 in a predefined subpopulation (as specified prospectively in the acute feeder studies and as defined in the HBBO statistical analysis plan [SAP]).

[redacted]

Study Design:
Study HBBO was a long-term, open-label study of the safety and tolerability of LY2140023, given orally twice daily (BID) in flexible doses (20/40/80 mg BID) in patients with schizophrenia. The study was to assess LY2140023 compared with atypical antipsychotic therapy deemed to be the current SOC for the treatment of schizophrenia. The study included 2 treatment periods. Study Period I began at patient randomization (enrollment into Study HBBO) and was to continue through the first 2 years of treatment. Patients who qualified for enrollment were randomized in a 3:1 ratio (LY2140023 versus SOC, respectively) into 2 treatment groups: flexible, BID dose of LY2140023 or SOC (aripiprazole, olanzapine, quetiapine, or risperidone). Patients in either treatment group whose schizophrenia symptoms worsened or who remained markedly ill during the first year were eligible to initiate adjunctive antipsychotic treatment, which included aripiprazole, olanzapine, quetiapine, or risperidone. Eligible patients treated with LY2140023 were to have first maximized their LY2140023 dose; those in the SOC group were to have their dose increased to the upper half of the approved dose range. All eligible patients had to meet other prespecified criteria. Study Period II was to be only for patients randomized to treatment with LY2140023, and was to begin after the patient had completed the second year of treatment if deemed appropriate by the investigator for the patient to continue on LY2140023 treatment.

Number of Patients:
Planned: 800-1500
Randomized: 419 to LY2140023 and 141 to SOC
Treated (at least 1 dose): 411 LY2140023, 141 to SOC
Completed: 1 SOC patient completed Study Period I and therefore was a study completer. There were no other completers due to the early termination of the study. Five LY2140023 patients completed Study Period I and moved on to Study Period II prior to the termination of the study.

Diagnosis and Main Criteria for Inclusion:
Study participants were male or female patients with schizophrenia (18 to 65 years of age, inclusive, at study entry) who met entry criteria for, and completed, an acute monotherapy trial of LY2140023 (H8Y-MC-HBBM, H8Y-MC-HBBN, or H8Y-JE-HBDC). Patients with a history of seizures were not eligible to participate in this study. Patients also were not eligible to participate if they had demonstrated suicidal intent or ideation.

Test Product, Dose, and Mode of Administration:
LY2140023 [20, 40, or 80 mg], given orally BID

Reference Therapy/Comparator, Dose and Mode of Administration:
Standard of care: Aripiprazole, olanzapine, quetiapine, or risperidone, given orally, consistent with approved labeling and local practices.

Duration of Treatment:
52 weeks (for primary analysis).

Variables:
Primary Outcome: The primary safety outcome was the time to discontinuation due to AEs during the first year of Study Period I.
Efficacy: Efficacy variables used in the analysis of secondary endpoints included the CGI-S, PANSS, NSA-16, PSP and SWN-S.
Safety: Safety assessments included comparisons of LY2140023 with SOC treatment in terms of the incidence and characterization of AEs; analyses of EPS (as measured by the Barnes Akathisia Scale [BAS], Simpson-Angus Scale [SAS], and Abnormal Involuntary Movement Scale [AIMS]); vital signs, weight, and laboratory tests, neurological examination; and suicidal ideation/behavior (based on the C-SSRS).
Bioanalytical: The samples were analyzed for LY2140023 (methionine prodrug) and LY404039 (active compound) using a validated Liquid Chromatography/Mass Spectrometry/Mass Spectrometry method.
Health Outcomes: Health outcomes assessments included quality of life, as measured by the EQ-5D questionnaire; and resource utilization, as measured by the S-RUM.

Statistical Evaluation Methods:

General Considerations: All analyses were conducted on an intent-to-treat (ITT) basis. The ITT population included all patients according to the treatment group to which they were assigned and had received at least 1 dose, even if the patient did not receive the correct treatment or otherwise did not strictly adhere to the protocol. Based on the population, baseline and endpoint, patients were assigned to the *All*, *Monotherapy*, or *Adjunctive Antipsychotic Treatment* analysis set. In Study Period I, the *All* analysis set included all ITT patients with Visit 1 as baseline and the patient's last visit or Visit 32 (whichever occurred first) as endpoint; the *Monotherapy* analysis set includes all ITT patients with Visit 1 as baseline and patient's last visit or Visit 32 or last assessment prior to receiving adjunctive antipsychotic treatment(whichever occurred first) as endpoint. In Study Period II, only data listings were provided.

Primary Outcome: Kaplan-Meier estimated survival curves of time to discontinuation (measured in days) for AEs were compared between LY2140023 and SOC treatment. The comparison of time to discontinuation curves was tested by the stratified log-rank test controlling for prior treatment. The analysis was based on the *Monotherapy* analysis set during the first year of Study Period I.

Efficacy: A mixed-effects model with repeated measures (MMRM) was used to model changes from baseline in PANSS total score (range 30-210), PANSS positive subscore, PANSS negative subscore, PANSS general psychopathology subscore, NSA-16 total score, and CGI-S score, to each post-baseline visit during Study Period I. The model for these analyses included the fixed categorical effects of treatment, gender, investigative site, visit, prior treatment, treatment-by-visit and prior treatment-by-visit interactions, as well as the continuous, fixed covariates of baseline score 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. These analyses were done for the *All* and the *Monotherapy* analysis sets separately.

Safety: The pre-existing conditions and study AEs were listed in actual terms and Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. Serious adverse events (SAEs), discontinuations due to AEs, and AEs reported as reason for dose reduction were listed and summarized, respectively. These listings and summaries were only presented for the *All* analysis set. The incidence rates of TEAEs and SAEs were analyzed using the Cochran-Mantel-Haenszel (CMH) test controlling for prior treatment. Treatment group comparisons of the categorical change in laboratory analytes and treatment-emergent significant changes in fasting glucose and lipids were also assessed using the CMH test controlling for prior treatment. The incidence of patients with treatment-emergent EPS changes and patients with potentially clinically significant changes in vital signs were assessed using the CMH test as well. Changes from baseline in EPS, vital signs, and body weight were assessed using repeated-measures analysis with a model similar to that used for the efficacy variables. These analyses were applied to *All* and the *Monotherapy* analysis sets. Suicide-related thoughts and behaviors based on the C-SSRS were summarized by treatment groups.

Health Outcomes: The change from baseline (Visit 1) to all applicable post-baseline visits in Study Period I (Visits 2-32) in the PSP, EQ-5D (dimension and Visual Analog Scale [VAS] global health state score), and SWN-S were assessed using a MMRM model. The model included the fixed, categorical effects of treatment, prior treatment, investigative site, visit, prior treatment-by-visit, and treatment-by-visit interaction, gender, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. These analyses were done for the *All* and the *Monotherapy* analysis sets separately. Schizophrenia Resource Use Model (S-RUM) between treatment group comparisons was performed using an analysis of covariance (ANCOVA).

Summary:

Patient Disposition

Of the 560 patients who entered the study, 411 patients received at least 1 dose of LY2140023 and 141 patients received at least 1 dose of SOC treatment. Five LY2140023 patients completed Study Period I and continued on into Study Period II. No LY2140023 patients completed the study. One SOC patient completed the study (Figure HBBO 1)

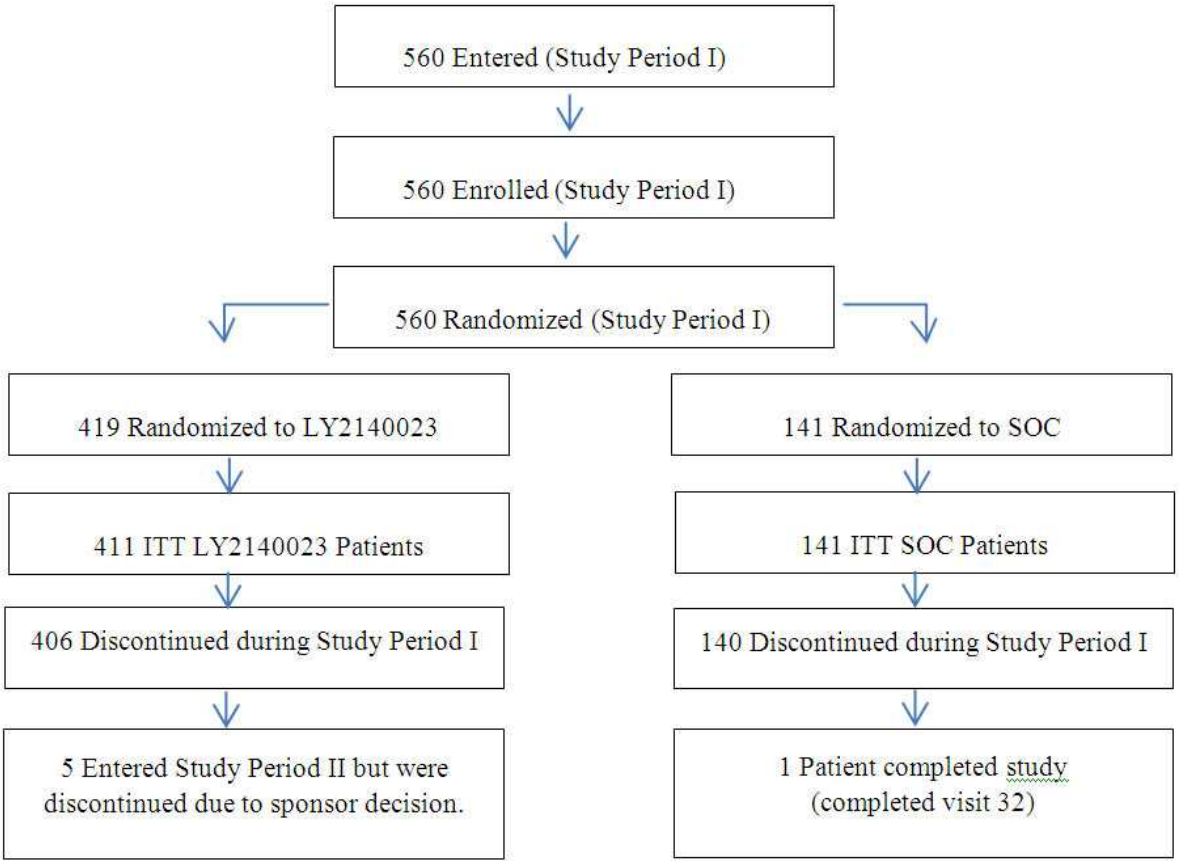

Figure HBBO 1. Patient disposition.

There were 39 patients in the LY2140023 group and 3 patients in the SOC group who received adjunctive treatment. Treatment group comparisons for the *Monotherapy* ITT and *All* ITT analysis sets were generally similar and unless otherwise indicated, data are presented for the *All* ITT patients. The most common reasons for early discontinuation during Study Period I of LY2140023 treatment were sponsor decision (147 patients, 35.8%), AEs-physician decision (59 patients, 14.4%), subject decision-consent withdrawn (56 patients, 13.6%), and perceived lack of efficacy-physician decision (40 patients, 9.7%). The most common reasons for early discontinuation during Study Period I of SOC treatment were sponsor decision (65 patients, 46.1%), subject decision-consent withdrawn (24 patients, 17.0%), and AEs-physician decision (12 patients, 8.5%). There were no statistically significant differences between the LY2140023

and SOC groups with respect to reason for discontinuation, with the exception of sponsor decision which primarily reflects the early study termination (p=.028).

Baseline characteristics

Of the 552 ITT patients who were administered LY2140023 or SOC, the mean (standard deviation [SD]) age was 41.32 (11.40) years and the majority of patients were male (59.4%). The majority of patients were white (59.8%) or black or African American (31.7%). At baseline, the mean (SD) weight was 82.27 (21.72) kg and the mean (SD) body mass index was 28.09 (7.26) kg/m^2. Patients' mean age (SD) at first treatment of schizophrenia was 26.76 (9.65) years, the mean duration of lifetime illness was 15.75 (11.06) years, and the mean number of previous psychiatric hospitalizations was 6.96 (8.47). The overall baseline mean (SD) PANSS total score was 70.6 (18.3). 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, PSP, SWN-S, or EQ-5D. Baseline values for EPS scales were similar across the treatment groups on the SAS Total Score, BAS Global Score, and AIMS 1-7 Total Score.

For the ITT patients, the mean (SD) exposure to LY2140023 during Study Period I was 161.36 (172.88) days, and the total patient exposure was 181.6 patient-years. Fifty-five patients had at least 52 weeks exposure to LY2140023. The mean (SD) exposure of patients to SOC during Study Period I was 190.77 (188.49) days, and the total patient exposure was 73.6 patient-years.

Safety

For the primary objective, time to discontinuation due to AEs was significantly shorter for LY2140023 compared with SOC (p=.009).

A total of 125 (22.6%) patients experienced at least 1 SAE during the Study Period I. The most frequently occurring SAEs were schizophrenia-related events; schizophrenia was reported in 62 (11.2%) patients, and psychotic disorder was reported in 22 (4.0%) patients. There was a statistically significantly higher occurrence of schizophrenia reported SAEs in patients receiving LY2140023 than SOC (p=.006). All other SAEs were reported in <1% of total patients. There was 1 patient with a confirmed seizure in the LY2140023 group that occurred approximately 6 weeks after starting LY2140023 treatment. Five LY2140023 patients completed the Study Period I and entered Study Period II; however, they were subsequently discontinued due to termination of the study. There was 1 patient of the 5 patients who entered Study Period II who had a reported SAE of psychotic disorder.

There were 3 completed suicides and 1 other sudden death with intracardial small vessel disease in the LY2140023 treatment group. Two of the patients who completed suicide had a history of previous suicide attempt and the other had history of suicidal ideation.There was an additional death reported due to sudden cardiac death 41 days after the last dose of LY2140023 and a death due to circulatory failure approximately 3 weeks after the last dose olanzapine for a patient in the SOC group. These events were not considered related to study treatment by the investigator and

are not reflected in the clinical database since they occurred after the patients had discontinued the study.

In Study Period I in the *All* ITT population, the overall incidence of AEs leading to study discontinuation was significantly higher in the patients receiving LY2140023 (p=.011). Overall, 93 (16.8%) patients discontinued due to AEs. There were 50 patients (12.2%) in the LY2140023 group who discontinued the study due to schizophrenia-related AEs (schizophrenia and psychotic disorder). There was a significantly greater number of patients who discontinued due to schizophrenia AEs in those receiving LY2140023 (n=39, 9.5%) than in those receiving SOC (n=3, 2.1%; p=.005). Although not statistically significant, the next most frequent reason for discontinuation in the LY2140023 group was psychotic disorder (p=.051).

A total of 369 (66.8%) patients in the *All* ITT population reported at least 1 TEAE in Study Period I; 69.1% of patients receiving LY2140023 and 60.3% of patients receiving SOC had ≥ 1 TEAE (p=.056).

The incidence of schizophrenia (LY2140023 15.3%; SOC 5.0%; p=.001), nausea (LY2140023 7.3%; SOC 0.7%; p=.003), agitation (LY2140023 4.1%; SOC 0.7%; p=.048), weight decrease (LY2140023 4.1%; SOC 0.0%; p=.014), and decreased appetite (LY2140023 3.4%; SOC 0.0%; p=.027) TEAEs were significantly greater in patients receiving LY2140023 than SOC. TEAEs such as increased appetite (LY2140023 0.5%; SOC 3.5%; p=.005), somnolence (LY2140023 2.2%; SOC 5.7%; p=.039), weight increased (LY2140023 1.7%; SOC 5.0%; p=.032), akathisia (LY2140023 0.5%; SOC 4.3%; p=.001), respiratory tract congestion (LY2140023 0.0%; SOC 1.4%; p=.015), rhinitis (LY2140023 0.0%; SOC 1.4%; p=.016), urinary incontinence (LY2140023 0.0%; SOC 1.4%; p=.015), and cogwheel rigidity (LY2140023 0.0%; SOC 1.4%; p=.016) were significantly greater in patients receiving SOC. Other notable TEAEs with incidence greater than 5% across treatment groups were insomnia (9.6%), headache (6.3%), and blood creatine phosphokinase increased (6.3%). See Appendix 1 for a summary of all TEAEs reported during this clinical trial.

There were differences in mean change from baseline to last observation in some laboratory results in LY2140023-treated patients compared with SOC-treated patients. SOC-treated patients had a statistically significant decrease in chloride and an increase in gamma glutamyltansferase and triglycerides when compared with LY2140023-treated patients. LY2140023-treated patients had a statistically significant decrease in cholesterol compared with SOC-treated patients.

Statistically significant overall differences for incidences of treatment-emergent abnormal, high or low laboratory values where LY2140023 had a greater occurrence than SOC at any time were UA-ketones abnormal (LY2140023 22.1%; SOC 11.6%; p=.010). Differences where the incidence was greater for SOC than LY2140023 included incidence of treatment-emergent alanine aminotransferase/serum glutamic pyruvic transaminase high (LY2140023 15.2%; SOC 25.4%; p=.011), fasting glucose high (LY2140023 15.2%; SOC 25.4%; p=.011), prolactin low (LY2140023 7.2%; SOC 14.7%; p=.009), hematocrit low (LY2140023 4.3%; SOC 10.2%; p=.015), monocytes high (LY2140023 3.4%; SOC 7.7%; p=.049), and positive methadone urine

drug screen (LY2140023 1.2%; SOC 4.2%; p=.044). See Appendix 2 for a summary of all treatment-emergent abnormal, high, or low laboratory test results during Phase I.

Due to sparse data as a result of study termination, only change from baseline in vital signs and physical characteristics during first year of Study Period I were analyzable. Although there were a few visits where statistically significant differences between treatment groups were observed in changes in vital signs, these changes were not considered to be clinically relevant. There were statistically significant differences between treatment groups in weight starting at week 4. The mean weight change at week 52 for the LY2140023 treatment group was -3.4 kg compared with 3.0 kg for the SOC treatment group (p<.001). In the analyses of potentially clinically significant or treatment-emergent orthostatic changes at any time, in vital signs and weight there were no significant differences between treatment groups in blood pressure or pulse. Compared with SOC, LY2140023-treated patients showed a potentially clinically significant (PCS) decrease in weight (LY2140023 22.1%; SOC 6.1%; p<.001). Compared with LY2140023, more SOC-treated patients showed a PCS increase in weight (LY2140023 8.6%; SOC 21.4%; p<.001).

C-SSRS: No statistically significant differences were noted between LY2140023 and SOC for treatment-emergent suicidal ideation or behavior during study treatment compared with lead-in baseline.

Extrapyramidal Symptoms: There were no statistically significant treatment group differences in change from baseline to each post-baseline visit in the AIMS total score the BAS global score, or the SAS total score during the first year of treatment. Sparse data due to the early termination of the study limited the interpretation of the second year data. There were no statistically significant differences from SOC in incidence of treatment-emergent akathisia as assessed by the BAS and treatment-emergent pseudoparkinsonism as assessed by the SAS. However, there was a statistically significant greater incidence of dyskinesia in the SOC group as assessed by the AIMS (LY2140023 1.8%; SOC 5.1%; p=.032).

Efficacy

Due to sparse data as a result of study termination only treatment differences in the first year are reported here for the efficacy analysis. There was statistically greater improvement from baseline for SOC compared with LY2140023 in the PANSS total score on Weeks 2 (LY2140023 2.4; SOC, -3.2), and 52 (LY2140023 -5.0; SOC -10.7). For the secondary efficacy variables there was statistically greater improvement for SOC compared with LY2140023 on the PANSS positive score at Week 36, on the PANSS negative score at Week 2, and PANSS general psychopathology subscore on Weeks, 2, 36, and 52. Standard of care separated statistically from LY2140023 on improvement of the CGI-S score on Weeks 12 through 44. There were no between-group statistically significant differences on the NSA-16 total score.

Health Outcome

The PSP, EQ-5D, SWN-S, and S-RUM were analyzed in accordance with the SAP. There were no statistically significant differences between treatment groups for the EQ-5D Dimension or VAS Health State Score. At certain visits there were significant treatment differences in the PSP

and SWN-S, but these did not demonstrate an overall pattern and were not considered clinically relevant. On the S-RUM, the LY2140023 treatment group demonstrated significantly fewer mean hours (h) worked for pay per week (LY2140023 3.0 h, SOC 4.6 h; p=.005) and significantly more times of getting help with shopping (LY2140023 4.8, SOC 3.3; p=.028), housing (LY2140023 3.8, SOC 1.0; p=.045), and scheduling an appointment (LY2140023 1.8, SOC 1.3; p=.037).

Conclusions

- The time to discontinuation due to AEs was significantly shorter for patients receiving LY2140023 compared with those receiving SOC.
- The most common AEs leading to discontinuation of LY2140023 treatment were schizophrenia-related AEs (schizophrenia and psychotic disorder).
- There was a statistically significantly higher SAE incidence in the LY2140023 group compared with SOC. This appears to be driven by schizophrenia-related SAEs (schizophrenia and psychotic disorder).
- There was 1 confirmed seizure in a patient treated with LY2140023.
- There were 3 SAEs of completed suicides and 1 additional sudden death due to coronary artery disease among LY2140023 patients.
- The incidences of TEAEs which were statistically significant in LY2140023-treated patients compared with SOC-treated patients included schizophrenia, nausea, agitation, weight decrease, and decreased appetite.
- There were no clinically relevant abnormal laboratory findings associated with LY2140023.
- LY2140023 was not associated with an increase from baseline in values for EPS scales or prolactin. There was significantly less dyskinesia in LY2140023-treated patients, based on the AIMS.
- Incidence of patients treated with LY2140023 who had PCS weight loss was significantly higher than the SOC group. In contrast, patients treated with SOC were significantly more likely to have PCS weight gain compared with the LY2140023 group.
- In general, there was significantly less efficacy of LY2140023, as measured by PANSS Total, PANSS Positive, PANSS Negative, PANSS General Psychopathology scores, and CGI-S compared to SOC.