1. H8Y-MC-HBBI Abbreviated Clinical Study Report

A Multi-Center, Inpatient, Phase 2, Double-Blind, Placebo-Controlled Dose Ranging Study of LY2140023 in Patients with DSM-IV Schizophrenia

LY2140023

A multi-center, inpatient, Phase 2, double-blind, placebo- and comparator-controlled, parallel arm study comparing twice daily doses of 5 mg, 20 mg, 40 mg, and 80 mg of LY2140023 or 15 mg olanzapine once daily with placebo during 4 weeks active treatment in patients with DSM-IV schizophrenia.

Eli Lilly and Company
Protocol H8Y-MC-HBBI
Phase 2
First patient enrolled (assigned to therapy): 21 September 2007
Last patient completed: 06 October 2008
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Coordinating/Principal Investigator: PPD , MD, PhD
Moscow, Russia

Responsible Medical Officer: PPD , MD

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5. Objectives and Design

5.1. Rationale

The glutamate hypothesis of schizophrenia suggests that drugs that modulate glutamatergic activity could be used to treat schizophrenia. Metabotropic glutamate 2/3 receptor agonists (mGlu2/3 receptor agonists) should decrease pathological overactivity in the glutamate system and have shown a preclinical pharmacological profile similar to that of clinically effective atypical antipsychotic drugs (Schoepp and Marek 2002). LY2140023 is the methionine prodrug of the potent mGlu2/3 receptor agonist LY404039.

The recent, well-controlled, proof of concept study (Study HBBD) demonstrated efficacy approaching that of olanzapine in patients treated with 40 mg twice daily (BID) of LY2140023 and clearly indicates 2 important needs. The first need is reproducibility of the effects of LY2140023 in reducing the symptoms of schizophrenia. As importantly, the dose-effect relationship needs to be more clearly mapped in order to identify where the optimal dose range lies for safety and efficacy.

This study (Study HBBI) examined doses above and below 40 mg BID to determine the doses for Phase 3 trials. The primary objective of Study HBBI was to test the hypothesis that 1 or more dose levels of LY2140023 given orally to patients with schizophrenia twice daily for 4 weeks will demonstrate significantly greater efficacy than placebo.

5.2. Objectives

5.2.1. Primary Objective

The primary objective of this study was to test the hypothesis that 1 or more dose levels of LY2140023 given orally to patients with schizophrenia twice daily for 4 weeks would demonstrate significantly greater efficacy than placebo. Efficacy was defined as clinical response measured by the Positive and Negative Syndrome Scale (PANSS) total score as assessed at 4 weeks.

5.2.2. Secondary Objectives

The secondary objectives of the study were as follows:

[1] To test if 1 or more dose levels of LY2140023 would demonstrate significantly greater efficacy than placebo as assessed at 4 weeks by the following measures:

- PANSS-positive subscore
- PANSS-negative subscore
- PANSS-general psychopathology subscore

- PANSS-cognitive subscore
- Clinical Global Impression-Severity (CGI-S).

[2] To evaluate the dose response relationships for:

- Efficacy as assessed by the PANSS total score and the subscores
- Efficacy as assessed by the CGI-S
- Patient subjective improvement as assessed by the Drug Attitude Inventory-10 (DAI-10).

[3] To evaluate the rates of response reduction in PANSS total score and subscores as assessed at 4 weeks for 4 doses of LY2140023 compared to placebo.

[4] To test if one or more dose levels of LY2140023

- would demonstrate significantly greater improvement in specific cognitive skills as measured by the Brief Assessment of Cognition in Schizophrenia (BACS) Symbol Coding Task score as compared to placebo
- would demonstrate significantly greater improvement in depressive symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) total score as compared to placebo.

[5] To assess the safety and tolerability of LY2140023 compared with placebo and olanzapine.

[6] To assess the efficacy of olanzapine versus placebo as measured by the PANSS total score.

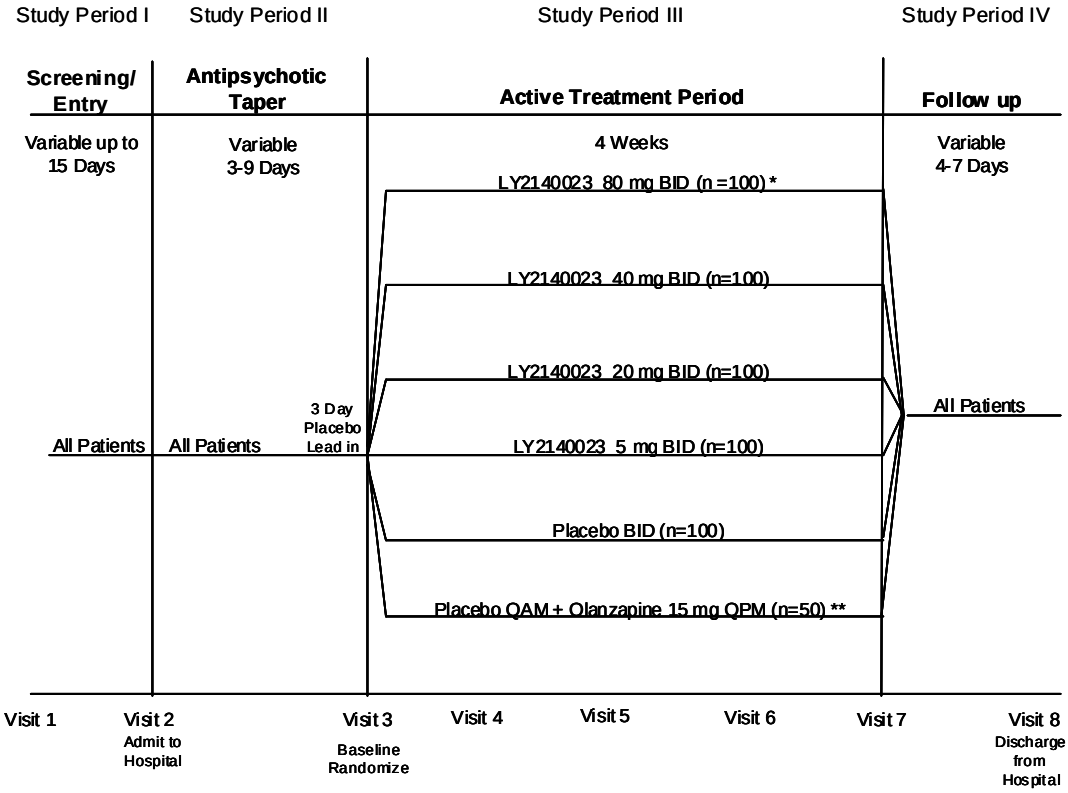
[7] To determine the pharmacokinetics and the variability of LY2140023 and LY404039 in schizophrenic patients and to explore the concentration response relationship using efficacy and safety clinical endpoints such as the PANSS total score.

[8] To assess adverse events (AEs) or changes in PANSS or CGI-S rating following discontinuation of LY2140023, olanzapine, or placebo study medication.

5.3. Design

Study H8Y-MC-HBBI (Study HBBI) was a multi-center, randomized, double-blind, parallel, placebo- and active comparator-controlled trial with 4 study periods (Figure HBBI.5.1). Approximately 870 patients who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV, APA 2000) criteria for schizophrenia as defined by the modified Structured Clinical Interview for DSM-IV Diagnosis (SCID) were to be entered into the study so that approximately 550 patients would be considered

evaluable (that is, randomized patients with a baseline and at least 1 postbaseline PANSS total score following study treatment). Male and female patients aged 18 to 65 years who qualified for enrollment into the study were randomized in a 2:2:2:2:2:1 ratio to receive 5 mg, 20 mg, 40 mg, or 80 mg twice daily LY2140023, placebo twice daily, or placebo once each morning and 15 mg olanzapine once each evening for approximately 28 days.



Abbreviations and Notes: BID = Twice daily; QAM = each morning; QPM = Each evening. n = desired number of evaluable patients (have baseline and at least 1 set of measurements after starting active treatment).
*LY2140023 40 mg BID x 3 Days then 80 mg BID. **Olanzapine 10 m g QPM X 3 Days then 15 mg QPM.

Study Design Figure for H8YMC-HBBI

Figure HBBI.5.1. Study design.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices (GCPs) and the applicable laws and regulations. A properly executed, signed informed consent document (ICD) was obtained from each patient. Key inclusion/exclusion criteria for this study were intended to ensure the enrollment of schizophrenic patients (as defined by the DSM-IV criteria for schizophrenia and confirmed by the modified SCID), between the ages of 18 and 65 years of age (inclusive). Female patients must have tested negative for pregnancy and, if of childbearing potential, must have been using a medically accepted means of contraception. All enrolled patients were willing to be inpatient for the duration of the trial, presented with acceptable results of physical examination, clinical laboratory tests, and electrocardiogram (ECG) at screening. To be included in the study, patients had to meet the following 2 requirements at Visit 1 and Visit 3:

- A Brief Psychiatric Rating Scale (BPRS) total score, extracted from the PANSS, of at least 45 (18-item version, in which 1 indicates "absent" and 7 indicates "severe"). Item scores of at least 4 (moderate) were required on 2 of the following BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and/or unusual thought content.
- A minimum score of 4 (moderately ill) on the Clinical Global Impression-Severity (CGI-S) scale.

Patients with any of the following were excluded from the study: (1) had taken any depot antipsychotic within 4 weeks before screening, (2) had active suicidal ideation, (3) those for whom treatment with olanzapine, LY2140023, or placebo was relatively or absolutely clinically contraindicated, (4) had a history of seizures, (5) had used olanzapine within 6 weeks prior to Visit 1. The protocol is included in an appendix in this report.

The rationale for the use of placebo was based on the desire that when developing a new therapy, it is desirable to minimize the number of patients who might be exposed to a sub-therapeutic or less well-tolerated substance. Furthermore, because treatment with LY2140023 may be associated with therapeutic improvements and/or adverse events (AEs) different than currently available antipsychotic drugs, a placebo-controlled design may optimize the demonstration of such effects. In the absence of a placebo arm, assay sensitivity becomes difficult and one may not be able to distinguish between an active and an inactive therapy for either side effects or efficacy. The rationale for the use of an olanzapine arm was to ensure the interpretability of the data in case of a negative result with this investigational new drug. Data from this positive control arm serves to validate the methodological approach of this study.

5.4. Drug Formulation and Administration

The following treatments were administered:

- LY2140023 5 mg, 20 mg, 40 mg, or 80 mg, supplied in 5 mg and 20 mg capsules, given orally BID for 28 days.
- Olanzapine 15 mg, supplied as 5 mg capsules, given orally BID for 28 days.
- Placebo capsules identical to LY2140023 and olanzapine capsules given orally BID for 28 days.

LY2140023 (5 and 20 mg capsules), olanzapine and placebo were supplied from CCI, CCI, CCI, and CCI.

The doses of LY2140023 had been carefully selected to help determine an optimal therapeutic dose of LY2140023, based on both efficacy and tolerability, to further develop as a potential treatment for schizophrenia. The dose of olanzapine was selected as an efficacious and tolerable dose that is consistent with product labeling.

9. Discussion and Overall Conclusions

9.1. Discussion

Of the 853 patients who entered Study HBBI, 669 were randomly assigned to treatment, 667 received at least 1 dose of study drug, 389 completed the study, and 280 did not complete the study. Patients enrolled in Study HBBI did not differ with respect to baseline characteristics or measures of baseline efficacy or EPS; however, there were some significant differences with respect to psychiatric history, previous psychiatric therapy, and concomitant medications that were not considered to be clinically relevant. The most common reasons for early discontinuation were lack of efficacy (157 patients), subject decision (48 patients), and adverse event (40 patients). The incidence of discontinuation due to lack of efficacy was significantly lower in the olanzapine group (12.9%) compared with the placebo group (p=0.038).

The primary analysis (MMRM) failed to demonstrate that any of the 4 LY2140023 monohydrate doses (5 mg, 20 mg, 40 mg, or 80mg BID) were more efficacious than placebo as measured by the PANSS total. Similarly, olanzapine (15 mg QD) failed to separate from placebo. A higher than anticipated response in the placebo group was observed (14.6 point improvement) on PANSS total.

No improvement for any LY treatments compared with placebo was observed on any of the secondary efficacy measures, including those measuring improvement in cognitive functioning or depression, at 4 Weeks. Although no improvement compared with placebo was observed, all treatment groups generally showed significant baseline to endpoint within-treatment-group improvements on most efficacy measures. Olanzapine, an approved treatment, served as an active control in this study. The olanzapine group showed significant improvement compared with placebo at Weeks 2, 3 and 4 on the PANSS Positive score, but did not show significant separation from placebo on any of the other secondary efficacy measures. A series of exploratory analyses were performed in order to better understand how such factors as heterogeneity of the patient population and higher than anticipated placebo response may have contributed to the inconclusive results of the trial.

LY2140023 monohydrate was generally well-tolerated, although serious adverse events of convulsions were reported in 4 patients. Furthermore, LY2140023 monohydrate showed little change in dopamine-related adverse events and weight. Common TEAEs (incidence >3% in all patients assigned to LY2140023 monohydrate) included insomnia, eosinophil count increased, anxiety, nausea, agitation and headache. There did not appear to be a dose response relationship in the incidence of adverse events. There were significant differences for some laboratory analytes, vital signs, and ECG measurements; these differences were not considered to be clinically relevant. Laboratory results that were significant for the olanzapine group compared with placebo were either consistent

with previous trial findings or not considered to be clinically relevant. Further efficacy, safety and tolerability testing of LY2140023 monohydrate is needed.

9.2. Conclusions

- The results of Study HBBI are considered to be inconclusive since LY2140023 monohydrate and the comparator molecule olanzapine did not separate from placebo in the treatment of patients suffering from acute schizophrenia.
- In Study HBBI, a greater than expected placebo response was observed. The change from baseline on PANSS total for the placebo group was approximately double that historically seen in schizophrenia clinical trials.
- In addition, convulsions were reported in 4 patients treated with LY2140023 monohydrate.
- Further efficacy, safety and tolerability testing is needed.