Clinical Study Report Synopsis

Drug Substance	Quetiapine fumarate
Study Code	D144AC00003
Edition Number	1.0
Date	1 September 2011

An International, Multicenter, Double-blind, Randomized, Placebo-controlled, Phase IV Study of the Safety and Efficacy of Lithium versus Placebo as an add on to SEROQUEL XR™ (Quetiapine Fumarate) in Adult Patients with Acute Mania

Study dates: First subject enrolled: 24 June 2009
Last subject last visit: 22 November 2010

Phase of development: Therapeutic use (IV)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was conducted at 38 study centers in 8 countries (India 11, Russia 7, Bulgaria 7, Ukraine 6, Poland 3, Germany 1, South Africa 2, and Belgium 1).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the effectiveness of lithium compared to placebo as an add-on to quetiapine XR in the treatment of acute mania in patients with bipolar I disorder, as assessed by the change from baseline to final assessment (Day 43) in YMRS total score.	Change in the YMRS total score from baseline to Day 43	Efficacy
Secondary	**Secondary**	
To evaluate the effectiveness of lithium compared to placebo as an add-on to quetiapine XR in achieving remission of acute mania in patients with bipolar I disorder.	Remission (defined as a YMRS total score ≤12 at Day 43).	Efficacy
To evaluate the effectiveness of lithium compared to placebo as an add-on to quetiapine XR in acute mania symptom response in patients with bipolar I disorder.	Response (defined as ≥50% reduction from baseline to Day 43 in the YMRS total score).	Efficacy
To evaluate the effectiveness of lithium compared to placebo as an add-on to quetiapine XR in the treatment of a broad range of bipolar symptoms in patients with bipolar I disorder.	• Change from baseline to Day 43 in the CGI-BP-S • CGI-BP-C score at Day 43 • Improvement in overall bipolar illness (CGI-BP-C score of Much or Very Much improved in the overall bipolar illness item at Day 43) • Change from baseline to Day 43 in each YMRS item score	Efficacy
To evaluate the effectiveness of lithium compared to placebo as an add-on to quetiapine XR in the treatment of depressive symptoms in patients with acute mania, as assessed by the change from baseline to final assessment (Day 43) in MADRS total score.	Change in the MADRS total score from baseline to Day 43	Efficacy

Objectives	Outcome variables	Type
To evaluate the effectiveness of lithium compared to placebo as an add-on to quetiapine XR in the treatment of agitation and aggression in patients with acute mania, as measured by a score change from baseline to Day 43 of the PANSS	Change in the PANSS activation subscale score from baseline to Day 43	Efficacy
To evaluate the effectiveness of lithium compared to placebo as an add-on to quetiapine XR in the treatment of psychotic symptoms in patients with acute mania with psychotic features, as measured by the change from baseline to final assessment (Day 43) in the PANSS positive subscale score and PANSS total score.	• Change in the PANSS positive subscale score from baseline to Day 43 • Change in the PANSS total score from baseline to Day 43	Efficacy
To assess the short-term safety of lithium compared to placebo as an add-on to quetiapine XR in patients with bipolar I disorder based on adverse events (AEs), laboratory values, vital signs, and electrocardiogram (ECG) findings, and abnormal involuntary movements for up to 6 weeks.	• Occurrence of AEs (aggregation of a predefined set of MedDRA preferred terms of specific safety areas), including EPS, somnolence, diabetes mellitus, QT prolongation, neutropenia/agranulocytosis, and suicidality • Change from baseline to each visit, when measured, in clinical lab tests and ECG results, vital signs • Change from baseline to Day 43 in weight • Occurrence of a ≥7% increase in weight from baseline to Day 43 • Change from baseline to Day 43 in SAS total score • Change from baseline to Day 43 in AIMS total score • Change from baseline to Day 43 in BARS global score • Occurrence of treatment-emergent EPS AEs, worsening of SAS or AIMS total scores, or BARS global score, and initiation of treatment with anticholinergic medication for new EPS with onset during the study • Occurrences of suicidal behavior and suicidal ideation after baseline as measured by the C-SSRS	Safety
To evaluate the proportion of patients exhibiting treatment-emergent depression among patients taking lithium compared to placebo as an add-on to quetiapine XR.	Occurrence of treatment-emergent depression, as measured by AEs of depression or depressed mood (aggregation of a predefined set of MedDRA preferred terms) and/or MADRS total score ≥18 on 2 consecutive assessments or on Day 43	Safety

Objectives	Outcome variables	Type
Exploratory	**Exploratory**	
To collect blood samples for optional exploratory genetic studies focusing on identification of genes that influence the disposition, efficacy, safety, and tolerability of quetiapine XR in patients with bipolar I disorder	Pharmacogenetics (PGx)	PGx (optional)

AIMS Abnormal Involuntary Movement Scale; BARS Barnes Akathisia Rating Scale; C-SSRS Columbia-Suicide Severity Rating Scale; CGI-BP-C Clinical Global Impressions for Bipolar Disorder-Change from Preceding Phase; CGI-BP-S CGI-BP-Severity of Illness; EPS extrapyramidal symptoms; MADRS Montgomery-Åsberg Depression Rating Scale; MedDRA Medical Dictionary for Regulatory Activities; PANSS Positive and Negative Syndrome Scale; SAS Simpson-Angus Scale; quetiapine XR quetiapine extended release formulation; YMRS Young Mania Rating Scale.
Note: There is currently no plan to conduct PGx exploratory analyses.

Study design

This was a 6-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study with a flexible dose design to evaluate the effectiveness of lithium compared with placebo as an add-on to quetiapine XR in the treatment of acute mania in male and female patients with bipolar I disorder.

Target subject population and sample size

Eligible patients aged 18 to 65 years (inclusive) with a primary diagnosis of bipolar I disorder with current (or most recent) episode manic or mixed (296.4x or 296.6x, respectively) were enrolled. A Young Mania Rating Scale (YMRS) total score of ≥20 was required at both enrollment (Visit 1) and at randomization (Visit 2), and a Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) primary diagnosis of bipolar I disorder with current episode manic or mixed as confirmed by the amended version of the Structured Clinical Interview for DSM-IV (SCID), prior to medication washout.

For each group, 166 evaluable patients (332 total) were needed to reject the statistical null hypothesis of no difference with a power of 80% when using a 2-sided t-test at an overall experiment type I error rate of 0.050. Evaluable was defined as patients who received at least 1 dose of each study medication (ie, quetiapine XR and lithium/placebo), who had a baseline YMRS total score value and at least 1 post-baseline YMRS total score assessment. Assuming a drop-out rate from the modified intent-to treat (mITT) analysis set (ie, evaluable patients) of approximately 5% meant that a total of 350 patients needed to be randomized.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The study drug, quetiapine XR was administered as open-label medication and taken orally, once daily in the evening. The starting dose of quetiapine was 300 mg/day (Day 1). On Day 2, and thereafter, a dose of 600 mg/day was administered. Patients already on quetiapine

continued on their previous dose at Day 1, which was increased to 600 mg at Day 2 if the dose at Day 1 was lower. Beginning on Day 3, the principal investigator (PI) was allowed to adjust the dose at a range between 400 mg and 800 mg/day depending on the efficacy and tolerability. The investigator prescribed the doses of 400 mg, 600 mg, or 800 mg/day. Individual batch numbers and further information are included in the Clinical Study Report (CSR) appendix.

Lithium or placebo was administered as double-blind medication and taken orally twice daily (morning and evening). On study visit days, the patient's morning lithium dose was taken after blood was drawn for serum lithium sampling. Lithium was prescribed at doses of 600, 900, 1200, 1500, or 1800 mg/day.

Duration of treatment

This study consisted of an enrollment period (Visit 1) of up to 28 days and a 6-week treatment period (Days 1 to 42; Visits 2 to 7). The enrollment period included a medication washout lasting 7 to 28 days (depending on the medications involved and at the discretion of the investigator). During the treatment period, all patients received open-label quetiapine XR; patients also received randomly assigned double-blind lithium or placebo in a 1:1 ratio.

Statistical methods

All statistical comparisons were based on 2-sided tests using a significance level of 5%, unless otherwise specified. No adjustment for multiplicity was made for any secondary endpoint.

All efficacy variables were descriptively presented and analyzed using the mITT analysis set. The primary efficacy variable was the change from baseline to Day 43 in the YMRS total score. Change from baseline in YMRS total score was analyzed using a mixed-model for repeated measures (MMRM) approach.

Subject population

There were 441 patients enrolled and 356 patients randomized. Of the 356 randomized patients, 99.7% (355/356 patients) received their assigned study treatment, 81.7% (291/356 patients) completed the study and 18.3% (65/356 patients) discontinued the study. All patients in the lithium add-on group received their assigned study treatment. One patient in the placebo add-on group did not receive the double-blind assigned study medication; this patient received one dose of the open-label study medication (quetiapine XR), but failed to receive at least one dose of the double-blind study medication (lithium/placebo).

The most common reason for study discontinuation was voluntary discontinuation by patient (6.7%, 24/356 patients).

In general, baseline demographic data were similar in both treatment groups. Most patients enrolled in this study were White (56.2%). Overall, the mean age was 38.3 years (range 18 to 65 years), with a higher percentage of males (62.4%) than females (37.6%) participating in the study. The mean weight and body mass index (BMI) at baseline were similar in both treatment groups.

Summary of efficacy results

Primary efficacy

In the mITT analysis set, mean (standard deviation [SD]) YMRS total scores were 29.9 (5.41) for the lithium add-on group and 30.0 (5.0) for the placebo add-on group at baseline. The mean YMRS total scores decreased from baseline to Day 43 for both lithium and placebo as add-on to quetiapine XR, indicating a reduction (or improvement) in manic symptoms in both treatment groups. The least squares (LS) mean reduction in YMRS total score was -22.8 for lithium add-on and -20.1 for placebo add-on. The difference between the treatment groups (-2.69) was statistically significant ($p<0.001$).

Secondary efficacy

As an add-on to quetiapine XR, lithium was:

- Superior in improving a broad range of acute mania symptoms in patients with bipolar 1 disorder at Day 43 compared to placebo as an add-on to quetiapine XR, as assessed by response (defined as ≥50% reduction at Day 43 in YMRS total score), remission (defined as YMRS total score ≤12 at Day 43), CGI-BP-S (severity of illness), CGI-BP-C (overall bipolar illness assessment), improvement of illness, and individual YMRS item scores.

- Not superior in improving depressive symptoms in patients with acute mania compared to placebo as an add-on to quetiapine XR, as measured by the change from baseline to Day 43 of the MADRS total score.

- Superior in reducing psychosis in patients with acute mania and psychotic features compared to placebo as an add-on to quetiapine XR, as measured by the change from baseline to Day 43 of the PANSS positive and PANSS total scores.

- Superior in reducing agitation and aggression in patients with acute mania compared to placebo as an add-on to quetiapine XR, as measured by the change from baseline to Day 43 of the PANSS activation subscale score.

Summary of safety results

- The overall incidence of treatment-emergent AEs (TEAEs) reported in lithium add-on treated patients was higher (63.0%) than the placebo add-on group (48.1%). The most frequent system organ class (SOC) associated with TEAEs in both treatment groups was nervous system disorders. Among the most common TEAEs (ie, those occurring at >2% in either treatment group), tremor, somnolence, dizziness, diarrhea and vomiting occurred at higher rates in the lithium add-on group compared to the placebo add-on group. Headache, constipation, dry mouth, and insomnia were the most frequently reported TEAEs in both treatment groups. Most TEAEs were mild to moderate in intensity.

- A higher number of patients in the placebo add-on group (7.1%) discontinued from the study due to an AE than did patients in the lithium add-on group (3.5%). No deaths occurred in the study. The incidence of serious adverse events (SAEs) was higher in the placebo add-on group (4.4%) than in the lithium add-on group (2.3%). Mania led to study discontinuation in 2 patients treated with lithium add-on and 6 patients in the placebo add-on group. All were SAEs.

- The incidences of potentially EPS-related TEAEs were low in both treatment groups. All potentially EPS-related TEAEs were mild to moderate in intensity. Among the EPS-related TEAEs, tremor occurred at higher rates in the lithium add-on group (15.6%) than in the placebo add-on (4.9%). Two of these TEAEs (tremor and dystonia) resulted in discontinuation from the study. The majority of patients showed no change in EPS over the course of the study, as assessed by the SAS, AIMS, and BARS scales. The odds of worsening were not different between the lithium add-on and placebo add-on groups, as assessed by AIMS and BARS, but were higher in the lithium add-on group as assessed by SAS.

- No TEAEs potentially related to diabetes mellitus, neutropenia or severe neutropenia, or QTc prolongation were reported in the study. There were few shifts in each treatment group from normal to abnormal values during the study.

- No patient committed suicide in this study. There were no TEAEs potentially related to suicidality during the study.

- The incidence of treatment-emergent depression was low in both treatment groups (1.2% for lithium add-on vs. 0.5% for placebo add-on).

- No clinically meaningful treatment group differences were seen in vital signs, other physical examination findings, hematology, clinical chemistry and urinalysis findings.

- A higher percentage of patients treated with lithium add-on (8.0%) had weight gain (≥7%) at the end of treatment compared to placebo add-on patients (4.7%).