AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Quetiapine fumarate
Study Code	D144AC00001
Edition Number	1.0
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An 8-week, Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Extended-release in Children and Adolescent Subjects with Bipolar Depression

Study dates: First subject enrolled: 27 January 2009
Last subject last visit: 1 November 2010

Phase of development: Therapeutic confirmatory (III)

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 centers

This study was conducted in 42 study centers in 7 countries (United States 29, India 3, Colombia 3, Serbia 3, Mexico 2, South Africa 1, and Taiwan 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 whether quetiapine XR formulation at a dose of 150 to 300 mg/day demonstrates superior efficacy compared to placebo in children and adolescents 10 to 17 years of age with bipolar depression after 8 weeks of treatment	Change in the CDRS-R total score from baseline to final assessment (Day 57)	Efficacy
Secondary	**Secondary**	
To evaluate whether quetiapine XR is superior to placebo in achieving remission	Proportion of remission, defined as CDRS-R total score ≤28 at final assessment (Day 57)	Efficacy
To evaluate whether quetiapine XR is superior to placebo in achieving depression symptom response	Proportion of response, defined as ≥50% reduction from baseline to final assessment (Day 57) in CDRS-R total score	Efficacy
To evaluate whether quetiapine XR is significantly more effective than placebo in the treatment of a broad range of bipolar depression symptoms in children and adolescents	Change from baseline to final assessment (Day 57) in the CGI-BP-S	Efficacy
	CGI-BP-C score at final assessment (Day 57)	Efficacy
	Proportion of patients at final assessment (Day 57) with improvement of overall bipolar illness	Efficacy
To evaluate the safety and tolerability of quetiapine XR in the treatment of bipolar depression in children and adolescents	AEs, discontinuation due to AEs, SAEs, death	Safety
	AEs of EPS and other specific safety areas, including QTc prolongation, somnolence, suicidality, neutropenia/agranulocytosis, and thyroid function	Safety
	Incidence of AEs of mania or hypomania and/or YMRS total score ≥16 on 2 consecutive assessments or at final visit	Safety

Objectives	Outcome variables	Type
	Change from baseline to each visit, when measured, in clinical laboratory test results (ie, clinical chemistry and hematology), ECG results, vital signs, and weight	Safety
	Categorized change from baseline to Day 29 and Day 57 in SAS total score: improved vs. no change/worse	Safety
	Categorized change from baseline to Day 29 and Day 57 in AIMS total score: improved vs. no change/worse	Safety
	Categorized change from baseline to Day 29 and Day 57 in BARS global score: improved vs. no change/worse	Safety
	Suicidal behavior and suicidal ideation occurrences after baseline up to final assessment (Day 57) as measured by the C-SSRS	Safety
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 or bipolar II disorder	PGx

AE adverse event; AIMS Abnormal Involuntary Movement Scale; BARS Barnes Akathisia Rating Scale; CDRS-R Children's Depression Rating Scale-Revised; CGI-BP-C Clinical Global Impressions for Bipolar Disorder-Change from Preceding Phase; CGI-BP-S Clinical Global Impressions for Bipolar Disorder-Severity of Illness; C-SSRS Columbia-Suicide Severity Rating Scale; ECG electrocardiogram; EPS extrapyramidal symptoms; PGx pharmacogenetics; SAE serious adverse event; SAS Simpson-Angus Scale; YMRS Young Mania Rating Scale.
Note: There is currently no plan to conduct pharmacogenetics (PGx) exploratory analyses.

Study design

This was an 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study evaluating the efficacy and safety of quetiapine XR 150 to 300 mg/day in the treatment of children and adolescents with bipolar disorder.

Target subject population and sample size

Eligible patients (male or female children and adolescents aged 10 to 17 years, inclusive), with a clinically established diagnosis of bipolar I or bipolar II disorder (current or most recent episode depressed) were enrolled. A Children's Depression Rating Scale-Revised (CDRS-R) total score of ≥45 and Young Mania Rating Scale (YMRS) total score ≤16 were required at both Visit 1 (screening) and Visit 2 (randomization) after washout of current medications.

Ninety-two patients were needed to provide 85% power to reject the null hypothesis of no difference assuming a true difference of 4 points on CDRS-R and a standard deviation of 9 when using a 2-sided t-test at a significance level of 5%.

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

The study drug, quetiapine XR, was studied at doses ranging from 150 to 300 mg/day. Quetiapine XR was administered orally, once daily in the evening. The study also included a placebo arm. Quetiapine XR or placebo was titrated up in 50 mg increments to reach the expected therapeutic dose of 150 mg over 3 days. The dose was to be increased to 300 mg in a step-wise manner if there was deterioration. Individual batch numbers and further information are included in the Clinical Study Report (CSR).

Duration of treatment

The study consisted of an up to 35-day enrollment period (including washout and baseline periods), an 8-week treatment period with 1 of 2 treatment regimens (quetiapine XR 150 to 300 mg/day or placebo), a 1-week safety follow-up period, 2- to 4-week safety follow-up period for patients with a blood pressure (BP) >95th percentile at the study completion or discontinuation visit.

Statistical methods

In general, all efficacy and safety variables were presented by treatment group using descriptive statistics and graphs as appropriate. Continuous and semi-continuous variables were presented using standard descriptive statistics (n, mean, standard deviation [SD], median, min, max), within treatment group.

All statistical comparisons were based on a 2-sided significance level of 5%, unless otherwise specified. Secondary analyses reported nominal 5% levels of significance. No other correction to the reported p-values was made for the analysis of secondary measures.

Subject population

There were 262 patients enrolled and 193 patients randomized from 42 study centers in 7 countries. Of the 193 patients randomized to the study, 99.5% (192/193 patients) received treatment, 74.6% (144/193 patients) completed the study, and 25.4% (49/193 patients) discontinued from the study.

Overall, the most common reason for study discontinuation was AEs (7.8%, 15/193 patients). The number and percentage of patients who discontinued due to AEs was higher in the placebo group (12.0%, 12/100 patients) than in the quetiapine group (3.2%, 3/93 patients).

In general, baseline demographic data were similar in both treatment groups. Most patients enrolled in this study were White (65.1%), with a higher percentage of patients in the 13-17 year age group (72.4%). The mean weight and body mass index (BMI) at baseline were similar in both treatment groups.

Summary of efficacy results

Primary efficacy

The primary efficacy outcome variable was the change from baseline to Day 57 in CDRS-R total score. Higher CDRS-R scores indicate more severe depression, thus, a negative change (or decrease) from baseline indicates a reduction (or improvement) in depression severity.

In the modified intent-to-treat (mITT) analysis set, the mean CDRS-R total scores decreased from baseline to Day 57 for both quetiapine XR and placebo, indicating a reduction in depression severity in both groups. The LS mean reduction in CDRS-R total scores was -29.6 for quetiapine XR and -27.3 for placebo. The difference between the treatment groups (-2.29) was not statistically significant (95% CI= -6.22 to 1.65, p=0.252).

Secondary efficacy

- Quetiapine XR was not superior to placebo in achieving remission in CDRS-R at Day 57.
- Quetiapine XR was not superior to placebo in achieving response in CDRS-R at Day 57.
- Quetiapine XR was not superior to placebo in reducing depression severity as measured by the following scales, CGI-BP-S and CGI-BP-C, at Day 57.
- Quetiapine XR was not superior to placebo in achieving improvement in overall bipolar illness in CGI-BP-C at Day 57.

Summary of safety results

- The incidence of AEs during the study was higher in the quetiapine XR group than in the placebo group (73.9% vs. 66.0%, respectively). Among the most common AEs (ie, those occurring at >2% in either treatment group), headache, dizziness, somnolence, diarrhoea, nausea, and fatigue occurred at higher rates in the quetiapine XR group compared to the placebo group. Infections and Infestations (ie, influenza, nasopharyngitis, gastroenteritis, sinusitis, urinary tract infection and ear infection) were more frequently reported with quetiapine XR than in the placebo group. Most AEs were mild to moderate in intensity.
  - In the analyses of the most common AEs by age group, headache and dizziness occurred more frequently in the quetiapine XR group in both age groups
- The incidence of SAEs was higher in the placebo group (4 patients) than in the quetiapine XR group (1 patient) during the study period. All 5 SAEs led to study discontinuation. Of these, one SAE (aggression) was assessed by the investigator as related to the study drug (placebo). Most of the SAEs were reported in patients

aged 13-17 years in the placebo group. Two SAEs were reported at the recall visit. No deaths occurred in the study.

- Discontinuation from the study due to an AE was higher in the placebo group (12.0%) than in the quetiapine XR group (3.3%).

- The incidence of potentially EPS-related AEs was low in both treatment groups (quetiapine XR, 1.1% vs. none in the placebo group). All potentially EPS-related AEs were mild to moderate in intensity. The majority of patients showed no change in EPS over the course of the study, as assessed by the SAS, AIMS, and BARS. The odds of worsening were not different between the quetiapine XR and placebo groups, as assessed by the SAS, AIMS and BARS.

- Adverse events potentially related to somnolence (somnolence or sedation) were higher in the quetiapine XR group (14.1%) than in the placebo group (11.0).

- The incidence of AEs potentially related to suicidality and diabetes mellitus was low in the quetiapine XR group (1.1% and 3.3%, respectively). None were reported in the placebo group.

- Adverse events potentially related to neutropenia or severe neutropenia were higher in the placebo group. None were reported in the quetiapine XR group. One patient in the placebo group experienced a shift in neutrophil count during the study to levels representing severe neutropenia.

- There were no AEs potentially related to QT prolongation in either treatment group during the study.

- No patient committed suicide in this study. The incidences of suicidal ideation and suicidal behavior, as assessed by C-SSRS and Columbia-Classification Algorithm for Suicide Assessment (C-CASA), were similar between the quetiapine XR and placebo groups. One patient (1.0%) in the placebo group had worsening of ideation during the study.

- The incidence of treatment-emergent mania or hypomania was higher in the placebo group than in the quetiapine XR group (10.0% vs. 2.2%, respectively) during the study.

- No clinically meaningful treatment group differences were seen in ECG, other physical examination, eye examination, hematology, clinical chemistry or urinalysis findings.

- Due to the time intervening between randomized treatment and the recall visit, the thyroid and prolactin results from the recall visit are confounded and difficult to interpret. Shifts from normal to low values for triiodothyronine (T_3) and free

thyroxine (T_4), as well as shifts from normal to high values for thyroid-stimulating hormone (TSH), and prolactin were low in both treatment groups at the recall visit.

- Potentially clinically significant orthostatic changes in systolic blood pressure (SBP) were more frequently noted with placebo than with quetiapine XR (10.0% vs. 1.1%, respectively) during the study. Additionally, placebo patients were more likely to have potentially clinically significant orthostatic changes in pulse rate and in the combined criteria.

- A higher percentage of patients treated with quetiapine XR (15.2%) had weight gain (≥7%) at the end of treatment compared to the placebo-treated patients (10.0%).