Drug product:	Seroquel	**SYNOPSIS**	
Drug substance:	quetiapine fumarate		
Study code:	D1441C00150		
Date:	10 July 2008		

A 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

Study centers

This study was conducted at 59 international sites.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to assess the safety and tolerability of quetiapine in children and adolescent patients with bipolar I disorder and in adolescents with schizophrenia who were treated with doses of 400 mg/day to 800 mg/day for up to 26 weeks. The primary objective was assessed by:

- the incidence and nature of overall AEs
- the rate of patient withdrawal due to AEs
- the changes from the open-label (OL) baseline to Week 26 in clinical laboratory test results (eg, prolactin concentration), vital signs, weight, body mass index (BMI), electrocardiogram (ECG) results, and physical examination findings. The OL baseline was defined as the final assessment in the preceding double-blind study (Study 149 or Study 112).
- the changes from OL baseline to Week 26 in the Simpson-Angus Scale (SAS) total score, the Barnes Akathisia Rating Scale (BARS) global score, and the Abnormal Involuntary Movement Scale (AIMS) total score

- the proportion of patients treated with anticholinergic medication for emergent extrapyramidal symptoms (EPS)

The secondary objectives were as follows:

1. To evaluate the growth and development of patients receiving long-term treatment with quetiapine at doses of 400 mg/day to 800 mg/day, as assessed by change from OL baseline to Week 26 in the Tanner stage, initiation of or changes in menses for female patients, and changes from OL baseline to Week 26 in weight and BMI

2. To evaluate the level of functioning in patients receiving long-term treatment with quetiapine at doses of 400 mg/day to 800 mg/day, as assessed by changes from OL baseline to Week 26 in the Children's Global Assessment Scale (CGAS) score

Exploratory objectives were as follows:

1. To explore the long-term treatment effects of quetiapine at doses of 400 mg/day to 800 mg/day on the overall caregiver burden, as assessed by the change from OL baseline to Week 26 in the results of the Caregiver Strain Questionnaire (CGSQ)

2. To explore the long-term treatment effects of quetiapine at doses of 400 mg/day to 800 mg/day in the treatment of bipolar I disorder, as assessed by:

    - the change from OL baseline to Week 26 in the Young Mania Rating Scale (YMRS) total score

    - the change from OL baseline to Week 26 in the Clinical Global Impression - Bipolar (CGI-BP) Severity of Illness score

    - the CGI-BP Global Improvement score at Week 26

    - the percentage of patients with remission, defined as a YMRS total score ≤12 at Week 26

    - the percentage of patients with response, defined as a ≥50% reduction from OL baseline in the YMRS total score at Week 26

3. To explore the long-term treatment effects of quetiapine at doses of 400 mg/day to 800 mg/day in schizophrenia, as assessed by:

    - the change from OL baseline to Week 26 in the Positive and Negative Syndrome Scale (PANSS) total score

    - the change from OL baseline to Week 26 in the Clinical Global Impression (CGI) Severity of Illness score

    - the CGI Global Improvement score at Week 26

- the percentage of patients with response, defined as a ≥30% reduction from OL baseline in the PANSS total score at Week 26

Study design

This was a 26-week, multicenter, OL, uncontrolled safety and tolerability study of quetiapine in children and adolescents with bipolar I disorder and adolescents with schizophrenia. Patients entered after completing or discontinuing participation in 1 of 2 double-blind efficacy and safety studies (Study 149 or Study 112).

Target population and sample size

Male and female children and adolescents (aged 13 to 17 years at randomization of Study 112 or aged 10 to 17 years at baseline of Study 149) with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for schizophrenia or bipolar I disorder, as confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version (K-SADS-PL) at entry into the preceding double-blind Study 149 or Study 112, were recruited for this study. Prior participation in Study 149 or Study 112 for ≥14 days was required. Due to birthdays during this 26-week study occurring in patients who were 17 years old at entry into Study 149 or Study 112, the age range of patients in Study 150 was 10 to 18 years.

This study was designed in accordance with the criteria outlined in a Written Request from the FDA dated 11 February 2003 (and amended 7 May 2004 and 3 February 2005). As part of the request to provide pediatric information about quetiapine, the FDA asked that AstraZeneca collect "longer-term safety data, for a minimum duration of 6 months exposure to the drug." The selected study duration was in accordance with the criteria outlined in the Written Request; over 100 patients were exposed for at least 6 months.

Investigational product: dosage, mode of administration and batch numbers

All patients, regardless of the dose or previous treatment (placebo or quetiapine) in the acute feeder studies, began quetiapine treatment with a single 50-mg dose on the evening of Day 1. Beginning on Day 2, quetiapine was given twice daily, with dose escalation to reach 400 mg/day on Day 5. On Day 5 and thereafter, the target dose of 400 mg/day was to be maintained or could have been increased by no more than 100 mg/day up to 800 mg/day according to patient response and by investigator discretion. Patients were given total daily doses of at least 400 mg/day after Day 5. However, if there were specific tolerability concerns for an individual patient, a total daily dose as low as 200 mg was permitted. Quetiapine administration could have been changed to 3 times a day based upon the clinical judgment of the investigator. No more than four 100-mg tablets could be administered as a single dose.

AstraZeneca supplied quetiapine fumarate as 25 mg tablets (formulation F12804, batch numbers 6500J, MC4601) or 100 mg tablets (formulation F12689, batch numbers 6510J, 6512J, 6513J, 6514J, 6515J, KT4605, LK4601, LK4602, 7534K, 7536K).

Duration of treatment

26 weeks

Criteria for evaluation - efficacy (main variables)

- Secondary variable: Change from OL baseline to Week 26 in the CGAS total score.

- Exploratory variables: Change from OL baseline to Week 26 in the following assessment scores: YMRS; CGI-BP Severity of Illness; CGI-BP Global Improvement; proportion of patients with remission, defined as a YMRS total score ≤12 at Week 26; proportion of patients with response, defined as a ≥50% reduction from OL baseline in the YMRS total score at Week 26; PANSS; CGI Severity of Illness; CGI Global Improvement; and proportion of patients with response, defined as a ≥30% reduction from OL baseline in the PANSS total score at Week 26.

- Patient reported outcomes (exploratory): Change from OL baseline to Week 26 in overall caregiver burden, as assessed by the CGSQ total score.

Criteria for evaluation - safety (main variables)

- Primary variables: Incidence and nature of overall adverse events (AEs); rate of patient withdrawal due to AEs; changes from OL baseline to final visit in clinical laboratory test results (eg, prolactin concentration), vital signs, and ECG results; changes from OL baseline to final visit in weight, BMI, and physical examination findings; changes from OL baseline to Week 26 in SAS, BARS, and AIMS-7 scores; and the proportion of patients treated with anticholinergic medication for emergent EPS.

- Secondary variables: Changes from OL baseline to Week 26 in Tanner stage, weight, and BMI; proportion of female patients who initiate or have changes in menses at Week 26.

Statistical methods

Only descriptive techniques were used to summarize data in this OL study. Summaries of data were based on the safety population, which included all patients who took at least 1 dose of study drug.

Subject population

Of the 381 patients enrolled in this study, 380 patients received at least 1 dose of study drug (205 patients with bipolar I disorder and 175 patients with schizophrenia). The safety population had a mean age of approximately 14 years. Nearly 60% of the population was male, and approximately 70% was Caucasian. The demographic characteristics by diagnosis were similar to the total safety population, with the exception of mean age (bipolar I disorder patients, mean age 13.3 years; schizophrenia patients, mean age 15.7 years), as expected due to the different age ranges studied for each diagnosis (10-18 years old for bipolar I disorder

and 13-18 years old for schizophrenia). There were no notable differences in rates of study completion, reasons for discontinuation, or demographic characteristics when compared by previous treatment group (previous placebo compared with previous quetiapine) in the acute feeder studies. For both diagnoses, OL baseline disease characteristics were milder in the patients who had previously received quetiapine in the acute feeder studies compared with those who were previously treated with placebo during the acute feeder studies.

Summary of efficacy results

Evaluations of efficacy in this 26-week OL study were secondary to safety and were limited to descriptive statistics. As expected, patients who were previously treated with placebo during the acute feeder studies, and thus had not been exposed to quetiapine, had the greatest changes from baseline in this OL study. For bipolar I disorder and schizophrenia patients, efficacy measures continued to improve numerically for all variables after 26 weeks of OL treatment with quetiapine. The majority of bipolar I disorder patients (56.7%) achieved remission. The percentage of bipolar I disorder patients achieving response was higher from beginning of double-blind (BODB) baseline (67.4% of the total population) compared with the response from OL baseline (30.9%). Similarly, the percentage of schizophrenia patients achieving response was higher from BODB baseline (62.6% of the total population) compared with the response from OL baseline (17.4%).

Summary of safety results

The overall incidence of AEs in the total safety population was 84.5%, and 63.2% of patients had an AE that was considered related to study treatment. Serious AEs (SAEs) were experienced by 11.3% of patients, and 9.7% of patients experienced an AE that led to withdrawal from the study. There were no deaths during the study.

The most common AEs (ie, those occurring in >5% of the total population), as summarized by preferred term, are shown in Table S1.

Table S1 Number (%) of patients with the most commonly reported adverse events (safety population)

Preferred term	Total (N=380)	
	n	%
Somnolence	87	22.9
Headache	71	18.7
Sedation	54	14.2
Weight increased	51	13.4
Vomiting	41	10.8
Nausea	36	9.5
Dizziness	33	8.7
Fatigue	31	8.2

Preferred term	Total (N=380)	
	n	%
Insomnia	31	8.2
Increased appetite	27	7.1
Upper respiratory tract infection	26	6.8
Agitation	20	5.3
Irritability	19	5.0
Tachycardia	19	5.0

NOTE: This Table uses a cutoff of 5% for the total safety population.

Analysis of AEs indicated that nervous system events predominated. Somnolence, headache, sedation, weight increased, and vomiting were reported by at least 10% of the total population. Most AEs were judged to be mild or moderate in intensity by the investigator.

The incidences of AEs of prespecified special interest were less than 2%. These included AEs potentially associated with QTc prolongation, neutropenia, syncope, diabetes, and suicidality. Discontinuations due to AEs of special interest included neutropenia (1 patient), glycosylated hemoglobin increased (1 patient), syncope (1 patient), and 1 patient who discontinued due to AEs of suicidal ideation and suicide attempt.

Adverse events potentially associated with EPS were reported for 38 patients (10.0%). Approximately 94% of AEs potentially associated with EPS were judged to be mild or moderate in intensity by the investigator; 1 patient discontinued due to severe akathisia. Changes in EPS were also analyzed by several sensitive and objective scales. The majority of patients showed no change in EPS over the course of the study, as assessed by the SAS, AIMS-7, and BARS scales. The incidence of anticholinergic medication use for the treatment of emergent EPS during the study was 4.2%.

Mean changes from OL baseline to final visit for hematology and clinical chemistry parameters were small. Clinically important changes in laboratory values, reflected in changes from normal to pre-defined values of potential clinical importance and by AEs, occurred in ≤5% of the safety population for most parameters, with the exception of a higher incidence of potentially clinically important shifts to low HDL (14.9%), high triglycerides (10.2%), and high prolactin concentration (6.3%). In comparing hematology and clinical chemistry parameters between younger (10-12 years old) versus older (13-18 years old) bipolar I disorder patients, more older bipolar I disorder patients shifted from normal to high triglycerides and prolactin (14.5% and 6.1%, respectively) compared with younger bipolar I disorder patients (8.8% and 1.4%, respectively), and more younger bipolar I disorder patients shifted from normal to low ANC values (6.8%) compared to older bipolar I disorder patients (1.0%). In addition, mean increases in triglycerides were greater in older bipolar I disorder patients compared with younger bipolar I disorder patients.

Mean increases from OL baseline to final visit for vital signs and to Week 26 for ECG parameters were small. Pulse and heart rate elevations of potential clinical importance occurred in <10% of the total population and 19 subjects (5.0%) reported AEs of tachycardia. Shifts to potentially clinically important rapid pulse (standing and supine) occurred more frequently in older (13-18 years old) compared with younger (10-12 years old) bipolar I disorder patients. Shifts from normal to potentially clinically important low and potentially clinically important high systolic and diastolic blood pressures were observed in <10% of patients, with the exception of shifts to high standing diastolic blood pressure (14.0%).

Weight gain, as measured by increases from OL baseline in mean weight (3.7 kg) and BMI (0.9 kg/m^2), was observed after 26 weeks of OL treatment with quetiapine. Adverse events of weight increased occurred in 51 patients (13.4%), and 35.6% of patients experienced ≥7% weight gain after 26 weeks. The mean height of the safety population at OL baseline was 162 cm, and the mean change in height from OL baseline to the final visit was 1.7 cm. Most patients did not change Tanner stage during the study, and the majority of female patients in this study had normal menstruation cycles, indicating normal development of children and adolescents during 26 weeks of exposure to quetiapine.