Clinical Trial Disclosure Synopsis

Drug Substance	Quetiapine fumarate XR
Study Code	D144CC00005
Edition Number	1

A Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) Extended Release as Mono-therapy in the Treatment of Patients with Bipolar Depression

Study dates:	First patient enrolled: 21 December 2010
	Last patient last visit: 5 November 2012
Phase of development:	Therapeutic confirmatory (III)

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

Study centers

This study was conducted at 19 centers in China.

Publications

There were none at the time of writing this report.

Objectives and criteria for evaluation

Table S1 presents the study objectives and the respective outcome variables.

Table S1 Objectives and outcome variables

Priority (Type)	Objective	Outcome variable
Primary (Efficacy)	To evaluate the superior efficacy of quetiapine XR mono-therapy administered once daily, compared to placebo, in the treatment of depressive symptoms in patients with bipolar I disorder and bipolar II disorder	Change from baseline (Visit 2) to end of study (Week 8) in the MADRS total score
Secondary (Efficacy)	To evaluate the relative efficacy of quetiapine XR compared to placebo in achieving response in bipolar depression	MADRS total score response (patients with ≥50% reduction from baseline to Week 8 in MADRS total score)
Secondary (Efficacy)	To evaluate the relative efficacy of quetiapine XR compared to placebo in achieving remission in bipolar depression	MADRS total score remission (the proportion of patients with a MADRS total score ≤12 at Week 8 assessment)
Secondary (Efficacy)	To evaluate the relative efficacy of quetiapine fumarate XR compared to placebo from start to end of treatment of patients with bipolar depression	Change from baseline to each assessment in MADRS total score
Secondary (Efficacy)	To evaluate the efficacy of quetiapine XR compared to placebo in the treatment of depressive symptoms in patients with bipolar I disorder and bipolar II disorder	Change from baseline to Week 8 in HAM-D scores
Secondary (Efficacy)	To evaluate the relative efficacy of quetiapine XR compared to placebo in the treatment of overall clinical status of bipolar depression	Change from baseline to Week 8 assessment in the CGI-BP-S The proportion of patients at Week 8 with a CGI-BP-C of "much" or "very much" improved
Secondary (Efficacy)	To evaluate the efficacy of quetiapine XR compared to placebo in reducing suicidal ideation	Change from baseline to Week 8 in item 10 of MADRS for suicidal ideation
Secondary (Efficacy)	To evaluate the relative efficacy of quetiapine XR compared to placebo in preventing treatment-emergent mania/hypomania	Incidence of treatment-emergent mania (AE of mania or hypomania, defined as YMRS score ≥16 on 2 consecutive assessments or final assessment
Secondary (Safety)	To evaluate the safety and tolerability of quetiapine XR compared to placebo in the treatment of patients with bipolar depression	Incidence of AEs; the change from enrollment or baseline in laboratory values, vital signs, weight and the proportion of patients with a ≥7% increase in weight from baseline to final visit; the change in SAS score and BARS score to final visit and AEs of EPS; physical examinations; and ECG

AE Adverse event; BARS Barnes Akathisia Rating Scale; CGI-BP-C Clinical Global Impression-Bipolar-Change from preceding phase; CGI-BP-S Clinical Global Impression-Bipolar-Severity of illness; ECG Electrocardiogram; EPS Extrapyramidal symptoms; HAM-D Hamilton Rating Scale for Depression; MADRS Montgomery-Asberg Depression Rating Scale; SAS Simpson-Angus Scale; XR Extended release; YMRS Young Mania Rating Scale.

Study design

This multi-center, parallel-group, fixed-dose Phase III study compared the short-term efficacy and safety of quetiapine extended release (XR) with placebo in the treatment of patients with bipolar depression. Eligible patients were randomly assigned (ratio 1:1), using an interactive voice response system/interactive web response system and a computer-based randomization system, to receive 8 weeks of double-blind treatment (using appropriate blinding methods) with either quetiapine XR 300 mg once daily or placebo.

Target subject population and sample size

The target population comprised Chinese male and female patients aged 18 to 65 years, inclusive, who met the Diagnostic and Statistical Manual of Mental Disorders-4th edition criteria for bipolar I disorder or bipolar II disorder, most recent episode depressed (296.5x and 296.89x), had a Hamilton Rating Scale for Depression (HAM-D) 17-item total score of ≥20, and had a HAM-D item 1 (depressed mood) score ≥2 at enrollment and randomization. In order to yield approximately 266 evaluable patients, 296 patients were planned to be randomized after successful enrollment (148 patients in the quetiapine XR 300 mg group and 148 patients in the placebo group).

Investigational product and comparator: Dosage, mode of administration, and batch numbers

Patients were provided blinded quetiapine XR and placebo to match during the treatment phase. Quetiapine XR was administered orally, once daily in the evening. The dose was 50 mg on Day 1, 100 mg on Day 2, and 200 mg on Day 3. From Day 4 to Day 56, the dose of quetiapine XR was 300 mg/day. Matching placebo was administered. The following batches of investigational products were used: FY301X (quetiapine XR 50 mg); FY311X and GH975X (quetiapine XR 300 mg); FY897X (placebo to match quetiapine XR 50 mg); and FY900X (placebo to match quetiapine XR 300 mg).

Duration of treatment

This study consisted of an enrollment period of up to 28 days and an 8-week treatment period.

Statistical methods

All statistical tests were 2-sided with a significance level of 5%. Where appropriate, nominal 95% confidence intervals and p-values were presented, with no adjustment for multiplicity issues. The change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score (observed cases) was analyzed by means of a mixed model repeated measures (MMRM) analysis. The full analysis set (FAS) was used for all efficacy data, and analysis based on the per-protocol (PP) population was used as a consistency check. An analysis of covariance (ANCOVA) using last observation carried forward (LOCF), adjusting for the same covariates as the MMRM model, was used as a sensitivity analysis. All secondary analyses were made in order to yield supportive evidence that quetiapine XR 300 mg was more effective than placebo.

Subject population

A total of 361 patients were enrolled at 19 centers in China. The first patient was enrolled on 21 December 2010, and the last visit for the last patient in the study was completed on 5 November 2012. Overall, 296/361 patients were randomized to receive study treatment (148 patients in each treatment group). The majority of the randomized patients completed study treatment: 112/148 (75.7%) patients in the quetiapine XR group and 98/148 (66.2%) patients in the placebo group. Fewer patients in the quetiapine XR group than in the placebo group discontinued study treatment due to lack of therapeutic response (2 patients versus 11 patients, respectively). In the quetiapine XR group, patient decision (22 patients) and adverse events (AEs) (9 patients) were the most common reason for withdrawal from the study. In the placebo group, patient decision (23 patients) and lack of therapeutic response (11 patients) were the most common reasons for withdrawal from the study. The most common important protocol deviation identified in this study was final MADRS assessment being performed >5 days after the last dose of study treatment (5% patients in each treatment group).

The distribution ratio of patients with bipolar I and bipolar II disorder was 1:1 among all randomized patients. The number of female patients (145/279 patients) was higher than the number of male patients (134/279 patients). The mean age at study entry was 33.1 years (range: 18 years to 64 years). The majority of patients (207/279 patients) were in the age group of 18 years to 39 years. The majority of patients (174/279 patients) were in the body mass index group of 18.5 kg/m^2 to <25 kg/m^2. The median duration since bipolar diagnosis was 1 year in both treatment groups. The study patients had moderate to severe depression as shown by validated scales of depression at baseline. The number of patients using medication before study entry and the types of medications used were consistent with that expected in a relatively young Chinese population with a short duration of diagnosis of bipolar depression. The study treatment compliance was >90% in both treatment groups. Treatment with quetiapine XR was associated with lower concomitant use of lorazepam and sleep medication and higher concomitant use of anti-cholinergic medication than treatment with placebo.

Summary of efficacy results

The least squares (LS) mean change in MADRS total score from baseline to Week 8 was significantly greater in the quetiapine XR group than in the placebo group (-18.48 versus -15.27, respectively, with an effect size of -3.22; p=0.004). All 10 individual MADRS item scores were reduced more in the quetiapine XR group than in the placebo group. The LS mean change in MADRS item scores from baseline to Week 8 was significantly greater in the quetiapine XR group than in the placebo group for Inner tension (p=0.013), Reduced sleep (p<0.001), Reduced appetite (p=0.020), Concentration difficulties (p=0.039), and Suicidal thoughts (p=0.005). For the remaining 5 MADRS items of Apparent sadness, Reported sadness, Lassitude, Inability to feel, and Pessimistic thoughts, the difference between the treatment groups trended in the same direction, although it was not statistically significant.

A significantly greater reduction in the MADRS total score in the quetiapine XR group compared with the placebo group was apparent as early as Week 1 (LS mean change

-5.62 versus -4.14, respectively; p=0.029), and this remained consistent at each subsequent assessment point up until Week 8. At Week 8, a significantly higher percentage of patients in the quetiapine XR group than in the placebo group achieved response (66.9% versus 44.3%, respectively, p<0.001) and achieved remission (63.3% versus 42.1%, respectively; p<0.001).

The LS mean change in HAM-D total score from baseline to Week 8 was significantly greater in the quetiapine XR group than in the placebo group (-15.16 versus -12.92, respectively, with an effect size of -2.24; p=0.007). The LS mean change in the CGI-BP-S score from baseline to Week 8 was significantly greater in the quetiapine XR group than in the placebo group for overall bipolar illness (-2.24 versus -1.73, respectively; p=0.003) and for depression (-2.28 versus -1.81, respectively; p=0.007). At Week 8, the percentage of patients with CGI-BP-C scores of "much improved" or "very much improved" was significantly higher in the quetiapine XR group than in the placebo group (65.47% versus 46.43%, respectively; p=0.004).

Treatment with quetiapine XR was demonstrated to be more effective than treatment with placebo in reducing suicidal ideation in patients with bipolar depression (LS mean change -0.98 versus -0.76, respectively; p=0.005). The difference between the treatment groups in the percentage of patients who were less likely to have treatment-emergent mania/hypomania was statistically not significant (0.7% in the quetiapine XR group versus 2.9% in the placebo group; p=0.233).

Summary of safety results

Overall, 294/296 patients who were randomized into the study received ≥1 dose of study treatment and were included in the safety analysis set (147/148 patients in each treatment group). The average number of days on randomized treatment was higher in the quetiapine XR group (48.3 days) than in the placebo group (44.9 days).

The percentage of patients with any AE was higher in the quetiapine XR group (96/147 [65.3%] patients) than in the placebo group (72/147 [49.0%] patients). A higher proportion of patients in the quetiapine XR group (80/147 patients) than in the placebo group (41/147 patients) reported AEs that were considered by the investigator to be causally related to study treatment. The most common AEs reported in the study were consistent with the known safety profile of quetiapine. The majority of reported AEs had resolved by the end of the study. The most common AEs reported by ≥10% patients in the quetiapine XR group were related to Nervous system disorders (67/147 [45.6%] patients), Gastrointestinal disorders (39 [26.5%] patients), and General disorders and administration site conditions (21 [14.3%] patients). The 5 most common AEs reported by patients in this study were somnolence, dizziness, dry mouth, constipation, and fatigue. All these AEs were reported by a higher proportion of patients in the quetiapine XR group (24.5%, 19.7%, 14.3%, 11.6%, and 8.8%, respectively) than by patients in the placebo group (7.5%, 10.9%, 4.8%, 2.7%, and 1.4%, respectively).

There were no deaths reported in this study. Three patients (all from the placebo group) experienced serious adverse events, and 17 patients had an AE leading to discontinuation of

treatment (DAE; 9/147 [6.1%] patients in the quetiapine XR group and 8/147 patients [5.4%] in the placebo group). Except 1 patient in each treatment group, all DAEs were considered to be causally related to study treatment as assessed by the investigator. The majority of the patients reported mild AEs (110/294 [37.4%] patients) or moderate AEs (56/294 [19.0%] patients). In the quetiapine XR group, the majority or all of the reported AEs were judged by the investigator to be causally related to study treatment (somnolence [30/36 patients], dizziness [23/29 patients], dry mouth [17/21 patients], constipation [17/17 patients], and fatigue [13/13 patients]).

AEs related to extrapyramidal symptoms (EPS) were low in both treatment groups, and all of these AEs were reported as mild to moderate. A slight increase in the incidence of AEs associated with EPS was noted in the quetiapine XR group. The incidence of AEs of treatment-emergent mania was low during this study. The proportion of patients with weight increase of ≥7% (from baseline to Week 8) was higher in the quetiapine XR group compared with the placebo group, which is in line with the known safety profile of quetiapine. There were no clinically important differences between treatment groups from baseline to last observation for any hematology assessments, clinical chemistry assessments, vital signs, or electrocardiogram. The majority of patients in both treatment groups had no change from baseline to last observation in the Simpson-Angus Scale total scores and the Barnes Akathisia Rating Scale global assessment scores.