Drug product:	Seroquel XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate extended-release		
Edition No.:	Final		
Study code:	D144CC00004		
Date:	20 November 2007		

A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL®) Sustained-release as Monotherapy in Adult Patients with Acute Bipolar Mania

Study center(s)

This study was conducted at 50 centers in the United States; 48 sites actually enrolled patients.

Publications

None.

Study dates		**Phase of development**
First patient enrolled	22 December 2006	Therapeutic confirmatory (III)
Last patient completed	31 July 2007	

Objectives

Primary objective

The primary objective was to demonstrate superior efficacy of quetiapine extended-release (XR)[1] formulation administered once daily (QD) as monotherapy at a dose of 400 to 800 mg

[1] Quetiapine XR was referred to as quetiapine sustained release (SR) in the protocol.

per day compared to placebo in decreasing the manic symptoms in patients with bipolar manic or mixed episode, after 3 weeks of treatment.

Secondary objectives

- To evaluate the efficacy and time course of quetiapine XR compared to placebo in decreasing the manic symptoms in patients with bipolar mania at each visit, including Day 4;
- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing agitation and aggression in patients with bipolar mania;
- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing psychotic symptoms in patients with bipolar mania;
- To evaluate the efficacy of quetiapine XR compared to placebo in decreasing depressive symptoms in patients with bipolar mania;
- To evaluate the safety and tolerability of quetiapine XR QD in patients with bipolar mania.

Study design

This was a 3-week, multicenter, randomized, parallel-group, double-blind, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XR with flexible doses in the range of 400 to 800 mg or placebo given QD in the evening in the treatment of patients with bipolar I disorder with an acute manic episode. This study consisted of an enrollment period of up to 35 days and a 3-week treatment period with 1 of 2 treatment regimens (quetiapine XR 400 to 800 mg QD or placebo). Quetiapine XR was not down-titrated at the end of the study.

Target patient population

The per-protocol plan was to enroll approximately 447 patients, with approximately 313 randomized to receive study treatment to obtain 288 evaluable patients (ie, patients receiving at lease 1 dose of investigational product who had at least 1 post-baseline Young Mania Rating Scale [YMRS] assessment).

Patients were male or female, 18 to 65 years of age, inclusive with a diagnosis of bipolar I disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Text Revision 4th Edition (DSM-IV-TR 2000) criteria of 296.4x (Bipolar I Disorder, Most Recent Episode Manic) or 296.6x (Bipolar I Disorder, Most Recent Episode Mixed) confirmed by the amended version of the Structured Clinical Interview for DSM-IV (SCID). Patients who experienced rapid cycling as defined in DSM-IV-TR were eligible to participate in the study.

To be enrolled in the study, patients must have had at least 1 bipolar manic or mixed episode in the prior 5 years, a YMRS total score at screening of ≥20 with a score of ≥4 on 2 of 4 of the following core YMRS items: irritability, speech, content, and disruptive/aggressive behavior;

and must have a Clinical Global Impression – Bipolar – Severity of Illness (CGI-BP-S) score of ≥4 on the overall bipolar illness item at randomization (Visit 2).

Both hospitalized and non-hospitalized patients were enrolled in the study. Patients were hospitalized at randomization and for at least the first 4 days of treatment.

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

Quetiapine XR was given at a dose of 300 mg (one 300-mg tablet) on Day 1 and at 600 mg (three 200-mg tablets) on Day 2. From Day 3 to Day 21, quetiapine XR was given in flexible doses of 400 to 800 mg (two to four 200-mg tablets). Quetiapine XR was orally administered QD, in the evening. Batch numbers used in this study were LA4600 (200-mg tablets) and LH 4708 (300-mg tablets).

Comparator, dosage and mode of administration

Placebo matching quetiapine XR 300-mg and 200-mg tablets was orally administered QD, in the evening. Batch numbers used in this study were CE889X (placebo matching quetiapine XR 200-mg tablets) and CE891X (placebo matching quetiapine XR 300-mg tablets).

Duration of treatment

Eligible patients had an up to 28-day washout period and an overall enrollment period of up to 35 days. Following the washout and enrollment period, patients were randomized and entered the 3-week treatment period.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

– **Primary outcome variable:**

- Change from baseline (randomization [Visit 2]) to final visit (Visit 6) in the YMRS total score.

– **Other variables supporting the primary objective:**

- Change from baseline (randomization [Visit 2]) to final visit in YMRS total score response (patients with ≥50% reduction of YMRS);
- YMRS total score remission (patients with a YMRS total score ≤12 at final visit [Visit 6]);
- Change from baseline (randomization [Visit 2]) to final visit (Visit 6) Clinical Global Impression – Bipolar – Severity (CGI-BP-S);
- Final visit (Visit 6) assessment in Clinical Global Impression – Bipolar – Change (CGI-BP-C);

- Proportion of patients at final visit (Visit 6) with a CGI-BP-C of "much improved" or "very much improved" in overall assessment.

– **Secondary outcome variables:**

- Change from baseline (randomization [Visit 2]) to each visit (including Day 4) in the YMRS total score;

- Score change from baseline (randomization [Visit 2]) to final visit (Visit 6) of Items 5 Irritability, or 9 Disruptive – Aggressive Behavior, of the YMRS;

- Score change from baseline (randomization [Visit 2]) to final visit (Visit 6) of Item 8, Content (Thought Content) of the YMRS;

- Change from baseline (randomization [Visit 2]) to final visit (Visit 6) of the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Safety

- Change from baseline (defined as the sample/procedure taken closest to the randomization visit) in physical examinations, laboratory values (including glucose/lipids), vital signs, electrocardiogram (ECG);

- Adverse events (AEs), including somnolence, extrapyramidal symptoms (EPS) including akathisia, diabetes mellitus, QT prolongation, neutropenia/agranulocytosis, and suicidality;

- Serious adverse events (SAEs);

- Treatment-emergent EPS, as measured by the change in Simpson Angus Scale (SAS) total score and Barnes Akathisia Rating Scale (BARS) global assessment score from baseline (randomization [Visit 2]) to final visit (Visit 6) and AEs of EPS;

- Incidence of treatment-emergent depression (AE of depression or depressed mood, and or MADRS scores ≥18 on 2 consecutive assessments or on the final assessment);

- Proportion of patients withdrawing due to AEs;

- AEs leading to withdrawal;

- Change in weight from baseline (randomization [Visit 2]) to final visit (Visit 6);

- Proportion of patients with a ≥7% increase in weight from baseline (randomization [Visit 2]) to final visit (Visit 6);

- Incidences of suicidality using a suicidality classification similar to the one established by Columbia University.

Statistical methods

The power was set at 90% for a 2-sided test at α=0.05 for the comparison between quetiapine XR and placebo, using a 5-unit difference from placebo (YMRS total score) with a pooled standard deviation of 13.

Efficacy analyses were based on the following patient populations, which were finalized before unblinding of the data.

- The modified intention-to-treat (MITT) analysis set (full analysis set) included all randomized patients who received at least 1 dose of study treatment and who had baseline (randomization [Visit 2]) values and at least one post-randomized YMRS assessment, classified by the randomized treatment assignment. Data from the MITT analysis set were used for analysis of the efficacy objectives.

- The per protocol (PP) analysis set, a subset of the MITT analysis set, included patients who had no major protocol violations or deviations affecting efficacy. Data from this population were used for a consistency check only for the analysis of the primary objective.

- The safety analysis set included all randomized patients who took ≥1 dose of investigational product, classified according to the treatment actually received.

All statistical tests were 2-sided with a significance level of 5%, ie α=0.05. Where appropriate, 95% confidence intervals are presented. Missing data resulting from patient withdrawal were imputed using a last observation carried forward (LOCF) approach. Patients with post-randomization data had their last study assessment carried forward as the final visit assessment for analysis. Also, descriptive statistics are provided for all variables.

Patient population

Baseline demographic and weight characteristics and patient disposition are shown in Table S1.

Table S1 Demographic and weight characteristics, and disposition (MITT population)

Demographic or Baseline Characteristic	Quetiapine XR (N=149)	Placebo (N=159)
Gender, n (%)		
Male	92 (61.7)	93 (58.5)
Female	57 (38.3)	66 (41.5)
Age (years)		
Mean ± SD	41.3 (10.3)	40.8 (10.7)
Median	42.0	43.0
Min, Max	19, 64	19, 63
Age category (years), n (%)		
18 - 39	61 (40.9)	65 (40.9)
40 - 65	88 (59.1)	94 (59.1)
Race, n (%)		
Caucasian	72 (48.3)	73 (45.9)
Black/ African American	70 (47.0)	77 (48.4)
American Indian/ Alaskan Native	3 (2.0)	0
Asian	1 (0.7)	1 (0.6)
Native Hawaiian/ Pacific Islander	0	1 (0.6)
Other	3 (2.0)	7 (4.4)
Weight (kg)		
Mean (SD)	91.8 (23.7)	91.0 (24.8)
Median	90.0	86.5
Min, max	48, 207	44, 189
Waist circumference (cm)		
n	149	156
Mean (SD)	100.0 (19.8)	100.0 (20.7)
Median	98.0	97.0
Min, max	66, 183	64, 183

Table S1 Demographic and weight characteristics, and disposition (MITT population)

Demographic or Baseline Characteristic	Quetiapine XR (N=149)	Placebo (N=159)
BMI (kg/m^2)		
n	149	159
Mean (SD)	31.0 (9.0)	30.9 (8.2)
Median	29.3	28.8
Min, max	19, 78	17, 65
BMI category, n (%)		
0 to <18.5	0	2 (1.3)
18.5 to <25	39 (26.2)	36 (22.6)
25 to <30	37 (24.8)	47 (29.6)
30 to <40	53 (35.6)	50 (31.4)
≥40	20 (13.4)	24 (15.1)
Disposition		
N (%) of patients who completed	111 (71.6)	116 (72.0)
N (%) of patients who withdrew	44 (28.4)	45 (28.0)
N analyzed for safety[a]	151 (97.4)	160 (99.4)
N analyzed for efficacy (MITT)	149 (96.1)	159 (98.8)
N analyzed for efficacy (PP)	124 (80.0)	129 (80.1)

BMI Body mass index. MITT Modified intention-to-treat. n Number of patients. N Number of patients in treatment group. PP Per Protocol. SD Standard deviation. XR Extended-release.

[a] Number of patients who received at least 1 dose of study drug.

Note: Denominators are N in treatment group by gender and characteristic.

In the MITT population, the 2 treatment groups were well matched with respect to age, race, and weight. Overall, a higher percentage of patients were male (60.1%) and the mean age was 41 years. Median weight and BMI were slightly lower in the placebo group compared to the quetiapine XR group (90.0 kg and 29.3 kg/m^2 for the quetiapine XR group and 86.5 kg and 28.8 kg/m^2 for the placebo group, respectively). By BMI category, there were more patients in the 25 to <30 kg/m^2 category for placebo (29.6%) than quetiapine XR (24.8%). The 30 to <40 kg/m^2 category had slightly more quetiapine XR patients (35.6%) than placebo patients (31.4%).

Baseline disease characteristics and psychiatric history are presented in Table S2.

Table S2 Baseline disease characteristics and psychiatric history (MITT population)

Baseline disease characteristics	Quetiapine XR (N=149)	Placebo (N=159)
Baseline YMRS score		
Mean (SD)	28.8 (5.4)	28.4 (5.1)
Min, max	20, 47	20, 47
Baseline CGI-BP-S depression score		
n	148	159
Mean (SD)	2.4 (1.2)	2.4 (1.2)
Min, max	1, 5	1, 5
Baseline CGI-BP-S mania score		
n	148	159
Mean (SD)	4.5 (0.7)	4.5 (0.7)
Min, max	4, 7	4, 7
Baseline CGI-BP-S overall bipolar illness score		
n	148	159
Mean (SD)	4.5 (0.7)	4.5 (0.7)
Min, max	4, 7	4, 7
Baseline MADRS score		
n	148	159
Mean (SD)	14.3 (7.0)	14.6 (6.4)
Min, max	0, 38	4, 34
Current episode, n (%)		
Manic	86 (57.7)	88 (55.3)
Mixed	63 (42.3)	71 (44.7)
Psychiatric history		
Rapid cycling[a], n (%)	45 (30.2)	52 (32.7)
Years since bipolar diagnosis		
Median	18	17
Min, max	1.0, 50.0	2.0, 45.0

Table S2 Baseline disease characteristics and psychiatric history (MITT population)

Baseline disease characteristics	Quetiapine XR (N=149)	Placebo (N=159)
Duration of present mania episode (weeks)		
n	146	154
Median	4	4
Min, max	0.1, 29.7	0.1, 44.9
Attempted suicide, n (%)		
Yes	84 (56.4)	91 (57.2)
No	65 (43.6)	68 (42.8)

CGI-BP-S Clinical Global Impression – Bipolar -Severity of illness. MADRS Montgomery-Åsberg Depression Rating Scale. n Number of patients. N Number of patients in treatment group. SD Standard deviation. XR Extended-release. YMRS Young Mania Rating Scale.

[a] Defined as ≥4 and ≤8 mood episodes in the past year.

The 2 treatment groups were well-matched with respect to baseline disease characteristics. The majority of patients in both treatment groups had only manic episodes (versus mixed) at baseline (58% and 55% in the quetiapine XR and placebo groups, respectively); approximately 30% and 33% of patients in the quetiapine XR and placebo groups, respectively, had rapid cycling. Mean baseline YMRS scores were similar (28.8 and 28.4 for the quetiapine XR and placebo groups, respectively). Study patients in both treatment groups had greater severity of illness for mania in comparison with depression. The mean baseline CGI-BP-S score for mania was 4.5 in each treatment group and the mean CGI-BP-S score for depression was 2.4 in each treatment group. Mean baseline MADRS scores were also low at 14.3 (range 0 to 38) and 14.6 (range 4 to 34) for the quetiapine XR and placebo groups, respectively.

Efficacy results

Key efficacy results are presented for the MITT population in Table S3.

Table S3 Key efficacy results (LOCF, MITT population)

Outcome variable	Quetiapine XR (N=149)		Placebo (N=159)		p-value at Day 4, Week 3
	Day 4	Week 3	Day 4	Week 3	
YMRS change , LS mean (SE)	-9.89 (0.79)	-14.34 (0.91)	-6.87 (0.77)	-10.52 (0.88)	<0.001, <0.001
Proportion with ≥50% YMRS response, n (%)	33 (22.6)	82 (55.0)	24 (15.2)	53 (33.3)	0.086, <0.001

Table S3 Key efficacy results (LOCF, MITT population)

Outcome variable	Quetiapine XR (N=149)		Placebo (N=159)		p-value at Day 4, Week 3
	Day 4	Week 3	Day 4	Week 3	
Proportion with YMRS remission (total score <=12), n (%)	27 (18.5)	62 (41.6)	20 (12.7)	44 (27.7)	0.112, 0.006
CGI-BP-S overall LS mean change from baseline (SE)	-0.81 (0.09)	-1.51 (0.11)	-0.56 (0.09)	-1.02 (0.11)	0.001, <0.001
CGI-BP-C overall, LS mean (SE)	2.86 (0.09)	2.58 (0.12)	3.32 (0.09)	3.18 (0.12)	<0.001, <0.001
CGI-BP-C "much improved" or "very much improved", n (%)	44 (30.1)	80 (53.7)	23 (14.6)	52 (32.7)	0.001, <0.001

CGI-BP-S Clinical Global Impression - Bipolar - Severity of Illness. CGI-BP-C Clinical Global Impression – Bipolar – Change. LOCF Last observation carried forward. LS Least square. MITT Modified intention-to-treat. N Number of patients in treatment group. SE Standard error. XR Extended-release. YMRS Young Mania Rating Scale.

Quetiapine XR monotherapy at a dose of 400 to 800 mg QD for 3 weeks of treatment in patients with bipolar I mania (both manic and mixed at baseline) was superior to placebo in reducing the level of mania symptoms as measured by the change from baseline on the YMRS total score as early as Day 4 and continuing through the end of treatment ($p \leq 0.003$). The therapeutic effects of quetiapine XR were not restricted to any subgroup examined (gender, age group, race, manic/mixed episode, rapid/non-rapid cycling).

When analyzed by episode subgroup (patients with mixed versus only manic episodes at baseline), the MMRM results using OC data for the MITT population showed improvement in YMRS for both subgroups; the difference was statistically significant in favor of quetiapine XR over placebo for the manic subgroup ($p \leq 0.001$) but not for the mixed subgroup ($p=0.107$) at Week 3. The analysis by rapid cycling subgroups also showed improvement in YMRS for both subgroups; the difference was statistically significant in favor of quetiapine XR over placebo for the non-rapid cycling subgroup ($p<0.001$) but not for the rapid cycling subgroup ($p=0.056$).

Analysis of other secondary outcome variables also supported the superiority of quetiapine XR 400 to 800 mg QD over placebo in the treatment of mania in patients with bipolar disorder. The proportions of patients showing ≥50% reduction in YMRS total score (responders) and a YRMS total score ≤12 (remission) were statistically significantly higher for the quetiapine XR group compared to the placebo group by Day 8 (Week 1) and at the end of treatment ($p \leq 0.024$). The changes in CGI -BP-S and CGI -BP-C overall illness scores were statistically significant in favor of quetiapine XR beginning at Day 4 and continuing to the end of treatment ($p \leq 0.011$) with the exception of CGI-BP-C overall illness score at Day 15 ($p=0.058$). Quetiapine XR patients were2.44 times more likely to have CGI-BP-C for overall

bipolar illness score of "much improved" or "very much improved" as placebo patients beginning at Day 4 and continuing to the end of treatment ($p<0.001$).

For the 4 key individual YMRS item scores used for eligibility criteria, including those related to secondary efficacy assessments (irritability, speech, thought content, and disruptive-aggressive behavior), all were reduced more by quetiapine XR treatment than by placebo treatment. Statistically significant separation from placebo was observed in the quetiapine XR group ($p\leq0.011$) with the only exception being disruptive-aggressive behavior ($p=0.063$).

Quetiapine XR monotherapy at a dose of 400 to 800 mg QD for 3 weeks was also superior to placebo in decreasing depressive symptoms in patients with bipolar I mania as measured by the change from baseline in MADRS total score beginning at Day 4 and continuing to the end of treatment ($p\leq0.022$).

Safety results

For patients treated with quetiapine XR, the mean daily dose over the treatment period was 603.8 mg with 47% of patients having a final dose level of 600 mg/day; approximately 22% and 29% of patients had final dose levels of 400 and 800 mg/day, respectively.

A summary of AEs is presented in Table S4.

Table S4 Overview of adverse events (safety population)

AE category	Number (%) of patients[a]			
	Quetiapine XR (N=151)		Placebo (N=160)	
Any AE	128	(84.8)	107	(66.9)
Any AE with an outcome of death	0		1	(0.6)
Any SAE	6	(4.0)	13	(8.1)
Any SAE leading to discontinuation of treatment	4	(2.6)	9	(5.6)
Any non-serious AE leading to discontinuation of treatment	3	(2.0)	4	(2.5)
Any other significant AE[b]	0		1	(0.6)

AE Adverse event. N Number of patients in treatment group. SAE Serious adverse event. XR Extended-release.

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Any AE that led to dose of treatment being temporarily stopped, or deemed by the sponsor to be significant, excluding AEs reported as SAEs or led to discontinuation of treatment.

The percentage of patients with AEs was higher in the quetiapine XR (84.8%) than the placebo group (66.9%); however, the incidences of SAEs and discontinuations due to SAEs were higher in the placebo group (8.1% and 5.6%, respectively) compared with the quetiapine XR group (4.0% and 2.6%, respectively). The percentages of patients with discontinuation of

treatment due to non-serious AEs were comparable between the 2 treatment groups (2.0% in the quetiapine XR group and 2.5% in the placebo group). There was one "unexplained" death (placebo group).

The most common AEs were sedation, dry mouth, and somnolence, and all were reported more frequently in the quetiapine XR group (34.4%, 33.8%, and 16.6%, respectively) compared with placebo (7.5%, 6.9%, and 4.4%, respectively). Among AEs reported by >5% of patients in any group, AEs reported by at least twice as many patients in the quetiapine XR group compared to placebo included sedation, dry mouth, somnolence, constipation, dizziness, and weight increased.

Mean changes from baseline in glucose- and insulin-related laboratory variables were generally higher for the quetiapine XR-treated patients compared to placebo for patients both with and without diabetic risk factor(s) and for patients with diabetes mellitus; there was a large variability in results. For patients with diabetic risk factors at baseline, the incidence of clinically-important glucose values ≥100 and <126 mg/dL at Week 3 was lower in the quetiapine XR than the placebo group (46.4% vs. 54.4%); however, a greater percentage of patients in the quetiapine XR group had clinically-important glucose values ≥126 mg/dL compared with patients in the placebo group (10.1% vs. 4.4%). The incidence of clinically-important HbA_{1c} values (>7.5%) was similar between the 2 treatments (4.3% and 2.9%). For patients with diabetes mellitus at baseline, the incidences of clinically-important glucose values ≥126 mg/dL and >200 mg/dL were also higher in the quetiapine XR group compared to the placebo group (57.1% vs. 33.3% and 28.6% vs. 0, respectively); none of these patients had clinically-important HbA_{1c} values. A higher frequency of high glucose or HbA_{1c} was not observed in patients with no diabetic risk factors at baseline.

Patients treated with quetiapine XR showed a slight mean increase in body weight consistent with findings of this treatment in other patient populations (1.3 kg for quetiapine XR and 0.1 kg for placebo). Increases in weight ≥7% were observed in 7 (5.1%) patients in the quetiapine XR group; no increases ≥7% occurred in placebo patients. There was no differential shift to ≥3 metabolic risk factors at end-of-treatment with quetiapine XR.

An increase in the incidence in the composite of AEs potentially related to EPS was noted for the quetiapine XR group compared with the placebo group (6.6% vs. 3.8%). The incidences of individual AEs potentially related to EPS were low in both treatment groups. No AEs were encoded to QT prolongation. There were no AEs potentially related to neutropenia/agranulocytosis during the study; however, clinically laboratory assessments showed that 3 patients (2 quetiapine XR and 1 placebo) had shifts in neutrophil values from non-clinically significant at baseline to clinically-important low values ($<1.5 \times 10^9$/L) at the end of treatment.

Treatment-emergent depression, as defined by criterion of MADRS and AEs relating to depression, was reported for 1 patient in the placebo group. Patients in the placebo group showed a slightly higher incidence of suicidal behavior/ideation and possible suicidal

behavior/ideation than patients treated with quetiapine XR (3.1% in the placebo group vs.1.3% in the quetiapine XR group).