Drug product:	Seroquel XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate extended-release		
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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 Depression

Study center(s)

This study was conducted at 64 study centers in the United States (US). Sixty-one (61) sites completed procedures and received drug; 3 sites did not enroll patients.

Publications

There were no publications based on this study by the date of final approval.

Study dates		**Phase of development**
First patient enrolled	01 December 2006	Therapeutic confirmatory (III)
Last patient completed	21 June 2007	

Objectives

The primary objective of this study was to evaluate whether quetiapine fumarate extended-release (XR)[1] formulation at a dose of 300 mg once daily (QD) demonstrated superior efficacy compared to placebo in patients with bipolar depression, after 8 weeks of treatment.

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[1] Referred to as quetiapine sustained-release (SR) in the protocol.

Secondary objectives were:

- To evaluate whether quetiapine XR is effective in decreasing depressive symptoms in both patients with rapid and non-rapid cycling
- To evaluate whether quetiapine XR is superior to placebo in achieving remission in bipolar depression
- To evaluate whether quetiapine XR is superior to placebo in achieving response in bipolar depression
- To evaluate the efficacy of quetiapine XR compared to placebo in the treatment of a broad range of symptoms of bipolar depression
- To evaluate the safety and tolerability of quetiapine XR QD in patients with bipolar depression.

Study design

This was an 8-week multicenter, double-blind, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XR 300 mg QD given in the evening as monotherapy in the treatment of patients with an acute depressive episode in the framework of bipolar I or II disorder. This study consisted of an up to 35-day enrollment period followed by an 8-week treatment period with 1 of 2 treatment regimens (quetiapine XR 300 mg or placebo). Quetiapine XR was not down-titrated at the end of the study.

Target patient population and sample size

The per protocol plan was to enroll approximately 400 patients, with approximately 280 randomized to receive study treatment to obtain 266 evaluable patients (ie, patients receiving at lease 1 dose of investigational product that had at least 1 post-baseline MADRS assessment).

Patients were male or female outpatients (not hospitalized), 18 to 65 years of age, inclusive, with a diagnosis of bipolar I or bipolar II disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Text Revision 4th Edition (DSM IV TR) criteria most recent episode depressed (296.50-296.54 and 296.89 respectively) confirmed by the amended version of the Structured Clinical Interview for DSM-IV-TR. Patients who experienced rapid cycling course, defined as ≥4 episodes of mood disturbance but ≤8 episodes in the previous 12 months (mood episode defined as depressed, manic, mixed, or hypomanic) were allowed to participate.

To be enrolled in the study, patients must have had a Hamilton Rating Scale for Depression (HAM-D, 17-item) total score of ≥20, a HAM-D Item 1 (depressed mood) score ≥2 at enrollment (Visit 1) and randomization (Visit 2) and have had a Young Mania Rating Scale (YMRS) ≤12 at enrollment (Visit 1) and randomization (Visit 2).

In order to meet the statistical requirements of the study, it was estimated that a total of approximately 400 patients were required for enrollment. It was also anticipated that 280 patients would be randomized, resulting in 266 evaluable patients.

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

Quetiapine XR or placebo matching quetiapine XR tablets 50 mg, 200 mg, and 300 mg were orally administered QD, in the evening.

Duration of treatment

Eligible patients had a washout and enrollment period of up to 35 days. Following the washout and enrollment period, patients entered an 8-week treatment period. Patients were required to be outpatient (not hospitalized) at randomization.

Criteria for evaluation (main variables)

Efficacy

Efficacy

Primary outcome variable:

- Change from baseline (randomization [Visit 2]) in depression symptoms by final visit (Visit 10) as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) total score

Secondary variables supporting the primary objective

- MADRS Total Score response (patients with ≥50% reduction) from baseline (randomization [Visit 2]) to final visit (Visit 10)
- MADRS total score remission (patients with a MADRS total score ≤12 at final visit [Visit 10] assessment)·
- Change from baseline (randomization [Visit 2]) to final visit (Visit 10) assessment in the Clinical Global Impression - Bipolar - Severity of Illness (CGI-BP-S)·
- Final visit (Visit 10) assessment of Clinical Global Impression - Bipolar - Change (CGI-BP-C).
- Proportion of patients at final visit (Visit 10) with a CGI-BP-C of "Much improved" or "Very much" improved·
- Change from baseline (randomization [Visit 2]) to final visit (Visit 10) in MADRS item scores.

Secondary outcome variables:

- Change from baseline (randomization [Visit 2]) in depressive symptoms in rapid and non-rapid cyclers to final visit (Visit 10) as measured by the MADRS total score
- Percentage decrease in MADRS total score at final visit (Visit 10)
- Improvement in clinical Global Impression-Bipolar (CGI-BP) from baseline (randomization [Visit 2]) to final visit (Visit 10)

Safety variables

- Proportion of patients with serious adverse events (SAEs) in the different treatment groups.
- AEs that led to withdrawal; proportion of patients withdrawing due to AE.
- Incidence of AEs and the change from baseline in laboratory values, vital signs, weight and the proportion of patients with a ≥7% increase in weight from baseline to final visit
- EPS (including akathisia) as measured by the change in Simpson Angus Scale (SAS) score and Barnes Akathisia Rating Scale (BARS) score to final visit and AEs of EPS, physical examinations and ECG
- Proportion of patients with treatment-emergent mania (AE of mania or hypomania defined as YMRS score ≥16 on 2 consecutive assessments or final assessment)
- Incidences of suicidality using a suicidality classification similar to the one established by Columbia University in the 2 treatment groups

Statistical methods

The power was set at 90% for a 2-sided test at α=0.05 for the comparison between quetiapine 300 mg XR formulation to placebo, using a 4 unit difference from placebo with a pooled standard deviation of 10.

Efficacy analyses were based on the following patient populations, defined prior to unblinding of the data:

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

The Intent-to-treat (ITT) analysis set included all randomized patients who took ≥1 dose of study medication, classified according to the randomized treatment assignment. Data from the ITT analysis set was used for sensitivity analysis of the primary variable.

The per-protocol (PP) analysis set, a subset of the MITT analysis set, included patients who had no major protocol violations or deviations effecting 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 at least one dose of study medication, classified according to the treatment actually received.

Patient population

A total of 418 patients who were screened to achieve the planned sample size of 280 randomized patients, there were 138 screen failures. The most common reason for screen failure was incorrect enrolment, defined as the patient did not meet the required inclusion/exclusion criteria (25.4%); 3.6% patients were lost-to-follow-up.

Two hundred eighty patients were randomized, 140 in each treatment group. Similar percentages of randomized patients completed the study in each treatment group; 62.1% in the quetiapine XR group, and 68.6% in the placebo group.

The majority of patients in each treatment group completed the study. Among all randomized patients, the most common reason for discontinuation from the study was an AE, [2]reported for a higher percentage of patients in the quetiapine XR group (12.1%) than placebo (1.4%). A higher percentage of patients in the quetiapine XR group (8.6%) compared to placebo (5.7%) were lost-to-follow-up. A higher percentage of patients in the placebo group were discontinued from the study due to lack of therapeutic response (7.1%) than quetiapine XR (1.4%).

At least 98% of patients in each group were classified as being compliant on the basis of tablet counts that were consistent with ≥70% consumption of doses.

Baseline demographic and weight characteristics are shown in Table S1.

[2] Reasons for discontinuation are from the discontinuation page of the case report form.

Table S1 Demographic and baseline characteristics (MITT population)

Demographic or Baseline Characteristic	Quetiapine XR (n=133)	Placebo (n=137)
Gender n (%)		
Male	45 (33.8%)	51 (37.2%)
Female	88 (66.2%)	86 (62.8%)
Age (years)		
Mean (SD)	39.0 (11.3)	39.9 (12.8)
Median	39	40
Min, Max	18, 64	18, 64
Age category (years) n (%)		
18 - 39	69 (51.9%)	67 (48.9%)
40 - 65	64 (48.1%)	70 (51.1%)
Race, n (%)		
Caucasian	96 (72.2%)	98 (71.5%)
Black/ African American	29 (21.8%)	31 (22.6%)
American Indian/ Alaskan Native	3 (2.3%)	3 (2.2%)
Asian	2 (1.5%)	1 (0.7%)
Native Hawaiian/ Pacific Islander	0	1 (0.7%)
Other	3 (2.3%)	3 (2.2%)
Weight (kg)		
Mean (SD)	88.7 (22.1)	88.9 (22.7)
Median	86.4	86.4
Min, max	48, 142	49, 158
BMI (kg/cm^2)		
Mean (SD)	31.6 (7.9)	30.8 (7.1)
Median	30.0	29.9
Min, max	18, 55	17, 50
BMI (kg/cm^2) category, n (%)		
0 to <18.5	1 (0.8%)	1 (0.7%)
18.5 to <25	23 (17.3%)	30 (21.9%)
25 to <30	42 (31.6%)	38 (27.7%)
30 to <40	47 (35.3%)	54 (39.4%)
≥40	20 (15.0%)	14 (10.2%)

BMI Body mass index. MITT Modified Intention to Treat. SD Standard deviation.

The 2 treatment groups were well matched with respect to demographic and baseline characteristics. A higher percentage of patients in both groups were female; 66.2% and 62.8% for quetiapine XR and placebo, respectively. Mean age was 39 to 40 years. The majority of patients were Caucasian; 72.2% and 71.5% for quetiapine XR and placebo, respectively, followed by Black/African American (21.8% and 22.6% for quetiapine XR and placebo, respectively).

In the MITT population, the 2 treatment groups were well-matched with respect to baseline weight parameters. Mean weight and BMI were 88.7 kg and 31.6 kg/cm^2 for quetiapine XR and 88.9 kg and 30.8 kg/cm^2 for placebo. By BMI category, there were slightly more patients in the 30 to <40 kg/cm^2 category for placebo (39.4%) than quetiapine XR (35.3%). The ≥40 kg/cm^2 category had slightly more quetiapine XR patients (15.0%) than placebo (10.2%).

Baseline disease characteristics are shown in Table S2.

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

	Quetiapine XR	Placebo
Baseline disease characteristics, MITT population	**n = 133**	**n = 137**
Baseline MADRS total score		
Mean (SD)	29.8 ± 5.2	30.1 ± 5.5
Min, max	14 to 47	15 to 47
Baseline CGI-S depression score		
Mean (SD)	4.5 ± 0.6	4.5 ± 0.6
Min, max	3 to 7	3 to 6
Baseline CGI-S mania score		
Mean (SD)	1.6 ± 0.7	1.5 ± 0.7
Min, max	1 to 3	1 to 3
Baseline CGI score, overall bipolar illness score		
Mean (SD)	4.5 ± 0.6	4.4 ± 0.7
Min, max	3 to 6	1 to 6
Psychiatric history		
DSM-IV-TR diagnosis n (%)		
Bipolar I disorder	107 (80.5)	110 (80.3)
Bipolar II disorder	26 (19.5)	27 (19.5)
Rapid cycling n (%)		
No	97 (72.9)	99 (72.3)
Yes	36 (27.1)	38 (27.7)

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

	Quetiapine XR	Placebo
Years since bipolar diagnosis	n=132	n=137
Mean (SD)	18.8 (11.3)	19.7 (11.3)
Median	16	19
Min, max	2 to 47	2 to 50
Duration of present depressive episode (weeks)		
Mean (SD)	19.3 (12.8)	18.1 (11.2)
Median	14	14
Min, max	0.6 to 57.6	4.3 to 52.1
Attempted suicide n (%)		
No	91 (68.4)	87 (63.5)
Yes	42 (31.6)	50 (36.5)

CGI Clinical Global Impression; CGI-S Clinical Global Impression Severity; DSM-IV Diagnostic and Statistical Manuel of Mental disorders, 4th edition; MADRS Montgomery-Asberg Depression Rating Scale; MITT Modified-intention–to-treat; SD Standard deviation.

Overall, study patients had moderate to severe depression as shown by validated scales of depression. Mean baseline MADRS and HAM-D scores were approximately 30 and 25, respectively (HAM-D scores not shown in table). Mean baseline CGI-BP overall severity scores for bipolar illness were similar; 4.5 for the quetiapine group and 4.4 for the placebo group. Mean baseline CGI-BP severity score for depression was 4.5 for both groups. In both groups, approximately 80% had bipolar I diagnosis and approximately 27% in each group had rapid cycling.

Per protocol, lorazepam up to 2 mg/day for severe anxiety was permitted in the study. Lorazepam use was consistent and similar from week to week in both treatment groups. From Week 1 through Week 8, lorazepam was taken by approximately 9% to 10% of quetiapine XR patients, and 10% to 11% of placebo patients, by number of patients in the study by week. From Week 1 to Week 8 of the randomized treatment period, sleep medication use was consistent and was taken by a higher percentage of placebo patients (14% to 16%) than quetiapine XR patients (9% to 10%), by number of patients in the study by week. From Week 1 to Week 8 of the randomized treatment period, anticholinergics were taken by approximately 5% to 7% of quetiapine XR and 5% to 6% of placebo patients in the study by week.

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=133)		Placebo (n=137)		
	Week 1	Week 8	Week 1	Week 8	p-value at Week 1 Week 8
MADRS change , LS mean, n (SE)	-10.16 (0.91)	-17.43 (1.24)	-6.54 (0.87)	-11.92 (1.18)	<.001 <.001
Proportion with ≥50% MADRS response, n (%)	35 (26.5%)	87 (65.4%)	23 (16.9%)	59 (43.1%)	.054 <.001
Proportion with MADRS remission (total score <=12), n (%)	26 (19.7%)	72 (54.1%)	14 (10.3%)	54 (39.4%)	.029 .018
CGI-BP-S overall LS mean change from baseline (SE)	-	-1.82	-	-1.25	<.001
CGI-BP-C overall, LS mean change from baseline (SE)	3.03 (0.10)	2.38 (0.13)	3.47 (0.09)	2.90 (0.13)	<.001 <.001
CGI-BP-C much improved or very much improved, n (%)	37 (28.0%)	84 (63.2%)	22 (16.2%)	54 (39.4%)	.019 <.001

CGI-BP-S Clinical Global Impression Bipolar Severity scale; CGI-C Clinical Global Impression Change ; LOCF Last observation carried forward; LS Least square; MITT Modified-Intention- to-Treat; MADRS Montgomery-Asberg Depression Rating Scale; SE Standard error. XR Extended release.

In patients with bipolar disorder, quetiapine XR at a dose of 300 mg QD was demonstrated to be superior to placebo in reducing the level of depressive symptoms as early as Day 8 (Week 1) and for up to 8 weeks of treatment, as assessed by the change from baseline in the total MADRS score (p<.001). At the end of the 8-week course of treatment, quetiapine XR patients in the MITT population had a least square (LS) mean decrease -5.5 points (standard error 1.2) greater than placebo-treated patients (P<.001). Quetiapine XR patients were 2.5x (relative risk=2.50) more likely to achieve MADRS response (≥50% reduction) at end-of-treatment than placebo patients. Quetiapine XR patients were 1.8x more likely to achieve remission (total score ≤12) as placebo patients (relative risk=1.81).

In addition, both bipolar I and II patients and rapid and non-rapid cycling patients treated with quetiapine XR 300 mg QD showed statistically significant greater improvements in MADRS total score compared to patients treated with placebo. For bipolar I patients least squares (LS) mean versus placebo was –6.5 (95% confidence interval [CI] –9.05, -4.00; p<.001) and for bipolar II patients LS mean versus placebo was –4.4 (95% CI –7.91, -0.80; p=.016). For patients with rapid cycling, LS versus placebo was –6.8 (95% CI –11.92, -1.76; p=.008) and for patients with non-rapid cycling LS versus placebo was –5.7 (95% CI –7.98, -3.51; p<.001).

Analysis of other secondary outcome variables also supported the superiority of quetiapine XR over placebo in the treatment of depression in patients with bipolar disorder. For most secondary outcome variables the treatment advantage for quetiapine XR was apparent by Day 8 (Week 1) and continued through Day 57 (Week 8). The proportion of patients showing ≥50% reduction in MADRS total score (responders) was statistically significantly higher for the quetiapine XR group compared to the placebo group by Week 2 and continued to end-of-treatment ($p<.001$). Likewise, the proportion of patients showing a MADRS total score ≤12 (remitters) was statistically significantly higher for the quetiapine XR group compared to the placebo group by Week 1 and continued to end-of-treatment ($p<.05$). Change in CGI Severity of Illness score was also statistically significant at Week 8 ($p<.001$). Quetiapine XR, at a dose of 300 mg QD, significantly improved a broad range of symptoms, including core symptoms of depression, as assessed by the item analysis of the MADRS. Item scores for suicidal thoughts and lassitude were improved numerically with quetiapine XR but were not statistically significant.

Safety results

A summary of AEs is presented in Table S4.

Table S4 Overview of adverse events during randomized treatment period (safety population)

AE category	Number of patients[a] n (%)	
	Quetiapine XR (N=137)	Placebo (N=140)
Any AE	121 (88.3%)	96 (68.6%)
Any AE with an outcome of death	0	0
Any SAE	2 (1.5%)	2 (1.4%)
Any SAE leading to discontinuation of treatment	1 (0.7%)	0
Any AE leading to discontinuation of treatment	18 (13.1%)	5 (3.6%)
Any other significant AE[b]	0	1 (0.7%)

AE Adverse event; N number of patients; 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 temporarily stopped, or deemed by the sponsor to be significant, excluding AEs reported as SAEs or led to discontinuation of treatment.

Note: Events were reported as AEs if they occurred after first dose to 30 days post-randomization.

The 300 mg QD dose of quetiapine XR was generally well tolerated. The percentage of patients with AEs was higher in the quetiapine XR (88.3%) versus the placebo group (68.6%). There were no deaths in the study; there were 2 SAEs in each group. The SAEs were asthma and depression in the quetiapine XR group; both patients with SAEs in the placebo group had suicidal ideation. The percentage of patients with discontinuation of treatment due to any AE

was higher in the quetiapine XR (13.1%) than placebo group (3.6%).[3] Most AEs were mild or moderate in intensity and the majority resolved by the end of study. Events of the nervous and gastrointestinal systems were most common. Two of the most common AEs, somnolence and sedation, tended to occur within the first week of treatment. A higher percentage of quetiapine XR patients (77.4%) had AEs considered by the investigator to be related to study drug, compared to placebo (40.7%).

The incidences of AEs potentially related to EPS were low in each treatment group; 4.4% for quetiapine XR and 0.7% for placebo with the majority reported as mild to moderate. In the quetiapine XR group, 4 patients had AEs of EPS that resolved while on treatment. There were no AEs of neutropenia, agranulocytosis, or QTc prolongation. One AE of diabetes mellitus occurred prior to randomization to quetiapine XR. An AE related to suicidality (suicidal ideation) was reported for 1 patient (0.7%) in the quetiapine XR group and 2 placebo patients (1.4%). One "other significant AE of hypotension" was reported for 1 placebo patient (0.7%) and no quetiapine XR patient.

For lipids, percentages of patients with shifts from normal to clinically-important high total cholesterol values were higher for quetiapine XR than placebo; 6 (7.1%) and 3 (2.8%) of patients, respectively. Percentages of patients with shifts from normal at baseline to clinically-important high triglycerides at end of treatment were similar for quetiapine XR (8.3%) and placebo (7.5%). Percentages of patients with shifts from normal at baseline to clinically-important low HDL-C at end of treatment were similar for quetiapine XR (9.0%) and placebo (7.2%). Percentages of patients with shifts from normal at baseline to clinically-important high LDL-C at end-of-treatment were 3.5% for quetiapine XR and 1.9% for placebo.

Mean changes in glucose regulation laboratory parameters were generally higher for quetiapine XR patients with diabetic risk factors; there was no trend for patients without diabetic risk. Among non-diabetic patients, a higher percentage of placebo patients (12; 21.8%) than quetiapine XR patients (6; 12.0%) had glucose ≥100 and <126 mg/dL at Week 8. The percentages of patients with glucose or HbA1c outside of the specified ranges at Week 8 was otherwise similar for quetiapine XR and placebo overall by diabetic risk category.

Including triglycerides, among patients with <3 metabolic risk factors at baseline, 17.0% (17/100) in the quetiapine XR group and 10.1% (9/89)[4] in the placebo group had ≥3 treatment-emergent metabolic risk factors.

Treatment-emergent criterion for increase in waist circumference was met by a higher percentage of quetiapine XR patients (9.9%) than placebo (6.6%). Shifts for other subcriteria in the quetiapine XR group were similar or lower than those for placebo. There was no

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[3] Per the AE page of the case report form.

[4] Denominator is patients with <3 metabolic risk factors at baseline.

differential shift to any subcriteria of metabolic risk factors at end-of-treatment with quetiapine XR.

Overall, mean weight gain was higher in the quetiapine XR group (1.3 ± 3.7 kg) than placebo (-0.2 ± 2.3 kg). Weight gain of ≥7% at end-of-treatment was reported for 8.2% of quetiapine XR and 0.8% of placebo patients.

Quetiapine XR treatment is not associated with induction of mania or hypomania in bipolar I or II patients treated for acute bipolar depression. There were no AEs of treatment-emergent mania or hypomania. By YMRS mania criteria (score of ≥16 at 2 consecutive visits or at last visit), there was a slightly lower percentage of patients with YMRS-defined mania in the quetiapine XR group (4.4%) compared to the placebo group (6.4%).

In summary, quetiapine XR 300 mg is well-tolerated; there are no new safety findings.