Drug product: Drug substance(s): Study code: Date:	SEROQUEL quetiapine fumarate D1447C00135 01 December 2005	**SYNOPSIS**	

A Confirmatory Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Use of Quetiapine Fumarate (SEROQUEL) in the Treatment of Patients with Bipolar Depression

Study center(s)

This study was conducted in 42 centers in the USA

Publications

None

Study dates		**Phase of development**
First patient enrolled	30 June 2004	Therapeutic confirmatory (IIIb)
Last patient completed	26 August 2005	

Objectives

Primary:

To evaluate the efficacy of quetiapine compared to placebo in the treatment for a major depressive episode in patients with bipolar disorder after receiving treatment for up to 8 weeks as assessed by comparing

1. The change from baseline to final assessment in the Montgomery-Asberg Depression Rating Scale (MADRS) total score

2. The percentage of patients with a ≥50% reduction from baseline in the MADRS total score at final assessment

3. The change from baseline to each assessment in the MADRS total score

4. The change from baseline to each assessment in the Hamilton Rating scale for Depression (HAM-D), HAM-D Item 1, the Clinical Global Impression – Severity (CGI-S), and the Clinical Global Impression – Improvement (CGI-I)[1]

Secondary:

1. To evaluate the incidence of treatment-emergent mania[2] compared to placebo by comparing the percentage of patients with a score of ≥16 points on the Young Mania Rating Scale (YMRS) at 2 consecutive visits or at the Week 8

2. To evaluate the superiority of quetiapine compared to placebo in treatment of anxiety symptoms by the change from baseline to final assessment in the Hamilton Rating Scale for Anxiety (HAM-A) total score

3. To evaluate the safety and tolerability of quetiapine in the treatment of patients with bipolar depression

4. To demonstrate that quetiapine is superior to placebo in improving patient's overall quality of life by the change from baseline (day 1, visit 2) in the Quality of Life Enjoyment Satisfaction Questionnaire (Q-LES-Q)[3]

5. To demonstrate that quetiapine is superior to placebo in improving patient's productive days at work, their family and social lives by the change from baseline (Day1, Visit 2) in Sheehan Disability Score (SDS)

Study design

This study was a randomized, multicenter, double-blind, placebo-controlled, parallel group, fixed-dose comparison of quetiapine vs placebo in the treatment of bipolar depression. This study was stratified by diagnosis (bipolar I and bipolar II), and monitored to obtain an overall ratio of 2:1, respectively.

Target patient population and sample size

Outpatients, aged 18 to 65 years inclusive, with a diagnosis of bipolar I or bipolar II disorder with a current major depressive episode of duration less than 1 year but greater than 4 weeks from the screening visit will be enrolled in the study. The HAM-D (17-item scale) score must be ≥20, the HAM-D item 1 (depressed mood) score must be ≥2, and the YMRS score must be ≤12 at both Visit 1 and Visit 2 (randomization) to be eligible for entry into the study. Approximately 540 patients were expected to be enrolled in the study to obtain 504 evaluable patients.

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[1] The abbreviation for the CGI Global Improvement scale was changed from "CGI-C" as used in the protocol to "CGI-I" to be consistent with the clinical literature.
[2] Modified to include adverse events as defined in the statistical analysis plan.
[3] For this study, Q-LES-Q was designated as a secondary endpoint of particular interest.

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

Quetiapine fumarate was increased in a blinded manner to a total daily dose of 300 mg/day by Day 4 in the 300-mg/day treatment group and to a total daily dose of 600 mg/day by Day 8 (Week 1) in the 600 mg/day treatment group. Thereafter, oral doses of the study drug were administered in a blinded fashion once daily at bedtime in a dose of 300 or 600 mg/day. One-time dose reductions for intolerability of 100 mg/day in all treatment groups were allowed at the discretion of the investigator after Day 8 (Week 1). The resulting dose for patients with reduced dosing would be 200 mg/day, 500 mg/day, or no dosing change for placebo (3 tablets/dose rather than 4 in all treatment groups). Placebo was administered once daily with tablets matching in number and appearance to blinded quetiapine dosing. Study treatment was given in tablets of the following doses (lot #): quetiapine 25 mg (6500J), quetiapine 100 mg (6510J, 6514J), quetiapine 200 mg (7542F, 0215K), placebo 25 mg match (7553F), placebo 100 mg match (1011C, 7550F, ST70142-015-FA02), placebo 200 mg match (1509C, 1510C).

Duration of treatment

Patients received double-blind treatment for up to 8 weeks (56 days), following an initial washout period of between 7 to 28 days (depending on the medications involved) and came in to the clinic on Day 57 (Week 8) for final assessments.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- **Primary variable**: Montgomery-Asberg Depression Rating Scale (MADRS) total score change from baseline at last assessment

- **Secondary variables**: MADRS response (>=50% reduction from baseline; MADRS remission (total score <=12), change from baseline for the following: MADRS total score at each visit, MADRS Item scores, Hamilton Rating Scale for Depression (HAM-D) total score, HAM-D Item 1, Clinical Global Impression Severity of Illness (CGI-S), Hamilton Rating Scale for Anxiety (HAM-A) total score, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Sheehan Disability Scale (SDS); and Clinical Global Impression Improvement (CGI-I) response (very much improved or not very much improved) at each visit.

Safety

Safety assessments included: adverse events, patient withdrawal due to adverse events, adverse events of special interest (EPS, diabetes mellitus, mania/hypomania, suicidality, QT prolongation, neutropenia/agranulocytosis), treatment emergent mania/hypomania (composite based on AE and Young Mania Rating Scale [YMRS] total score), hematology and chemistry findings, vital signs, Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and specific inquiries of relevant data for metabolic syndrome risk factors, cardiac function, neutropenia/agranulocytosis and thyroid function.

Statistical methods

All statistical tests were 2-sided. The primary analyses used last observation carried forward (LOCF) for the time period of interest. A Bonferonni parallel gatekeeping strategy was employed to control for multiple comparisons. Bonferonni adjustments were made for the 2 comparisons with placebo for the MADRS and Q-LES-Q change from baseline assessments. The primary variable MADRS change from baseline test served as a gatekeeper, with testing of Q-LES-Q as a secondary outcome variable of particular interest dependent on at least 1 comparison for MADRS reaching statistical significance. Analysis of Covariance (ANCOVA) was used for comparative analysis of continuous variables with the baseline score as the covariate and including treatment and diagnosis strata as fixed effects and center as a random effect in the model. Cochran-Mantel-Haenszel Chi square tests (CMH) were used for categorical comparisons. Descriptive statistics were provided for all safety assessments with statistical analyses performed and presented for safety variables predefined in the Statistical Analysis Plan.

Subject population

Baseline patient characteristics are shown in Table S1.

Table S1 Patient population and disposition

		Quetiapine 300 mg	Quetiapine 600 mg	Placebo
Demographic characteristics (ITT population)				
N		155	151	161
Sex (n and % of patients)	Male	69 (44.5)	68 (45.0)	64 (39.8)
	Female	86 (55.5)	83 (55.0)	97 (60.2)
Age (years)	Mean (SD)	37.2 (10.53)	38.2 (11.01)	37.7 (11.75)
	Minimum	18	18	18
	Maximum	64	64	63
Race; n (%)	Caucasian	107 (69.0)	115 (76.2)	138 (85.7)
	Black	25 (16.1)	21 (13.9)	11 (6.8)
	Oriental	3 (1.9)	0	1 (0.6)
	Other	20 (12.9)	15 (9.9)	11 (6.8)
Baseline disease characteristics (ITT population)				
N		155	151	161
DSM-IV diagnosis [n and (%)]				
Bipolar I disorder		104 (67.1)	101 (66.9)	110 (68.3)
Bipolar II disorder		51 (32.9)	50 (33.1)	51 (31.7)
Baseline MADRS	Mean (SD)	31.1 (5.7)	29.9 (5.6)	29.6 (5.4)
Screening HAM-D	Mean (SD)	24.8 (3.39)	24.5 (3.06)	24.3 (3.27)

Table S1 Patient population and disposition

		Quetiapine 300 mg	Quetiapine 600 mg	Placebo
Baseline HAM-A	Mean (SD)	19.1 (5.98)	18.4 (5.78)	18.2 (5.69)
Screening YMRS	Mean (SD)	5.8 (3.30)	5.4 (2.79)	5.8 (3.00)
Baseline CGI-S	Mean (SD)	4.5 (0.56)	4.4 (0.57)	4.4 (0.55)
Baseline Q-LES-Q	Mean (SD)	35.4 (7.77)	37.5 (7.51)	37.8 (6.90)
Disposition (all enrolled)				
N safety[a]		171	168	167
N efficacy ITT[b]		155	151	161
N efficacy PP		139	133	150
N (randomized)	Completed	101	90	110
	Discontinued	71	79	58

[a] Number of patients who received at least 1 dose of study drug
[b] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.
CGI-S Clinical Global Impression Severity scale; MADRS Montgomery-Asberg Depression Rating Scale, HAM-A Hamilton Rating Scale for Anxiety, HAM-D Hamilton Rating Scale for Depression; Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire; ITT Intention to treat; N Number; PP Per-protocol.

The 3 groups were well-matched as to number and demographic and baseline disease characteristics. Subject not willing to continue was the main reason for withdrawal across the 3 treatment groups.

Efficacy results

In patients with bipolar disorder, quetiapine at a dose of either 300 mg once daily or 600 mg once daily 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. In addition, both bipolar I and bipolar II patients treated with 300 mg or 600 mg of quetiapine showed greater improvements in MADRS total score compared to patients treated with placebo. Patients receiving quetiapine 300 mg reported statistically superior improvements ($p=0.034$) compared to placebo in change from baseline in Q-LES-Q total score at 8 weeks. Patients receiving quetiapine 600 mg reported numerically greater improvements ($p=0.068$) than placebo in change from baseline in Q-LES-Q total score at 8 weeks. Analysis of other secondary outcome variables also supported the superiority of quetiapine 300 mg or 600 mg over placebo in the treatment of depression in patients with bipolar disorder. For most secondary outcome variables the treatment advantage for both doses of quetiapine 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 300 mg group and the quetiapine 600 mg group compared to the placebo group by Day 15 and

continued to end of treatment. Likewise, the proportion of patients showing a MADRS total score ≤12 (remitters) was statistically significantly higher for the quetiapine 300 mg group and the quetiapine 600 mg group compared to the placebo group by Day 22 and continued to end of treatment. Quetiapine, at a dose of either 300 mg or 600 mg once daily, also improved a broad range of symptoms, including core symptoms of depression and suicidal thoughts, as assessed by the item analysis of the MADRS.

Table S2 Efficacy results at final assessment (LOCF, ITT population)

Outcome variable	Quetiapine 300 mg (N=155)		Quetiapine 600 mg (N=151)		Placebo (N=161)	
	Day 8	Day 57	Day 8	Day 57	Day 8	Day 57
MADRS LS mean change from baseline	-9.42[a]	-16.94[a]	-9.14[a]	-16.00[a]	-6.10	-11.93
Proportion with ≥50% MADRS response	20.3%	60.0%[b]	21.8%	58.3%[c]	14.9%	44.7%
Proportion with MADRS remission (total score <=12)	15.0%	51.6%[c]	16.3%	52.3%[b]	11.2%	37.3%
HAM-D LS mean change from baseline	-8.02[a]	-13.81[a]	-7.88[a]	-12.97[a]	-5.66	-9.92
HAM-D Item 1 LS mean change from baseline	-0.7	-1.76[a]	-0.7	-1.57[c]	-0.6	-1.29
Q-LES-Q total score LS mean change from baseline	NA	9.86[c]	NA	9.19	NA	7.12
CGI-S LS mean change from baseline	-0.6[b]	-1.68[a]	-0.5[b]	-1.59[a]	-0.3	-1.12
Proportion improved on CGI-I	18%	61%[a]	20%[c]	60%[a]	12%	39%

Note: For the analyses of MADRS and Q-LES-Q change from baseline, p-values were adjusted and compared with α=0.05 using the Bonferonni procedure within the parallel gatekeeping strategy.

[a] p<0.001 comparison with placebo

[b] p<0.01 comparison with placebo

[c] p<0.05 comparison with placebo

CGI-S Clinical Global Impression Severity scale; CGI-I Clinical Global Impression Improvement scale; MADRS Montgomery-Asberg Depression Rating Scale, HAM-D Hamilton Rating Scale for Depression; Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire; LOCF Last observation carried forward; ITT Intention to treat; NA Not applicable; LS Least square.

Safety results

Both the 300 mg and 600 mg once-daily doses of quetiapine were generally well tolerated. Analysis of adverse events indicated that nervous system and gastrointestinal events predominated, with dry mouth, sedation, somnolence, dizziness, and constipation occurring at higher rates with quetiapine compared to placebo. Most adverse events were mild to moderate. Larger proportions of patients in the quetiapine dose groups discontinued due to an AE than did patients in the placebo group. No deaths occurred in the study. SAEs were infrequent in all treatment groups. Treatment-emergent mania and hypomania were lower in incidence in the quetiapine treatment groups compared to placebo with a significantly lower rate in the quetiapine 300 mg treatment group compared to placebo. The incidences of individual EPS-related AEs were low in each treatment group with the majority of these AEs reported as mild to moderate for all groups. An increase in the incidence in the composite of AEs related to EPS was noted for both groups of quetiapine-treated patients (300 mg: 12.3%; 600 mg: 10.1%) compared to the placebo group (6.6%). The incidence of AEs related to suicidality was low in all treatment groups. There were 3 cases of clinically important shifts to low values ($\leq 1.5 \times 10^9$/L) in neutrophils reported during the study: 2 in the quetiapine 300 mg treatment group and 1 in the placebo group. There were no cases of agranulocytosis ($\leq 0.5 \times 10^9$ cells/L) reported during the study. The incidence of shift from baseline to reference ranges identified for metabolic risk factors was higher for quetaipine-treated patients compared to placebo in triglycerides, BMI, and blood pressure while differential shifts to either increased HDL or fasting glucose were lower in the quetiapine treatment groups compared to the placebo group.

Table S3 Adverse event overview (safety population)

Category of adverse event	Number (%) of subjects who had an adverse event in each category[a]					
	Quetiapine 300 mg (N=171)		Quetiapine 600 mg (N=168)		Placebo (N=167)	
Any adverse events	155	90.6	151	89.9	138	82.6
Serious adverse events	3	1.8	7	4.2	1	0.6
Serious adverse events leading to death	0		0		0	
Discontinuations of study treatment due to adverse events	14	8.2	19	11.3	2	1.2

[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.

Table S4 Adverse event incidence of at least 5% sorted by decreasing order within the quetiapine 300 mg group (safety population)

MedDRA Preferred term	Quetiapine 300 mg (N=171)		Quetiapine 600 mg (N=168)		Placebo (N=167)	
	n	(%)	n	(%)	n	(%)
Dry mouth	73	42.7	79	47.0	30	18.0
Sedation	55	32.2	46	27.4	17	10.2
Somnolence	51	29.8	50	29.8	8	4.8
Dizziness	24	14.0	27	16.1	9	5.4
Fatigue	16	9.4	19	11.3	13	7.8
Headache	15	8.8	14	8.3	28	16.8
Constipation	14	8.2	17	10.1	5	3.0
Increased appetite	13	7.6	7	4.2	7	4.2
Nausea	13	7.6	18	10.7	22	13.2
Dyspepsia	12	7.0	11	6.5	8	4.8
Extrapyramidal disorder	11	6.4	10	6.0	4	2.4
Lethargy	9	5.3	2	1.2	3	1.8
Vomiting	9	5.3	9	5.4	10	6.0
Back pain	8	4.7	3	1.8	13	7.8
Upper respiratory tractiInfection	7	4.1	10	6.0	14	8.4
Weight increased	7	4.1	9	5.4	3	1.8
Nasopharyngitis	6	3.5	11	6.5	10	6.0
Insomnia	5	2.9	3	1.8	12	7.2
Nasal congestion	5	2.9	10	6.0	6	3.6
Diarrhea	4	2.3	8	4.8	11	6.6
Orthostatic hypotension	4	2.3	10	6.0	3	1.8
Dysarthria	3	1.8	9	5.4	1	0.6

Note: This table uses a cut-off of 5% in any group. Data are ordered by descending incidence in the quetiapine 300 mg group.
MedDRA Medical Dictionary for Regulatory Affairs.

Date of the report 01 December 2005