Clinical Study Report

Drug substance:	Quetiapine fumarate
Study code:	D1444C00132
Date:	21 June 2007

A 6-week, International, Multicenter, Double-blind, Double-dummy, Randomized Comparison of the Efficacy and Safety of Sustained-Release Formulation Quetiapine Fumarate (SEROQUEL™) and Placebo in the Treatment of Acutely Ill Patients with Schizophrenia

Study dates:	First patient enrolled: 8 November 2004 Last patient completed: 12 December 2005
Phase of development:	Phase III
International Co-ordinating Investigator:	None assigned.
Sponsor's Responsible Medical Officer:	Martin Brecher, MD, DMSc

This study was performed in compliance with Good Clinical Practice.

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Drug product:	SEROQUEL SR™	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate		
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A 6-week, International, Multicenter, Double-blind, Double-dummy, Randomized Comparison of the Efficacy and Safety of Sustained-Release Formulation Quetiapine Fumarate (SEROQUEL™) and Placebo in the Treatment of Acutely Ill Patients with Schizophrenia

International co-ordinating investigator

None.

Study center(s)

This study was conducted at 39 centers in South Africa, Russia, Romania, Bulgaria, Greece, India, Indonesia, and the Philippines.

Publications

None at report time

Study dates		**Phase of development**
First patient enrolled	8 November 2004	Therapeutic confirmatory (III)
Last patient completed	12 December 2005	

Objectives

Primary objective

The primary objective was to demonstrate superior efficacy of sustained-release (SR) quetiapine (SEROQUEL, quetiapine SR) for the 3 doses, 400 mg/day, 600 mg/day and 800 mg/day, compared with placebo in the treatment of patients with schizophrenia. The primary outcome variable was the change from baseline of the Positive and Negative Syndrome Scale (PANSS) total score at the end of treatment at Day 42 (Last Observation Carried Forward [LOCF]).

Secondary objectives

Efficacy

1. To demonstrate a higher response rate to treatment for the 3 doses of quetiapine SR tablets compared to placebo.

2. To demonstrate superior efficacy in patients' overall clinical status for the 3 doses of quetiapine SR tablets compared to placebo.

3. To document efficacy on psychiatric symptoms for all doses of quetiapine tablets, SR and IR.

Safety

1. To assess the safety and tolerability of quetiapine SR tablets administered once daily.

2. To compare the safety and tolerability profiles of quetiapine SR and quetiapine immediate-release (IR).

Study design

This was a 6-week, multicenter, double-blind, double-dummy, randomized, placebo-controlled study comparing the efficacy and safety of quetiapine SR 400 mg/day, 600 mg/day and 800 mg/day and quetiapine IR 400 mg/day with that of placebo in the treatment of adult male and female patients with schizophrenia.

Target patient population and sample size

Acutely ill male and female patients, =18 to =65 years of age, diagnosed with schizophrenia as stated in The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, were enrolled in the study. The patients were required to have a Positive and Negative Syndrome Scale (PANSS) total score of at least 70 and a Clinical Global Impression (CGI) Severity of Illness score of at least 4 at randomization to be eligible for the study. A total of 535 randomized patients were required to obtain 97 evaluable patients per treatment group (485 in total).

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

Quetiapine SR was increased in a blinded fashion to a total daily dose of 400 mg/day by Day 2 in the 400 mg/day treatment group, to a total daily dose of 600 mg/day by Day 2 in the 600 mg/day treatment group and to a total daily dose of 800 mg/day by Day 3 in the 800 mg/day treatment group (ie, dose escalation scheme). Quetiapine IR was increased in a blinded fashion to a total daily dose of 400 mg/day by Day 5. Thereafter, oral doses of the blinded investigational product were administered twice daily in the morning and in the evening (with or without food). Doses were given in a double-dummy fashion owing to the difference in administration frequency between the quetiapine SR and IR formulations. Quetiapine SR treatment was given in the evening. Placebo was administered twice daily with tablets matching in number and appearance to blinded quetiapine dosing.
Study treatment was given in tablets of the following doses (batch #): quetiapine IR 25 mg (21033K04), quetiapine IR 100 mg (21035E04), quetiapine IR 200 mg (21036B04), placebo 25 mg quetiapine IR match (21037J04), placebo 100 mg quetiapine IR match (21039D04), placebo 200 mg quetiapine IR match (21040E04), quetiapine SR 200 mg

(21041B04), quetiapine SR 300 mg (21042J04), quetiapine SR 400 mg (21440G04), placebo 200 mg quetiapine SR match (21157H04), placebo 300 mg quetiapine SR match (21043G04), placebo 400 mg quetiapine SR match (21305B04).

Duration of treatment

Patients received double-blind, double-dummy treatment for up to 6 weeks (42 days) following an enrollment period of up to 7 days.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Change from baseline of the PANSS total score at the end of treatment at Day 42 (LOCF).

- Secondary variables: PANSS response rates, defined as a reduction of at least 30% from baseline PANSS total score at the end of treatment at Day 42 (LOCF); CGI Global Improvement rating ≤ 3 at the end of treatment at Day 42 (LOCF); change in the CGI Severity of Illness score from baseline at the end of treatment at Day 42 (LOCF); change from baseline PANSS total score at all subsequent visits; change in PANSS positive, negative and general psychopathology subscales from baseline at all subsequent visits; change in PANSS aggression/hostility and PANSS depression clusters from baseline at all subsequent visits.

Safety

Safety assessments included: adverse events, laboratory measurements (clinical chemistry, hematology and urinalysis), electrocardiogram (ECG), vital signs (blood pressure and pulse rate), weight, Barnes Akathisia Rating Scale (BARS), Simpson-Angus Scale (SAS), use of anticholinergic medication, safety data with regards to diabetes mellitus including fasting glucose/insulin, glycosylated haemoglobin (HbA1c) and Body Mass Index (BMI; weight/height^2) and data for other specific safety areas (QT prolongation, metabolic risk factors, neutropenia/agranulocytosis, suicidality).

Statistical methods

The primary objective of the statistical analysis was to demonstrate superior efficacy of each of the quetiapine SR doses compared to placebo. All statistical tests were 2-sided with a significance level of 5%; ie, a=0.05. Where appropriate, 95% confidence intervals were presented. Missing data resulting from patient dropouts were imputed using a LOCF approach. Patients with post baseline data (modified intention to treat population) had their last study assessment carried forward as the final assessment for analyses. The primary statistical analysis utilized an analysis of covariance (ANCOVA) model for the change from baseline at the end of treatment in the PANSS total score. The model included the fixed effect treatment and the random effect center and baseline PANSS as a covariate. The multiplicity problem concerning the false-positive error rate for the 3 quetiapine SR comparisons with placebo in the primary analysis was handled by utilizing the Hommel procedure. For the analysis of the change in CGI Severity of Illness score from baseline at Day 42, an analysis of covariance (ANCOVA) model equivalent to the

one utilized in the primary analysis was applied. A Cochran-Mantel-Haenszel (CMH) technique was used for the analysis of the PANSS response rate and the CGI Global Improvement score response rate. Descriptive statistics were used for safety assessments.

Patient population

Baseline patient characteristics are presented in Table S1. The randomized study population comprised 588 patients enrolled from 39 centers. The number of patients discontinuing early ranged from 21 (19%) in the quetiapine SR 600 mg/day group to 33 (28%) in the placebo group, most commonly because of lack of efficacy, consent was withdrawn, or AEs. A total of 446 patients completed study treatment (72% of placebo patients, 74% of quetiapine SR 400 mg/day patients, 81% of quetiapine SR 600 mg patients, 74% of quetiapine SR 800 mg/day patients and 78% of quetiapine IR patients). The MITT population included more men (60.2%) than women (39.8%), and a greater percentage of patients aged 18 to 39 years (70.2%) than aged 40 to 65 years (29.8%). Caucasian and Oriental patients (59.2% and 36.1%, respectively) made up the largest part of the population. Overall, the treatment groups were similar with respect to demographic characteristics and baseline disease characteristics.

Of the 588 patients assigned to treatment and included in the safety analyses, 15 were excluded from the MITT population because post-baseline PANSS scores were missing. The proportion of patients excluded from the MITT population was evenly distributed across the treatment groups. Of the 573 patients included in the MITT analyses, 17 were fully excluded from the PP analysis set, with few differences among treatment groups in reasons for exclusion.

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Table S1 Patient population and disposition

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
Demographic characteristics (MITT)					
Sex: n (%)					
Male	67 (58.3)	78 (70.3)	61 (55.0)	70 (59.8)	69 (58.0)
Female	48 (41.7)	33 (29.7)	50 (45.0)	47 (40.2)	50 (42.0)
Age (years)[a]					
Mean (SD)	34.1 (12.1)	34.1 (9.6)	34.2 (9.9)	34.4 (10.3)	34.4 (10.2)
Range	18 to 64	18 to 61	18 to 58	18 to 60	18 to 62
Race/ethnicity: n (%)					
Caucasian	68 (59.1)	63 (56.8)	66 (59.5)	71 (60.7)	71 (59.7)
Black	5 (4.3)	5 (4.5)	4 (3.6)	5 (4.3)	7 (5.9)
Oriental	42 (36.5)	43 (38.7)	40 (36.0)	41 (35.0)	41 (34.5)
Other	0	0	1 (0.9)	0	0
Baseline disease characteristics (MITT)					
DSM-IV diagnosis, schizophrenic subtype: n (%)					
Disorganized	5 (4.3)	8 (7.2)	5 (4.5)	5 (4.3)	2 (1.7)
Catatonic	1 (0.9)	2 (1.8)	0	0	1 (0.8)
Paranoid	79 (68.7)	71 (64.0)	72 (64.9)	75 (64.1)	88 (73.9)
Undifferentiated	30 (26.1)	30 (27.0)	34 (30.6)	37 (31.6)	28 (23.5)
PANSS at randomization[b]					
Mean (SD)	96.2 (13.3)	95.8 (13.9)	96.8 (14.1)	97.3 (14.7)	96.5 (16.0)
CGI severity of illness at randomization[c]					
Mean (SD)	4.9 (0.7)	4.9 (0.7)	4.9 (0.7)	5.0 (0.7)	4.9 (0.6)
Disposition (randomized patients): n					
Completed randomized treatment	85	83	92	90	96
Premature discontinuation	33	30	21	31	27
N analyzed for safety	118	113	113	121	123
N analyzed for efficacy (MITT)	115	111	111	117	119
N analyzed for efficacy (PP)	112	108	108	113	115

[a] At enrollment.
[b] Inclusion criteria was PANSS score at randomization ≥70.
[c] Inclusion criteria was CGI score at randomization ≥4.

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CGI Clinical Global Impression. DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition. IR Immediate-release. MITT Modified intention-to-treat. N Number of patients in treatment group. n Number of patients. PANSS Positive and Negative Syndrome Scale. PLA Placebo. PP Per protocol. QTP Quetiapine. SR Sustained-release.

Efficacy results

A summary of efficacy results at Day 42 (LOCF) is presented in Table S2.

Table S2 Summary of efficacy results at Day 42 (LOCF, MITT population)

	PLA N=115	QTP SR 400 mg N=111	QTP SR 600 mg N=111	QTP SR 800 mg N=117	QTP IR 400 mg N=119
PANSS total score, LS mean change from baseline[a]	-18.8	-24.8*	-30.9***	-31.3***	-26.6**
PANSS response, % of patients responding[b]	30.4	44.1*	60.4***	56.4***	52.9**
CGI Severity of Illness score, LS mean change from baseline	-1.0	-1.3	-1.5***	-1.6***	-1.3*
CGI Global Improvement score, % of patients showing improvement[c]	60.0	73.9*	79.3**	76.9**	75.6*

*** p<0.001 comparison with placebo

** p<0.01 comparison with placebo

* p<0.05 comparison with placebo

[a] The comparisons of QTP SR doses with placebo refer to p-values adjusted with Hommel's procedure for multiplicity.

[b] Response was defined as a ≥30% improvement in PANSS total score.

[c] Improvement was defined as a rating of 'much improved', 'improved' and 'minimally improved' on the CGI Global Improvement scale.

CGI Clinical Global Impression Improvement. LOCF Last observation carried forward. LS Least squares. MITT Modified intention-to-treat. PANSS Positive and Negative Syndrome Scale. PLA Placebo. QTP Quetiapine. SR Sustained-release.

Note: The MITT population included all patients who took study medication and who had a baseline PANSS assessment and at least 1 valid post-baseline PANSS assessment.

Analysis of the primary variable, the change from baseline in the PANSS total score at Day 42, showed significant improvement in all tested quetiapine SR doses (SR 400 mg/day, 600 mg/day, and 800 mg/day) compared to placebo. The magnitude of change from baseline compared to placebo was -6.1 in the quetiapine SR 400 mg/day, -12.1 in the quetiapine SR 600 mg/day group, and -12.5 in the quetiapine SR 800 mg/day group. Quetiapine IR 400 mg/day was demonstrated to be superior to placebo (p=0.004) with a difference of -7.8. LOCF analyses based on the PP population at Day 42 as well as OC (observed cases) analyses for the MITT and PP populations supported the robustness of the primary analysis with regard to the efficacy of the 3 quetiapine SR doses.

All 3 quetiapine SR doses demonstrated superior improvements from baseline at Day 42 compared to placebo for the key secondary efficacy measurements PANSS response rate and CGI Global Improvement score, further supporting the robustness of the primary analyses. In addition, quetiapine SR 600 mg/day and SR 800 mg/day demonstrated

significant improvement compared to placebo for the key secondary outcome variable CGI Severity of Illness score.

Consistent with the key secondary efficacy measurements, the 3 quetiapine SR doses demonstrated efficacy on a broad range of symptoms of schizophrenia as measured by the PANSS Positive and General Psychopathology subscale scores, and the PANSS aggression and hostility cluster score. In addition, the quetiapine SR 600 mg/day and SR 800 mg/day groups demonstrated significant improvement compared to placebo for the PANSS Negative symptom subscale score and PANSS depression cluster score at Day 42.

Safety results

The number (%) of patients who had at least 1 adverse event in any category is summarized in Table S3. Overall, quetiapine SR was generally safe and well tolerated at all doses (400 mg/day, 600 mg/day, 800 mg/day) tested in this study. Analysis of adverse events indicated that psychiatric, nervous and gastrointestinal events predominated, with somnolence and dizziness occurring at higher rates with quetiapine compared to placebo. There was 1 death of unknown cause in the study, which was not considered related to study treatment (quetiapine IR 400 mg/day) by the investigator. Most adverse events were mild to moderate. SAEs and discontinuations due to AEs were infrequent in all treatment groups. The incidence of drug-related AEs was slightly higher in the quetiapine treatment groups compared to placebo.

The type, pattern, and intensity of AEs in the 3 quetiapine SR groups were similar to those observed in the quetiapine IR 400 mg/day group. The proportion of patients with drug-related AEs was generally consistent across the quetiapine SR and IR groups.

Table S3 Various categories of adverse events (safety population)

	PLA N=118	QTP SR 400 mg N=113	QTP SR 600 mg N=113	QTP SR 800 mg N=121	QTP IR 400 mg N=123
	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events [a]	50 (42.4)	51 (45.1)	62 (54.9)	56 (46.3)	66 (53.7)
Serious adverse events[a]	2 (1.7)	2 (1.8)	3 (2.7)	1 (0.8)	6 (4.9)
Serious adverse events leading to death[a]	0	0	0	0	1 (0.8)
Serious adverse events not leading to death[a]	2 (1.7)	2 (1.8)	3 (2.7)	1 (0.8)	5 (4.1)
Drug-related adverse events[a, b]	15 (12.7)	23 (20.4)	34 (30.1)	27 (22.3)	27 (22.0)
Adverse events leading to discontinuation[a]	3 (2.5)	6 (5.3)	3 (2.7)	3 (2.5)	6 (4.9)
Total number of adverse events					
Adverse events	117	123	148	148	136
Serious adverse events	2	2	4	1	8
Drug-related adverse events[b]	31	47	79	86	53

[a] Patients with multiple events in the same category are counted only once in that category.
[b] As judged by the investigator.
IR Immediate-release. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine. SR Sustained-release.

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The incidence of common adverse events (occurring at an incidence of =5% in any treatment group) is summarized by randomized treatment group in Table S4. The pattern of common AEs observed in the quetiapine SR treatment groups generally conformed to that which was anticipated based on the pharmacological profile of quetiapine IR; ie, the most common AEs associated with quetiapine were somnolence and dizziness. The incidence rate across the quetiapine SR groups for somnolence and dizziness AEs was higher than for placebo, although these AEs were generally mild and did not lead to discontinuation. There were no apparent quetiapine SR-specific AEs emerging from this study. There was 1 nonserious AE (neutrophil count decreased) potentially related to agranulocytosis reported during the study (quetiapine SR 800 mg/day) that led to discontinuation from the study. The neutrophil count increased from =0.5 x 10^9/L to >0.5 x 10^9/L upon repeat testing while the patient continued quetiapine treatment. There were no signs or symptoms of infection reported. There were no confounding factors and the investigator determined the agranulocytosis to be unrelated to study treatment.

An increase in common adverse events (somnolence, agitation, nausea, asthenia, and dizziness) over the first week of treatment was observed in all quetiapine groups compared with placebo. The 3-day quetiapine SR dose escalation (starting dose of 300 mg/day on Day 1 up to a maximum dose of 800 mg/day on Day 3) was well tolerated as indicated by the low number of discontinuations and SAEs during the first week of treatment.

The incidence of EPS-related adverse events was consistent across the quetiapine SR and IR groups and similar to placebo. Over the course of the study, there were few patients using anticholinergic medication for symptoms of EPS in the quetiapine groups and the placebo group. Overall the assessment of parkinsonian and akathisia symptomatology as assessed by mean SAS and BARS scores indicated that quetiapine SR and quetiapine IR treatment were similar to placebo, and an improvement or no worsening in symptomatology was noted in all active treatment groups at the end of treatment.

Small changes from baseline were observed at end of treatment for quetiapine SR patients in a number of clinical laboratory assessments, including mean hemoglobin and alkaline phosphatase values. These changes were not considered to be of clinical significance. These changes were also noted in the quetiapine IR group, and were consistent with previous studies with this formulation. Increases in triglycerides and total cholesterol were consistent with the known safety profile for quetiapine IR.

There were small increases in mean glucose and insulin levels with quetiapine SR treatment compared to placebo. There was no suggestion of a dose relationship. Similar changes were observed in the quetiapine IR group. Interpretation of the observed changes in insulin was obscured by the large standard deviations in mean plasma concentrations.

A small increase in mean pulse rate, confirmed by ECG measurement of heart rate, was also observed in the quetiapine SR groups. A similar change in pulse rate was noted in the quetiapine IR patients. The change in heart rate was well tolerated, as there were few AEs related to this change.

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Table S4 Common adverse events (safety population)

	PLA N=118	QTP SR 400 mg N=113	QTP SR 600 mg N=113	QTP SR 800 mg N=121	QTP IR 400 mg N=123
MedDRA Preferred term[a]	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Insomnia	23 (19.5)	13 (11.5)	7 (6.2)	9 (7.4)	13 (10.6)
Somnolence	2 (1.7)	8 (7.1)	10 (8.8)	14 (11.6)	9 (7.3)
Dizziness	1 (0.8)	6 (5.3)	10 (8.8)	8 (6.6)	7 (5.7)
Headache	8 (6.8)	6 (5.3)	4 (3.5)	4 (3.3)	2 (1.6)
Sleep disorder	11 (9.3)	4 (3.5)	6 (5.3)	4 (3.3)	6 (4.9)
Constipation	5 (4.2)	2 (1.8)	6 (5.3)	5 (4.1)	1 (0.8)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.

IR Immediate-release. MedDRA Medical Dictionary of Regulatory Activities. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine. SR Sustained-release.

Note: Common adverse events occurring at an incidence of >=5% in any randomized treatment group.

Note: Sorted by descending frequency in quetiapine SR 400 mg column.