Clinical Study Report

Drug substance:	Quetiapine fumarate
Study code:	D1444C00133
Date:	29 May 2006

A 6-week, 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: 23 July 2004 Last patient enrolled: 3 August 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		
Study code:	D1444C00133		
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A 6-week, 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 assigned.

Study center(s)

This study was conducted at 40 centers in the United States.

Publications

None at report time.

Study dates		**Phase of development**
First patient enrolled	23 July 2004	Phase III (Therapeutic confirmatory)
Last patient completed	13 September 2005	

Objectives

Primary objective

To demonstrate superior efficacy of sustained-release (SR) quetiapine (SEROQUEL SR, quetiapine SR) for the three 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 (Week 6) (Last Observation Carried Forward [LOCF]).

Secondary objectives

Efficacy

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

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

3. To document efficacy on psychiatric symptoms for all doses of quetiapine tablets, SR and immediate-release (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 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 800 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 defined in The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, were enrolled in the study. 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. Quetiapine IR was increased in a blinded fashion to a total daily dose of 800 mg/day by Day 7. 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 quetiapine IR formulations (the active quetiapine SR dose was administered 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 (7527F, 6500J), quetiapine IR 100 mg (7511H, 7536F, 6510J, 6516J), quetiapine IR 200 mg (7539F, 0215K, 7542F), placebo 25 mg quetiapine IR match (7553F), placebo 100 mg quetiapine IR match (1011C, 7550F, ST70142-015-FA02), placebo 200 mg quetiapine IR match (1509C, 1511C, ST70142-016-FA12), quetiapine SR 200 mg (9071H, 9004K), quetiapine SR 300 mg (9072H, 9005K), quetiapine SR 400 mg (9105F, 9008K), placebo 200 mg quetiapine SR match (KC2001050, KD2001004, ST73043-001-

FA02), placebo 300 mg quetiapine SR match (ST73042-001-FB08, ST73042-001-FC01), placebo 400 mg quetiapine SR match (ST76039-001-FA03, ST76039-001-FA05).

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

0Primary variable: Change from baseline in PANSS total score at the end of treatment at Day 42 (LOCF).

1Secondary 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 cluster and PANSS depression cluster 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 hemoglobin (HbA_{1C}) and Body Mass Index (BMI; weight/height^2) and data for other specific safety areas (QT prolongation, metabolic risk factors, neutropenia/agranulocytosis and 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 two-sided with a significance level of 5%, ie a=0.05. Where appropriate, 95% confidence intervals were presented. Missing data were imputed using an 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. No correction of multiplicity was applied to the quetiapine IR comparison with placebo. 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

The randomized study population comprised 565 patients, divided into 5 treatment groups of similar sizes. A total of 333 patients completed treatment. The number of patients discontinuing early ranged from 40 (35%) in the quetiapine SR 400 mg/day group through 49 (42%) in placebo to 54 (47%) in the quetiapine IR 800 mg/day group, most commonly because consent was withdrawn, AEs, or lack of efficacy.
Baseline patient characteristics are presented in Table S 1. The treatment groups were well balanced with respect to demographic and most baseline disease characteristics. The study was conducted on a predominantly male population (71.5%), and Black (African-American) and Caucasian patients comprised the bulk of the patient population (58.5% and 32.5%, respectively). Patient ages within the MITT population ranged from 19 to 65 years, with an overall mean of 41.4 years. Treatment groups were similar with respect to mean age. The overall mean baseline weight and BMI of patients in the MITT population were 91.1 kg and 30.7 kg/m^2, respectively, and means were similar across groups.
At screening, a large majority of patients in the MITT population were diagnosed as having paranoid schizophrenia. At baseline (Day 1), mean PANSS total scores ranged from 70 to 149 (overall mean 92.1) and mean CGI Severity of Illness scores ranged from 4 to 6 in all treatment groups (overall mean 4.5). The number of hospitalized patients at randomization in the MITT population was similar for all treatment groups.

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Table S 1 Patient population and disposition

	PLA N=111	QTP SR 400 mg N=113	QTP SR 600 mg N=101	QTP SR 800 mg N=110	QTP IR 800 mg N=109
Demographic characteristics (MITT)					
Sex: n (%)					
Male	77 (69.4)	79 (69.9)	82 (81.2)	82 (74.5)	69 (63.3)
Female	34 (30.6)	34 (30.1)	19 (18.8)	28 (25.5)	40 (36.7)
Age (years)[a]					
Mean (SD)	42.5 (10.8)	42.1 (10.1)	41.2 (10.8)	40.2 (9.1)	40.8 (10.4)
Range	20 to 65	19 to 61	19 to 61	20 to 63	19 to 65
Race/ethnicity: n (%)					
Caucasian	36 (32.4)	39 (34.5)	34 (33.7)	39 (35.5)	29 (26.6)
Black	59 (53.2)	66 (58.4)	63 (62.4)	62 (56.4)	68 (62.4)
Oriental	3 (2.7)	0	2 (2.0)	1 (0.9)	1 (0.9)
Other	13 (11.7)	8 (7.1)	2 (2.0)	8 (7.3)	11 (10.1)
Baseline disease characteristics (MITT)					
DSM-IV diagnosis, schizophrenic subtype: n (%)					
Disorganized	1 (0.9)	2 (1.8)	2 (2.0)	1 (0.9)	8 (7.3)
Catatonic	0	0	1 (1.0)	0	0
Paranoid	91 (82.0)	93 (82.3)	86 (85.1)	90 (81.8)	90 (82.6)
Undifferentiated	19 (17.1)	18 (15.9)	12 (11.9)	19 (17.3)	11 (10.1)
PANSS at randomization[b]					
Mean (SD)	90.8 (11.9)	91.1 (13.4)	93.1 (14.0)	92.6 (13.2)	93.0 (13.5)
CGI severity of illness at randomization[c]					
Mean (SD)	4.5 (0.6)	4.4 (0.5)	4.5 (0.6)	4.5 (0.6)	4.5 (0.6)
Disposition (randomized patients): n					
Completed randomized treatment	68	74	61	68	62
Premature discontinuation	49	40	44	45	54
N analyzed for safety	117	114	105	113	115
N analyzed for efficacy (MITT)	111	113	101	110	109
N analyzed for efficacy (PP)	104	98	94	101	97

[a] At enrollment.

[b] Inclusion criteria was PANSS score at randomization ≥70.

[c] Inclusion criteria was CGI score at randomization ≥4.

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.

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Efficacy results

A summary of efficacy results at Day 42 (LOCF) is presented in Table S 2.

Table S 2 Summary of efficacy results at Day 42 (LOCF, MITT population)

	PLA N=111	QTP SR 400 mg N=113	QTP SR 600 mg N=101	QTP SR 800 mg N=110	QTP IR 800 mg N=109
PANSS total score, LS mean change from baseline	-12.1	-13.8	-16.8	-14.8	-15.0
PANSS response, % of patients responding[a]	20.7	19.5	26.7	23.6	22.9
CGI Severity of Illness score, LS mean change from baseline	-0.5	-0.6	-0.6	-0.6	-0.6
CGI Global Improvement score, % of patients showing improvement[b]	56.8	65.5	67.3	62.7	61.5

Note: None of the QTP doses were statistically superior compared to placebo for any of the efficacy outcome variables at Day 42

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

[b] 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.

Improvement from baseline in PANSS total score at Day 42 was seen in all groups, with greater improvement in quetiapine dose groups than in the placebo group. The change from baseline in PANSS total score in the placebo group was pronounced and continued throughout the study. However, quetiapine SR at each of the 3 doses (400 mg/day, 600 mg/day and 800 mg/day) and quetiapine IR (800 mg/day) was not statistically superior to placebo at the end of treatment. Improvements were also seen at Day 42 in CGI Severity of Illness score (LOCF), PANSS response rate, CGI Global Improvement rating =3 (LOCF) and change in PANSS subscale scores (LOCF), most consistently with quetiapine SR 600 mg/day, but superiority to placebo was not demonstrated for any of the quetiapine dose groups. The quetiapine SR 600 mg/day group achieved separation from placebo in the PANSS general psychopathology, depression cluster and hostility/aggression cluster analyses, as shown by 95% CIs. At a dose of 800 mg/day, quetiapine IR, an atypical antipsychotic with proven efficacy against the symptoms of schizophrenia, was also unable to differentiate from placebo in any of the efficacy measurements assessed.

Safety results

The number (%) of patients who had at least 1 adverse event in any category is summarized in Table S 3. Quetiapine SR was generally safe and well tolerated across the dose range of 400-800 mg/day in patients with schizophrenia. The overall incidence of AEs was higher in the quetiapine SR groups (400 mg/day, 78.9%; 600 mg/day, 79.0%; and 800 mg/day, 73.5%) than the placebo group (70.1%). Incidences were similar across all dose groups of quetiapine SR and the quetiapine IR group, with no evidence to support a dose effect. The incidence of SAEs in the quetiapine SR treatment groups was low and similar to placebo. The number of patients with AEs considered by the investigator to be related to treatment was higher in the quetiapine groups than in the

placebo group, but was similar across all quetiapine SR dose groups and the quetiapine IR treatment group. The percentage of patients withdrawing from the study due to AEs was similar across all groups.

Table S 3 Various categories of adverse events (safety population)

	PLA N=117	QTP SR 400 mg N=114	QTP SR 600 mg N=105	QTP SR 800 mg N=113	QTP IR 800 mg N=115
	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events[a]	82 (70.1)	90 (78.9)	83 (79.0)	83 (73.5)	86 (74.8)
Serious adverse events[a]	9 (7.7)	10 (8.8)	10 (9.5)	10 (8.8)	7 (6.1)
Serious adverse events leading to death[a]	0	0	0	0	0
Serious adverse events not leading to death[a]	9 (7.7)	10 (8.8)	10 (9.5)	10 (8.8)	7 (6.1)
Drug-related adverse events[a b]	43 (36.8)	64 (56.1)	51 (48.6)	52 (46.0)	62 (53.9)
Adverse events leading to discontinuation[a c]	13 (11.1)	11 (9.6)	11 (10.5)	12 (10.6)	13 (11.3)
Total number of adverse events					
Adverse events	196	269	219	243	256
Serious adverse events	11	13	10	15	7
Drug-related adverse events[b]	91	148	121	137	167

[a] Patients with multiple events in the same category are counted only once in that category.
[b] As judged by the investigator.
[c] In addition 1 patient in the placebo group was discontinued in the randomized period due to an adverse event started before day of first dose.
IR Immediate-release. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine. SR Sustained-release.

The incidence of common adverse events (occurring at an incidence of =5% in any treatment group) is summarized by randomized treatment group in Table S 4. The common AEs observed in the quetiapine SR treatment groups generally conformed to type, frequency and intensity anticipated based on the pharmacological profile of quetiapine IR, ie the most common AEs in all dose groups were dry mouth, sedation, somnolence, and dizziness. The incidence rate across the quetiapine SR groups for all these AEs was higher than for placebo, although incidence did not appear to be related to the dose of quetiapine received. There were no apparent quetiapine SR-specific AEs emerging from this study.

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. Small changes from baseline were also observed at end of treatment for quetiapine SR patients in a number of clinical laboratory assessments, including mean hemoglobin, lymphocyte and alkaline phosphatase values. These changes were well tolerated and 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.

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 serum concentrations.

Overall the assessment of parkinsonian and akathisia symptomatology as assessed by mean SAS total score and BARS global assessment score 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. A higher percentage of patients with worsened SAS total scores were observed in the quetiapine SR 800 mg/day group than in the other quetiapine SR groups or in the placebo and quetiapine IR groups. The use of concomitant anticholinergic medication for EPS was low, and consistent with the neurological assessment, and was slightly higher in the quetiapine groups than the placebo group. There was a slight increase in EPS-related AEs in the quetiapine SR 800 mg/day and quetiapine IR 800 mg/day groups compared with placebo.

Table S 4 Common adverse events (safety population)

	PLA N=117	**QTP SR 400 mg N=114**	**QTP SR 600 mg N=105**	**QTP SR 800 mg N=113**	**QTP IR 800 mg N=115**
MedDRA Preferred term[a]	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Dry mouth	3 (2.6)	24 (21.1)	18 (17.1)	20 (17.7)	19 (16.5)
Sedation	11 (9.4)	24 (21.1)	18 (17.1)	15 (13.3)	25 (21.7)
Somnolence	3 (2.6)	19 (16.7)	11 (10.5)	15 (13.3)	17 (14.8)
Dizziness	8 (6.8)	14 (12.3)	10 (9.5)	8 (7.1)	11 (9.6)
Headache	18 (15.4)	12 (10.5)	7 (6.7)	12 (10.6)	10 (8.7)
Constipation	9 (7.7)	9 (7.9)	5 (4.8)	9 (8.0)	9 (7.8)
Dyspepsia	2 (1.7)	9 (7.9)	6 (5.7)	7 (6.2)	10 (8.7)
Insomnia	12 (10.3)	9 (7.9)	4 (3.8)	2 (1.8)	1 (0.9)
Arthralgia	2 (1.7)	7 (6.1)	0	2 (1.8)	2 (1.7)
Psychotic disorder	5 (4.3)	7 (6.1)	4 (3.8)	2 (1.8)	2 (1.7)
Agitation	7 (6.0)	6 (5.3)	6 (5.7)	3 (2.7)	4 (3.5)
Fatigue	0	4 (3.5)	5 (4.8)	3 (2.7)	6 (5.2)
Nausea	10 (8.5)	4 (3.5)	7 (6.7)	7 (6.2)	5 (4.3)
Schizophrenia	2 (1.7)	4 (3.5)	6 (5.7)	6 (5.3)	5 (4.3)
Diarrhoea	2 (1.7)	2 (1.8)	2 (1.9)	6 (5.3)	7 (6.1)
Stomach discomfort	3 (2.6)	2 (1.8)	1 (1.0)	3 (2.7)	6 (5.2)
Vomiting	6 (5.1)	2 (1.8)	4 (3.8)	8 (7.1)	3 (2.6)

[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.