AstraZeneca

Clinical Study Report

Drug substance: Quetiapine fumarate

Study code: 5077IL/0041

Date: 02 March 2006

A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Sustained-release Formulation Quetiapine Fumarate (SEROQUEL™) and Placebo in the Treatment of Patients With Schizophrenia

Study dates: First patient enrolled: 7 March 2001
Last patient completed: 16 May 2002

Phase of development: Phase III

International coordinating 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**	
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A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Sustained-release Formulation Quetiapine Fumarate (SEROQUEL™) and Placebo in the Treatment of Patients With Schizophrenia

International coordinating investigator

None assigned.

Study centers

This study was conducted at 49 centers in the United States (45) and Canada (4).

Publications

None at report time.

Study dates		**Phase of development**
First patient enrolled	7 March 2001	Phase III (Therapeutic confirmatory)
Last patient completed	16 May 2002	

Objectives

Primary: To demonstrate superior efficacy of quetiapine sustained-release (SR) tablets compared with placebo in the treatment of patients with schizophrenia.
Secondary: To assess the tolerability and safety of quetiapine SR tablets administered once daily as compared with placebo in patients with schizophrenia; to assess the tolerability and safety of quetiapine SR therapy initiated at a dose of 300 mg; and to assess the similarity of the safety and efficacy profiles of quetiapine SR tablets and marketed quetiapine immediate-release (IR) tablets.

Study design

This 6-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comprised a screening visit and a 42-day treatment period, which began within 7 days of screening. All patients were hospitalized for the first 10 days of treatment. After baseline assessments on Day 1, patients were assigned to 1 of 6 possible treatments: quetiapine SR at 300, 600, or 800 mg daily, quetiapine IR at 300 or 600 mg daily (in 2 divided doses), or placebo. Prohibited psychoactive

medications were discontinued at least 48 hours before baseline assessments, with depot and long-acting antipsychotics discontinued at least 1 dosing interval before baseline assessments. After a patient started treatment, efficacy and safety assessments were made on Days 4, 8 (Week 1), 15 (Week 2), 28 (Week 4), and 42 (Week 6) or last visit.

Target patient population and sample size

Patients, aged 18 to 65 years and hospitalized for ≤1 month with symptoms of schizophrenia,[1] were eligible for enrollment if they had a Positive and Negative Syndrome Scale (PANSS) total score of ≥60 on screening and Day 1, a score of ≥4 on at least one of the predesignated PANSS individual items (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution) on Day 1, and a score of ≥4 on the Clinical Global Impression (CGI) Severity of Illness item, with evidence of worsening in the 3 weeks before enrollment. Outpatients who otherwise qualified were eligible for enrollment as long as they agreed to be hospitalized for the first 10 days of treatment. Eighty evaluable patients per treatment group were sufficient for 90% power over all 3 quetiapine SR treatment groups (adjusted for multiple comparisons), assuming a mean (SD) difference of 15.5 (25.8) points between active treatment and placebo for change from baseline PANSS total score at Day 42.

Investigational product and control groups: dosage, mode of administration and batch numbers

Patients assigned to quetiapine SR began treatment at 300 mg/day on Day 1; patients assigned to higher doses had their doses increased according to the provided dose-administration scheme to reach either 600 mg on Day 5 or 800 mg on Day 8. For quetiapine SR doses, 200- and 300-mg oral tablets were provided (Batch/Formulation Nos. 9077C/F12840 and 9052C/F12527, respectively). Patients assigned to quetiapine IR began treatment at 50 mg/day on Day 1; daily doses were increased according to the provided dose-administration scheme (which matched current labeling instructions) to reach either 300 mg/day on Day 4 or 600 mg/day on Day 6. For quetiapine IR doses, 25-, 100-, and 200-mg oral tablets (Batch/Formulation Nos. 7501B/F12864, 6081C/F12689, and 6082C and 6083C/F12690, respectively) were provided. SR-treated patients took active tablets in the morning and placebo tablets in the evening; IR-treated patients took active tablets in the morning and evening, with placebo tablets per packaging configuration. Placebo tablets were available to match the 200- and 300-mg quetiapine SR tablets (Batch/Formulation Nos. ST73043-001-FA03/F12422 and ST73042-001-FB02 to FB06/F12416) and the 25-, 100- and 200-mg quetiapine IR tablets (Batch/Formulation Nos. 8021B/F12636, 8022B/F12637, and 1012C and 7552F/F12638).

Duration of treatment

Study medication was administered up to a maximum of 42 days, less if patients withdrew from the study early.

Criteria for evaluation: efficacy variables

0 Primary variable: change in PANSS total score from baseline to Day 42

[1] In accord with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition revised (DSM-IV 1994), for 1 of the 4 accepted subtypes of schizophrenia: catatonic, disorganized, paranoid, or undifferentiated.

1 Secondary variables: PANSS total score; Positive, Negative, and General Psychopathology subscale scores; activation factor score; and depression item score at each visit and changes from baseline at each postbaseline visit; change in PANSS total score from baseline to Day 4 (data for quetiapine-treatment groups pooled across doses within formulation); PANSS response at Day 42, ie, ≥30% decrease in PANSS total score from baseline (and alternative PANSS response at the ≥40% and ≥50% levels); CGI Severity of Illness score and change from baseline at each visit; and CGI Global Improvement score at each visit after baseline

Criteria for evaluation: safety variables

2 Overall adverse events (AEs), serious adverse events (SAEs), and AEs leading to withdrawal; special-interest AEs (and onset), including somnolence, tachycardia, and postural hypotension (and related AEs), dizziness, and syncope; special safety-area AEs, including AEs related to EPS, QT prolongation, diabetes mellitus, neutropenia/agranulocytosis, and suicidality; clinical laboratory test results, vital signs and electrocardiogram (ECG) results, and weight and body mass index—changes from baseline and clinically important results; metabolic syndrome risk factors; Simpson-Angus Scale and Abnormal Involuntary Movement Scale (AIMS) total scores per visit and changes from baseline; Barnes Akathisia Rating Scale Clinical Global Assessment score; and use of anticholinergic medications

Statistical methods

All variables were summarized using descriptive statistics, as appropriate. The analysis establishing the primary objective tested for differences between each of the SR groups versus the placebo group in change from baseline in PANSS total score, using an analysis of covariance (ANCOVA) that included terms for center, treatment, and baseline score. The Hochberg (1988) method was used to adjust for multiplicity in testing quetiapine SR treatments to ensure that the overall statistical significance of the trial was 0.05. P-values were calculated as pairwise differences between least-squares means of groups, and 95% confidence intervals (95% CIs) for each difference were constructed. Statistical tests for secondary efficacy endpoints and testing of either quetiapine IR group were not adjusted for multiplicity. Other secondary variables were analyzed with the same ANCOVA methods used in the primary analysis (without correcting for multiplicity). Categorical endpoints such as PANSS response or CGI Global Improvement scores were analyzed using the Cochran-Mantel-Haenszel chi-square test. All statistical analyses used last-observation-carried-forward (LOCF) values for patients who withdrew early or had missing data.

Patient population

The randomized study population comprised 532 patients enrolled from 49 centers. Treatment-group sizes were as follows: placebo, n=84; quetiapine SR 300 mg, n=91; quetiapine SR 600 mg, n=92; quetiapine SR 800 mg, n=89; quetiapine IR 300 mg, n=90; and quetiapine IR 600 mg, n=86. At least 50% of patients in each treatment group withdrew early (placebo, 66%; quetiapine SR 300 mg, 62%; quetiapine SR 600 mg, 57%; quetiapine SR 800 mg, 51%; quetiapine IR 300 mg, 54%; and quetiapine IR 600 mg, 62%). Early withdrawal was most commonly due to lack of efficacy or withdrawn consent and not AEs. In all, 222 patients completed treatment (placebo, 35%; quetiapine SR 300 mg, n=39%; quetiapine SR 600 mg, 44%; quetiapine SR 800 mg, 49%; quetiapine IR 300 mg, 46%; and quetiapine IR 600 mg, 38%). All 532 enrolled patients were included in the safety population, and 498 were included in the primary analysis data set (modified intent to treat [MITT]).

The study population comprised primarily white and black patients (49.2% and 37.2%, respectively); Hispanic patients and patients of other races comprised 11.1% and 2.4%, respectively. Mean age was 39 years (range: 18 to 64), with approximately 50% of the population between 18 and 39 years old and 50% between 40 and 65 years old. Mean weight and BMI were 87.2 kg and 29.4 kg/m^2, respectively, with similar proportions of patients having BMI values in each of the following ranges: 18.5 to <25 kg/m^2 (30.6%), 25 to <30 kg/m^2 (31.9%), and 30 to <40 kg/m^2 (27.2%). Median age at first treatment for illness was 22 years. Approximately 91% of patients entered the study with previous positive responses to antipsychotic medications (full response, 29%; partial response, 62%). Overall, treatment groups were similar with respect to demographic characteristics and baseline disease characteristics, with the majority of patients per treatment group having paranoid schizophrenia (75.6% to 88.0%).

Efficacy results

Table S1 Overview of efficacy results at Day 42 (LOCF, MITT population)

Summary statistic	Placebo (n=78)	QTP SR 300 mg (n=83)	QTP SR 600 mg (n=87)	QTP SR 800 mg (n=85)	QTP IR 300 mg (n=85)	QTP IR 600 mg (n=80)
PANSS total score, LSmean change from BL[a]	-5.19	-5.01	-13.01[b]	-11.17	-9.42	-6.97
PANSS response, % patients with ≥30% improvement[c]	14.1	12.0	24.1	23.5	18.8	13.8
CGI Severity of Illness score, LSmean change from BL	–0.42	–0.50	–0.66	–0.68	–0.59	–0.51
CGI Global Improvement, % patients with improvement[d]	48.7	50.6	64.4	55.3	57.6	53.8
% much/very much improved	19.2	30.1	33.3	35.3[e]	42.3[e]	26.3

[a] Mean baseline PANSS total scores across treatment groups were 91.1, 91.5, 92.4, 89.0, 89.5, and 88.6, respectively.
[b] Significantly different from placebo (analysis of covariance adjusted for multiplicity, p=0.033).
[c] In PANSS total score.
[d] Includes patients improved, much improved and minimally improved per CGI Global Improvement rating.
[e] Significantly different from placebo (Cochran-Mantel-Haenszel analysis, p=0.015 for SR 800 mg and 0.005 for IR 300 mg).

BL Baseline. CGI Clinical Global Impression. LOCF Last observation carried forward. LSmean Least-squares mean. MITT Modified intent-to-treat. PANSS Positive and Negative Syndrome Scale.
QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.

The primary efficacy objective was met for the quetiapine SR 600-mg dose. At the final visit, the estimated mean difference between SR 600 mg and placebo (–7.82) for change from baseline in PANSS total score (primary efficacy variable) was significant in favor of SR 600 mg (p=0.033, ANCOVA, adjusted for multiplicity). In the same ANCOVA, the estimated mean differences between SR 300 mg and placebo and between SR 800 mg and placebo were not statistically significant; however, a numerical advantage in symptom improvement was seen with SR 800 mg compared with placebo. In secondary analyses, a significant difference between quetiapine SR 600 mg and placebo was seen as early as Day 15 and was sustained from Day 28 through to Day 42 (LOCF).
Treatment with quetiapine SR 600 and SR 800 mg provided meaningful clinical improvement (≥30% decrease in PANSS total score) in numerically greater proportions of patients (24% each), compared with placebo (14%); however, differences were not statistically significant. On other secondary endpoints, quetiapine SR 600 and SR 800 mg also provided consistent numerical advantages, compared with placebo, but the only statistically significant difference was seen between SR 800 mg and placebo for proportions of patients much or very much improved per CGI Global Improvement score (p=0.015, Cochran-Mantel-Haenszel analysis).

The effects of quetiapine IR 300 and IR 600 mg on the endpoints selected to address the secondary efficacy objective[2] were not consistently different from those of placebo, although a statistically significant difference was seen for the proportion of patients much or very much improved per CGI Global Improvement at the IR 300-mg dose. Conclusions relative to the study's secondary efficacy objective were as follows: In reducing the symptoms of schizophrenia, quetiapine SR 600 mg achieved efficacy versus placebo, while quetiapine IR 600 mg—a dose with known efficacy in the treatment of schizophrenia—did not; neither quetiapine formulation differed from placebo at the 300-mg dose.

Safety results

Quetiapine SR was generally safe and well tolerated across the dose range of 300 to 800 mg. No deaths were reported and few SAEs occurred (Table S2).

Table S2 Number (%) of patients with AEs in any category (safety population)

Category	Placebo	QTP SR 300 mg	QTP SR 600 mg	QTP SR 800 mg	QTP SR Total	QTP IR 300 mg	QTP IR 600 mg	QTP IR Total
	(n=84)	(n=91)	(n=92)	(n=89)	(n=272)	(n=90)	(n=86)	(n=176)
Patients, number (%)[a]								
With any AE	64 (76.2)	78 (85.7)	83 (90.2)	75 (84.3)	236 (86.8)	75 (83.3)	73 (84.9)	148 (84.1)
With SAEs	3 (3.6)	2 (2.2)	4 (4.3)	0	6 (2.2)	1 (1.1)	2 (2.3)	3 (1.7)
SAEs leading to death	0	0	0	0	0	0	0	0
With DAEs	8 (9.5)	5 (5.5)	9 (9.8)	1 (1.1)	15 (5.5)	6 (6.7)	7 (8.1)	13 (7.4)
With drug-related AEs	40 (47.6)	53 (58.2)	60 (65.2)	48 (53.9)	161 (59.2)	47 (52.2)	54 (62.8)	101 (57.4)

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

AE Adverse event. DAE AE leading to discontinuation. QTP IR Quetiapine immediate release.
QTP SR Quetiapine sustained release. SAE Serious AE.

The most common AEs across all SR-treatment groups were those of the nervous, gastrointestinal, and vascular systems and included orthostatic hypotension, sedation or somnolence, headache, dry mouth, dizziness, and increased heart rate or tachycardia (Table S3). AEs were generally characterized as mild or moderate. A quetiapine SR 300-mg starting dose and the dose-administration schedule used to increase daily dose to 800 mg were well tolerated. Dose initiation at the SR 300-mg dose did not result in increased incidences of early withdrawal or increased rates of AEs assessed as drug-related, compared with IR 300 mg (Table S2). Increasing the SR dose to reach target doses of 600 and 800 mg daily (and treatment at those doses) did not produce consistent dose-related changes in safety indices.

There were no instances of agranulocytosis with any quetiapine treatment. The expected mean increases in pulse rate seen with quetiapine SR were also seen with quetiapine IR. Small mean and median weight gains of about 2 kg were seen for patients who completed 42 days of quetiapine treatment (SR or IR). Findings of clinically important laboratory, vital signs, or ECG findings were infrequent, with clinically important vital signs most commonly seen as increases in heart rate (≥15 bpm) in all treatment groups.

Incidences of extrapyramidal disorder (MedDRA preferred term) were low: 2.4%, 2.2%, and 0% among patients treated with placebo, quetiapine SR, and quetiapine IR, respectively. Individual AEs predesignated as potentially related to EPS were infrequent, rarely led to withdrawal, and were rated

[2]To assess the similarity of the efficacy profiles of quetiapine SR and marketed quetiapine IR tablets.

either mild or moderate. When these AEs were aggregated, overall rates for SR- and IR-treated patients were similar and somewhat greater than that with placebo; however, anticholinergic use for EPS was greatest among placebo-treated patients, compared with SR- and IR-treated patients. Anticholinergic use did not increase over time in any treatment group, and this was consistent with results of neurological assessments (Simpson Angus Scale, AIMS, and BARS global assessment scores), which showed that the majority of patients (all treatment groups) either improved or did not change relative to EPS, abnormal involuntary movements, or akathisia. Additionally, on each of the scales, slightly greater proportions of placebo-treated patients worsened, compared with quetiapine-treated patients (SR and IR), supporting a conclusion of little or no treatment-emergent EPS with quetiapine SR.

Overall, the safety profile of quetiapine SR was similar to that of quetiapine IR.

Table S3 Number (%) of patients with commonly reported AEs (incidence ³5% in any quetiapine treatment group) (safety population)

MedDRA preferred term [a]	Number (%) of patients [b]																					
	Placebo		QTP SR 300 mg		QTP SR 600 mg		QTP SR 800 mg		QTP SR Total		QTP IR 300 mg		QTP IR 600 mg		QTP IR Total							
	(n=84)		(n=91)		(n=92)		(n=89)		(n=272)		(n=90)		(n=86)		(n=176)							
Orthostatic hypotension	15	(17.9)	21	(23.1)	21	(22.8)	24	(27.0)	66	(24.3)	16	(17.8)	19	(22.1)	35	(19.9)						
Headache	21	(25.0)	15	(16.5)	18	(19.6)	14	(15.7)	47	(17.3)	17	(18.9)	13	(15.1)	30	(17.0)						
Sedation	10	(11.9)	14	(15.4)	22	(23.9)	24	(27.0)	60	(22.1)	17	(18.9)	22	(25.6)	39	(22.2)						
Dry mouth	1	(1.2)	12	(13.2)	18	(19.6)	13	(14.6)	43	(15.8)	8	(8.9)	9	(10.5)	17	(9.7)						
Somnolence	7	(8.3)	11	(12.1)	15	(16.3)	12	(13.5)	38	(14.0)	18	(20.0)	11	(12.8)	29	(16.5)						
Constipation	1	(1.2)	10	(11.0)	8	(8.7)	7	(7.9)	25	(9.2)	3	(3.3)	12	(14.0)	15	(8.5)						
Dizziness	3	(3.6)	9	(9.9)	17	(18.5)	11	(12.4)	37	(13.6)	9	(10.0)	10	(11.6)	19	(10.8)						
Hypotension	2	(2.4)	9	(9.9)	5	(5.4)	4	(4.5)	18	(6.6)	6	(6.7)	9	(10.5)	15	(8.5)						
Tachycardia	2	(2.4)	7	(7.7)	8	(8.7)	6	(6.7)	21	(7.7)	10	(11.1)	13	(15.1)	23	(13.1)						
BP diastolic decreased	2	(2.4)	7	(7.7)	2	(2.2)	4	(4.5)	13	(4.8)	3	(3.3)	7	(8.1)	10	(5.7)						
Fatigue	5	(6.0)	7	(7.7)	4	(4.3)	2	(2.2)	13	(4.8)	3	(3.3)	5	(5.8)	8	(4.5)						
Heart rate increased	4	(4.8)	6	(6.6)	11	(12.0)	12	(13.5)	29	(10.7)	5	(5.6)	10	(11.6)	15	(8.5)						
Insomnia	11	(13.1)	6	(6.6)	11	(12.0)	10	(11.2)	27	(9.9)	8	(8.9)	6	(7.0)	14	(8.0)						
Nausea	10	(11.9)	5	(5.5)	10	(10.9)	6	(6.7)	21	(7.7)	4	(4.4)	8	(9.3)	12	(6.8)						
Dyspepsia	5	(6.0)	5	(5.5)	6	(6.5)	5	(5.6)	16	(5.9)	2	(2.2)	8	(9.3)	10	(5.7)						
Agitation	6	(7.1)	5	(5.5)	6	(6.5)	2	(2.2)	13	(4.8)	2	(2.2)	3	(3.5)	5	(2.8)						
BP systolic decreased	3	(3.6)	4	(4.4)	1	(1.1)	5	(5.6)	10	(3.7)	3	(3.3)	5	(5.8)	8	(4.5)						
Back pain	3	(3.6)	4	(4.4)	2	(2.2)	1	(1.1)	7	(2.6)	3	(3.3)	4	(4.7)	7	(4.0)						
Weight increased	2	(2.4)	4	(4.4)	5	(5.4)	8	(9.0)	17	(6.3)	8	(8.9)	8	(9.3)	16	(9.1)						
Postural dizziness	2	(2.4)	3	(3.3)	4	(4.3)	4	(4.5)	11	(4.0)	1	(1.1)	4	(4.7)	5	(2.8)						
Anxiety	0		3	(3.3)	4	(4.3)	4	(4.5)	11	(4.0)	2	(2.2)	3	(3.5)	5	(2.8)						
Vomiting	7	(8.3)	2	(2.2)	9	(9.8)	2	(2.2)	13	(4.8)	3	(3.3)	1	(1.2)	4	(2.3)						
Restlessness	1	(1.2)	2	(2.2)	1	(1.1)	4	(4.5)	7	(2.6)	0		0		0							
Akathisia	1	(1.2)	0		4	(4.3)	1	(1.1)	5	(1.8)	3	(3.3)	4	(4.7)	7	(4.0)						
Tremor	0		1	(1.1)	4	(4.3)	1	(1.1)	6	(2.2)	1	(1.1)	4	(4.7)	5	(2.8)						
Vision blurred	0		1	(1.1)	6	(6.5)	2	(2.2)	9	(3.3)	1	(1.1)	1	(1.2)	2	(1.1)						
Lethargy	0		1	(1.1)	1	(1.1)	0		2	(0.7)	1	(1.1)	5	(5.8)	6	(3.4)						

[a] Sorted by decreasing order of frequency as summarized for the QTP SR 300-mg treatment group. AEs with incidence rates that rounded up to 5% (any QTP group) are included.

[b] Patients with multiple occurences of the same event are counted only once in that AE category.

AEs Adverse events. MedDRA Medical dictionary for regulatory activities. QTP IR Quetiapine immediate release. QTP SR Quetiapine sustained release.