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Clinical Study Report	
Drug Substance	Quetiapine Fumarate
Study Code	D1444C00146
Edition No	1
Date	9 June 2006

A 6-week International, Multicenter, Double-blind, Randomized, Parallel-group, Phase III Study to Evaluate the Feasibility of Switching from Immediate-release Quetiapine Fumarate (SEROQUEL â) to Sustained-release Quetiapine Fumarate (400 to 800 mg/day) in Outpatients with Schizophrenia

Study dates:	First subject enrolled: 2 November 2004 Last subject completed: 9 March 2006
Phase of development:	Therapeutic confirmatory (III)
International Co-ordinating Investigator:	None assigned

This study was performed in compliance with Good Clinical Practice.

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Drug Substance(s)	Quetiapine fumarate	**SYNOPSIS**	
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A 6-week International, Multicenter, Double-blind, Randomized, Parallel-group, Phase III Study to Evaluate the Feasibility of Switching from Immediate-release Quetiapine Fumarate (SEROQUEL®) to Sustained-release Quetiapine Fumarate (400 to 800 mg/day) in Outpatients with Schizophrenia

International co-ordinating investigator

None assigned.

Study center(s)

This study was conducted at 74 centers in 14 countries: Australia (6 centers), Bulgaria (5 centers), Canada (9 centers), Estonia (3 centers), Finland (4 centers), Germany (7 centers), Hungary (6 centers), Italy (4 centers), Latvia (3 centers), Lithuania (4 centers), South Africa (4 centers), Singapore (1 center), Spain (2 centers), United States (US) (16 centers).

Publications

None at issue.

Study dates		**Phase of development**
First subject enrolled	2 November 2004	Therapeutic confirmatory (III)
Last subject completed	9 March 2006	

Objectives

Primary objective

To demonstrate that the efficacy of the sustained release (SR) formulation of quetiapine was not inferior to the immediate release (IR) formulation by evaluating the proportion of patients who discontinued study treatment due to lack of therapeutic response or whose Positive and Negative Syndrome Scale (PANSS) total score increased 20% or more from randomization to any visit. The secondary outcome variable was the proportion of patients discontinuing study treatment due to adverse events (AEs) or lack of efficacy.

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Secondary objectives

Efficacy

1. To document maintained efficacy of quetiapine when switching from quetiapine IR treatment to quetiapine SR treatment, by evaluating clinical symptoms in patients with schizophrenia as assessed by the change in PANSS total score from randomization to Day 42.

2. To document maintained stability in PANSS Positive, Negative and General Psychopathology subscale scores from randomization to Day 42.

3. To document maintained stability of clinical global status when switching from quetiapine IR treatment to quetiapine SR treatment by evaluation of the proportion of patients with a CGI Global Improvement score =4 at Day 42 and the change in CGI Severity of Illness score from randomization to Day 42.

Safety

To document maintained stability of safety/tolerability when switching from quetiapine IR treatment to quetiapine SR treatment.

Study design

This 6-week international, multicenter, double-blind, randomized, parallel group, double-dummy study determined the feasibility of switching quetiapine IR treatment administered twice daily in clinically stable patients with schizophrenia (CGI Severity of Illness =3) to treatment with the same total dose of quetiapine SR administered once daily.

Run-in period: Prior to randomization the patients completed a 4-week run-in period to ensure that they were clinically stable (CGI Severity of Illness =3 with no change from enrollment) and were receiving a stable dose of quetiapine IR (400 mg/day, 600 mg/day, or 800 mg/day). Patients who were taking quetiapine IR 300 to 450 mg/day at enrollment received quetiapine IR 400 mg/day during the run-in period, patients who were taking 475 to 650 mg/day at enrollment received 600 mg/day during the run-in period, and patients who were taking 675 to 800 mg/day at enrollment received 800 mg/day during the run-in period.

Treatment period: The 6-week double-blind phase of the study started at randomization. Within each dose stratum (400 mg/day, 600 mg/day, or 800 mg/day) the patients were randomized at a ratio of 1:2 either to continue treatment with twice daily quetiapine IR at the same total daily dose taken during the run-in period, or to switch to once daily quetiapine SR at the total daily dose of quetiapine IR taken during the run-in period. To maintain blinding, patients randomized to once daily quetiapine SR took placebo in the morning and quetiapine SR in the evening.

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Target subject population and sample size

Male and female patients aged between 18 and 65 years with Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic criteria of schizophrenia, who were clinically stable (CGI Severity of Illness =3) and receiving a stable dose of quetiapine, were enrolled in the study.
With a sample size of 480 patients (320 patients in the quetiapine SR group and 160 patients in the quetiapine IR group), the upper limit of the observed 2-sided 95% confidence interval of the difference between the treatment groups with respect to the primary variable was expected to be less than 6% (the selected non-inferiority margin) with 80% power, assuming an expected rate of 6% for each group and no difference between the groups. Assuming that about 20% of the patients would be withdrawn during the run-in period, approximately 620 patients were planned for enrollment.

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

Study treatment was given in tablets of the following doses (formulation #/batch #): quetiapine IR tablet 100 mg (F12689/12965C03, 6510J, 6516J), quetiapine IR tablet 200 mg (F12690/21036B04, 22368F04, 23817H04, 23816K04, 0215K), quetiapine SR tablet 300 mg (F12527/21042J04, 9005K), quetiapine SR tablet 400 mg (F12910/ 21440G04, 22327C04, 9052K, 9008K), placebo quetiapine IR tablet 100 mg (F12637/ 12961D03, ST70142-015-FA06), placebo quetiapine IR tablet 200 mg (F12638/ 11272F03, 13809B03, 30941A05, 1509C), placebo quetiapine SR tablet 300 mg (F12416/ 22372I04, 21043G04, ST73042-001-FC01), placebo quetiapine SR tablet 400 mg (F12968/21305B04, 21306J04, ST76039-001-FA05).

Duration of treatment

After a run-in period of 4 weeks, the patients received up to 42 days (6 weeks) of double-blind treatment.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: The proportion of patients who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit.

- Secondary variables: The proportion of patients discontinuing study treatment due to AEs or lack of efficacy; the change in PANSS total score from randomization to Day 42; the change in PANSS Positive, Negative and General Psychopathology subscale scores from randomization to Day 42; the proportion of patients with a CGI Global Improvement score =4 at Day 42; the change in CGI Severity of Illness score from randomization to Day 42.

Safety

Safety assessments included: AEs, 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, and data for other specific safety areas (extrapyramidal symptom (EPS) events, diabetes mellitus, QT prolongation, neutropenia/agranulocytosis, metabolic risk factors, suicidality, and weight changes).

Statistical methods

The standard statistical approach for proof of non-inferiority by introducing a non-inferiority margin was used. Based on a study of a different atypical antipsychotic in which there was an observed difference between active treatment and placebo relapse rates of 15 percentage points at 6 weeks after randomization, 40% of this observed difference equal to a non-inferiority margin of 6% was selected for use in this study. A 2-sided 95% confidence interval was calculated for the difference between the proportion of patients who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomization to any visit in the quetiapine SR and quetiapine IR treatment groups, respectively. If the upper limit of this confidence interval was less than the selected 6% margin, the quetiapine SR treatment was considered not inferior to quetiapine IR treatment. The 2-sided confidence interval for the difference in withdrawal rates was computed with the method based on the Wilson score method for a single proportion without continuity correction.

The modified intention to treat (MITT) population was the population for the primary analysis. A per protocol (PP) analysis was performed to test the robustness of the MITT results. According to current International Conference on Harmonisation (ICH) and Committee for Proprietary Medicinal Products (CPMP) guidelines, the PP population should be accorded equal importance to the MITT population when assessing the primary objective in non-inferiority studies.

To support the primary analysis, a secondary variable - discontinuation due to AE or lack of efficacy - was analyzed in the same way as the primary variable as part of the confirmatory strategy of the study. The primary analysis and this secondary analysis were handled with a fixed sequence approach, ie, statistically significant non-inferiority for this secondary analysis was only claimed if statistically significant non-inferiority could be claimed for the primary analysis. An analysis of covariance (ANCOVA) model with mixed effects was used for the analysis of the change from baseline to the end of treatment for PANSS, SAS and BARS rating scales. For CGI Global Improvement, the proportions were calculated for each treatment sequence together with confidence intervals for these proportions using the Wilson score method. Descriptive statistics were used for safety assessments.

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Patient population

A total of 630 patients were enrolled in the study, and 562 patients were included in the enrolled safety population. Randomization was performed within each dose stratum to either quetiapine SR or quetiapine IR group. The randomized safety population comprised 497 patients, of which 331 were in the quetiapine SR group, and 166 in the quetiapine IR group. Three hundred three (91.5%) quetiapine SR-treated patients and 156 (94.0%) quetiapine IR-treated patients completed the randomized treatment phase. Seven (2.1%) quetiapine SR-treated patients and 1 (0.6%) quetiapine IR-treated patient withdrew due to lack of therapeutic response. The proportion of patients that discontinued due to an AE was small (1.5% in the quetiapine SR group, and 1.2% in the quetiapine IR group) and similar in the two quetiapine groups.

The quetiapine SR and quetiapine IR groups were well balanced with respect to demographic and baseline disease characteristics. The randomized safety, enrolled safety, and PP populations were similar to MITT population in distribution of demographic and baseline disease characteristics. The mean age of the patients was 39.9 years in both the quetiapine SR and quetiapine IR groups. Caucasian (approximately 84.0%) and Black (approximately 12.0%) patients made up the largest part of the population. In the quetiapine SR group, the sex distribution was even (50.9% men and 49.1% women), while in the quetiapine IR group there were slightly more men than women (57.8% men and 42.2% women). The average baseline weight of patients in the MITT population was approximately 83 kg, and the majority of patients had baseline BMI values in the 18.5 to <25 kg/m^2, 25 to <30 kg/m^2, or 30 to <40 kg/m^2 range. Approximately 85% of patients across the groups were diagnosed as having paranoid schizophrenia. At randomization, the mean PANSS total score was approximately 59.4, and the mean CGI Severity of Illness score was approximately 2.6 in the quetiapine SR and IR treatment groups.

Efficacy results

A summary of efficacy measurements in the quetiapine SR and quetiapine IR groups is provided in Table S-1.

Table S- 1 Efficacy results at Day 42 (Week 6) (LOCF, MITT population)

	QTP SR TOTAL N=330	**QTP IR TOTAL N=166**
Primary variable		
Patients who discontinued due to lack of efficacy or whose PANSS total score increased ≥20% from baseline at any visit: n(%)	30 (9.1)	12 (7.2)
Discontinued due to lack of efficacy	7 (2.1)	1 (0.6)
PANSS total score increased ≥20%	28 (8.5)	11 (6.6)
Secondary variables		
Discontinued study treatment due to adverse event or lack of efficacy, n (%)	11 (3.3)	3 (1.8)

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Table S- 1 Efficacy results at Day 42 (Week 6) (LOCF, MITT population)

	QTP SR TOTAL N=330	QTP IR TOTAL N=166
PANSS total score, LS mean change from baseline (SE)	-3.7 (0.8)	-4.2 (0.9)
PANSS positive score, LS mean change from baseline (SE)	-0.8 (0.2)	-0.9 (0.3)
PANSS negative score, LS mean change from baseline (SE)	-1.1 (0.2)	-1.3 (0.3)
PANSS general psychopathology score, LS mean change from baseline (SE)	-1.9 (0.4)	-2.0 (0.5)
CGI Global Improvement score, % of patients with no change or improvement [a]	92.7	93.4
CGI Severity of Illness score, mean change from baseline (SD)	-0.0 (0.6)	-0.1 (0.6)

[a] No change or improvement means that the patient was rated 'No change', 'Minimally improved', 'Much improved', or 'Very much improved' in the CGI Global Improvement scale.

CGI Clinical Global Impression. IR Immediate-release. LOCF Last observation carried forward. LS Least squares. MITT Modified intention-to-treat. PANSS Positive and Negative Syndrome Scale. 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.

Maintenance of treatment effect in clinically stable patients was observed in both quetiapine groups over the course of the study, with all efficacy measures remaining stable or showing improvement. The proportion of patients with lack of efficacy after switching to quetiapine SR was 9.1%, compared to 7.2% of patients maintained on quetiapine IR. The point estimate for the treatment difference between quetiapine SR and quetiapine IR in the MITT population was 1.86% (95% CI -3.78, 6.57, p-value for 1-sided test = 0.0431). As the upper limit of 95% CI exceeded the selected margin of 6%, non-inferiority could not be shown in this population. However, very few patients were discontinued due to lack of efficacy (2.1% and 0.6% in the quetiapine SR and quetiapine IR groups, respectively), and most patients with increase of 20% from baseline PANSS total score completed the study (19/28 [68%] quetiapine SR patients, 11/11 [100%] quetiapine IR patients). An examination of the lack of efficacy over time did not reveal differences in pattern between the 2 groups. Overall this suggests that efficacy is maintained when patients are switched to quetiapine SR.

The per protocol analysis provided further support that efficacy is maintained on switching from quetiapine IR to quetiapine SR. In this analysis the proportions of patients with lack of efficacy were 5.3% and 6.2% in the quetiapine SR and quetiapine IR groups, respectively, with a treatment difference of -0.83%. The upper limit of the 95% CI was lower than the selected margin of 6% (95% CI -6.75, 3.71: p-value for 1-sided test = 0.0017), demonstrating non-inferiority.

The maintained treatment effect of quetiapine after switching from the IR formulation to the SR formulation was also supported by the secondary analysis (patients discontinuing study treatment due to an AE or due to lack of efficacy). After 42 days of study treatment, the proportion of patients who discontinued due to AE or lack of efficacy was low, and similar between the two treatment groups (3.3% and 1.8% for quetiapine SR and quetiapine IR, respectively). Maintenance of treatment effect in patients switched to

quetiapine SR was further supported by the other efficacy measures, ie changes from baseline in PANSS total score at Day 42 (improvements of -3.7 points and -4.2 points in the quetiapine SR and quetiapine IR groups, respectively), CGI Global Improvement scores (absence of worsening for 93% of patients in both groups) and CGI Severity of Illness scores (no change from baseline and -0.1 point change from baseline to Day 42 in quetiapine SR and quetiapine IR groups, respectively).

Safety results

The number (%) of patients in the quetiapine SR and quetiapine IR groups who had at least 1 AE in any category is summarized in Table S- 2.

Table S- 2 Various categories of adverse events (randomized safety population)

	QTP SR TOTAL N=331	**QTP IR TOTAL N=166**
	n (%)	**n (%)**
Adverse events	128 (38.7)	59 (35.5)
Serious adverse events	8 (2.4)	4 (2.4)
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	8 (2.4)	4 (2.4)
Drug-related adverse events[a]	57 (17.2)	26 (15.7)
Adverse events leading to discontinuation[b]	4 (1.2)	2 (1.2)
Total number of adverse events		
Adverse events	249	108
Serious adverse events	9	6
Drug-related adverse events[a]	90	39

[a] As judged by the investigator.

[b] In addition 1 patient in the QTP SR group was discontinued in the randomized period due to an adverse event started in the run-in period.

IR Immediate-release. N Number of patients in treatment group. n Number of patients. QTP Quetiapine. SR Sustained-release.
Note: Patients with multiple events in the same category are counted only once in that category.

The safety analysis showed that switching from quetiapine IR to quetiapine SR treatment was safe and well tolerated. The two treatment groups were similar in their overall AE profiles, with similar percentages of patients in each group reporting an AE during the randomized period (quetiapine SR 38.7%, quetiapine IR 35.5%). Quetiapine treatment was well tolerated, with few patients reporting an SAE (2.4% in both the quetiapine SR and quetiapine IR groups) and few discontinuations in the study due to AEs. The percentage of AEs as determined by the investigator to be drug related, as well as the type and severity of AEs, was similar in the 2 treatment groups. The most common AEs recorded in both treatment groups were headache, dry mouth, somnolence, fatigue, dizziness and insomnia. The majority of AEs in both groups were either mild or moderate in intensity.

Changes in vital signs, ECG and laboratory parameters were similar in the 2 treatment groups. Other safety measures, including areas of specific safety interest, were also similar in the two treatment groups. 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, and an improvement or no worsening in symptomatology was noted in both groups at the end of treatment. Use of concomitant anticholinergic medication for treatment of EPS symptoms was low and similar in the 2 groups.

The low number of withdrawals due to AEs, and the overall similarity between the two treatment groups in AEs, vital signs and clinical laboratory data provide further evidence that switching to quetiapine SR from quetiapine IR treatment can be undertaken without additional clinical risk.