Drug product:	Seroquel™ tablets	**SYNOPSIS**	
Drug substance(s):	Quetiapine Fumarate		
Study code:	D1443L00004		
Date:	9 February 2008		

A 24-week, Multi-Centre, Open-label, Single-Arm, Phase IV Study of the Efficacy and Safety of Seroquel (Quetiapine Fumarate) with Daily Dose 600mg-750mg as Mono-therapy in the Treatment of Acute Schizophrenic Patients

Study dates		**Phase of development**
First patient enrolled	28 December 2006	Phase IV
Last patient completed	20 September 2007	

Objectives

Primary objective

The primary objective of the study was to evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy in the treatment of acute schizophrenic patients by evaluation of the change from baseline in PANSS total score at Day 56 using the last observation carried forward (LOCF) method.

Secondary objectives

Efficacy

1. To evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy to treat positive symptoms in acute schizophrenic patients by

evaluation of the change from baseline in PANSS positive symptom subscale score at Day 56 (LOCF).

2. To evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy to treat negative symptoms in acute schizophrenic patients by evaluation of the change from baseline in PANSS negative symptom subscale score at Day 56 (LOCF).

3. To evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy to treat aggression symptoms in acute schizophrenic patients by evaluation of the change from baseline in PANSS EC symptom score at Day 56 (LOCF).

4. To evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy to treat depressive symptoms in acute schizophrenic patients by evaluation of the change from baseline in MADRS total score at Day 56 (LOCF).

5. To evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy to improve sleep quality in acute schizophrenic patients by evaluation of the change from baseline in PSQI total score at Day 56 (LOCF).

6. To evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy in the treatment of acute schizophrenic patients by evaluation of the change from baseline in PANSS total score at Day 168 (LOCF).

7. To evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy to improve overall functioning in acute schizophrenic patients by evaluation of the change from baseline in GAS total score at Day 168 (LOCF).

8. To evaluate the efficacy of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy to improve sleep quality in acute schizophrenic patients by evaluation of the change from baseline in PSQI total score at Day 168 (LOCF).

Safety

1. To evaluate the safety of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy in the treatment of acute schizophrenic patients by evaluation of the incidence and severity of AEs from baseline at Day 168.

2. To evaluate the safety of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy in the treatment of acute schizophrenic patients by the change from baseline in prolactin level to Day 56 and Day 168 (LOCF).

3. To evaluate the safety of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy in the treatment of acute schizophrenic patients by the change from baseline in SAS total score to Day 56 and Day 168 (LOCF).

4. To evaluate the safety of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy in the treatment of acute schizophrenic patients by the change from baseline in AIMS total score to Day 56 and Day 168 (LOCF).

Study design

This was an open-label, single-arm, multi-centre, 24-week study to evaluate the efficacy and safety of quetiapine fumarate with daily dose 600mg-750mg used as mono-therapy in the treatment of schizophrenic patients (total psychiatric history between 1 month and 5 years). The eligible patient was allocated to study treatment with quetiapine fumarate on Day 1.

Target subject population and sample size

Male and female patients aged from 18 to 60 years old, hospitalised for the treatment of acute phase of schizophrenia (diagnosis based on CCMD-3) Approximately 120 patients from 10 centres were allocated to study treatment.

Investigational product: dosage, mode of administration and batch numbers

Quetipine fumarate was administered orally twice a day beginning on Day 1. The dose was started at 50mg/day on Day 1 and was increased to 300mg/day on Day 4 in line with the prescription information. Before Day 8, the quetiapine fumarate dose should be increased to at least 600mg/day but not more than 750mg/day. On Day 8-Day168, the quetiapine fumarate dose could be adjusted, at the investigator's discretion, from 600-750mg/day. A one-time dose reduction of 100 mg was allowed to improve patient tolerance at the discretion of the investigator from visit 4 to visit 6 (including visit 4 and vist 6). A one-time dose reduction of at most 200 mg was allowed to improve patient tolerance at the discretion of the investigator from visit 8 to visit 11 (including visit 8 and visit 11), but the daily dose of each patient should not be less than 400 mg. Once dose is reduced, it may not return to the original dose.

Study treatment was given in tablets of the following dose (formulation number): quetiapine fumarate 25 mg (MF3361), quetiapine fumarate 200 mg (MF3363), quetiapine fumarate 300 mg (MF3406).

Duration of treatment

Patients received open-label treatment for 168 days (24-week).

Criteria for evaluation (main variables)

Efficacy

- Primary variables: change from baseline in PANSS total score at Day 56 (LOCF)
- Secondary variables: change from baseline in PANSS positive symptom subscale score at Day 56 (LOCF); change from baseline in PANSS negative symptom subscale score at Day 56 (LOCF); change from baseline in PANSS EC symptom score at day 56; change from baseline in MADRS total score at Day 56 (LOCF);

change from baseline in PANSS total score at Day 168 (LOCF); change from baseline in GAS total score at Day 168 (LOCF); change from baseline in PSQI total score at Day 56 (LOCF); change from baseline in PSQI total score at Day 168 (LOCF).

Safety

Safety assessments included: the incidence and severity of AEs, change from baseline in prolactin level at Day 56 and Day168 (LOCF), change from baseline in SAS total score at Day 56 and Day 168 (LOCF), change from baseline in AIMS total score at Day 56 and Day 168 (LOCF).

Statistical methods

Analysis on efficacy endpoints was performed using the intent-to-treat population (ITT) as primary analysis and the per-protocol population (PP) for consistency check. Safety endpoints were performed in the safety population. The ITT population consisted of all allocated to study treatment patients who received at least one dose of study treatment and who had measurements at baseline and at least one post baseline PANSS assessment, PP population was defined as all ITT patients with no major protocol violations and/or deviations. The safety population consisted of all patients allocated to study treatment who received at least one dose of study treatment. LOCF method was used in the ITT analysis for missed efficacy data.

The changes from baseline in PANSS total score at Day 56 were analysed (using repeated analysis). Covariates included centre, visit, and baseline PANSS total score. If patients discontinued the study prior to Day 56, the last-visit observations were carried forward (LOCF). The results were presented in terms of mean changes and associated 95% confidence intervals.

The changes from baseline in PANSS positive symptom subscale, PANSS negative symptom subscale score, PANSS EC symptom score, and MADRS, PSQI total score at Day 56 and PANSS, PSQI, GAS total score at Day 168 were also analysed via repeated-measures analysis. No other correction to the reported p-values was made for the analysis of secondary measures. The result was presented in terms of mean changes and associated 95% confidence intervals.

Adverse events were coded using the Medical Dictionary for Regulatory Activity (MedDRA). Numbers of events and crude incidence rates were tabulated by preferred term and system organ class. The calculation of incidence rate was based on the safety population. An event that occurred 1 or more times on the date of, or subsequent to allocation to study treatment was counted as one event if the intensity or seriousness of the AE changes, the overall intensity or seriousness was the maximum intensity or seriousness of the multiple occurrences.

The changes from baseline in prolactin level, SAS and AIMS total score at Day 56 and Day 168 were also analysed via repeated-measures analysis. No correction to the reported p-values was made for the analysis of secondary measures.

Other safety variables including all laboratory test results, vital signs, weight and BMI were analysed using descriptive statistics for raw numbers and change from baseline. The proportions of patients with normal/abnormal ECG were compared to base line. The proportions of patients who have a ≥7% weight gain compared with baseline were tabulated.

The study outcomes were analysed as 2-step report. For the detail variables analysed in each stage was listed as bellows:

The 1st step statistical analysis and report were done for primary outcome variable, secondary outcome variables from baseline at Day 56, including changes from baseline in PANSS positive symptom subscale score, PANSS negative symptom subscale score, MADRS total score, PSQI total score, prolactin level, SAS total score, and AIMS total score at Day 56 (LOCF) with the incidence and severity of AEs.

The 2nd step statistical analysis and report were done for secondary outcome variables from baseline at Day 168, including change from baseline in PANSS total score, GAS total score, PSQI total score, prolactin level, SAS total score, and AIMS total score at Day 168 (LOCF) with the incidence and severity of AEs.

100 evaluable patients provided at least 90% power to detect a difference of 8 points between baseline and Day 56 with respect to mean changes from baseline PANSS total score. The sample size calculation assumed a standard deviation of 24.07 and a 2-tailed test at an overall experiment type I error rate of 0.050. Considering the rate of non-evaluable patients being approximately 20%, the total sample size was planed to be 120 patients. The sample size estimation was based on data from cochrane library in which the difference in PANSS total score with respect to short-term study was 18.7 with a standard deviation of 24.07.

Patient population

Baseline patient characteristics are presented in Table S1. The total study population comprised 129 patients enrolled from 11 center. The number of patients discontinuing early ranged from 29 (22.5%) in the acute phase (from visit 2 to visit 7) to 24 (24%) in the contiuous phase (from visit 7 to visit 12), most commonly because of withdrawal of informed consent, lack of efficacy, or AEs. A total 76 patients completed study treatment. In ITT population, the proportions of men (43.5%) and women (56.5%) were similar, while the percentage of patients aged 18 to 39 years (81.5%) was greater than aged 40 to 60 years (18.5%). Only Chinese patients were included in this study.

Of the the 129 patients assigned to study treatment and included in the safety analyses, 5 patients were exclude from the ITT population because post-baseline PANSS score were missing. Of the 124 patients included in the ITT analyses, 17 were fully excluded from the PP analysis set, because of using prohibited drug in protocol or treatment period less than 28 days.

Table S1 Patient population and disposition

	Quetiapine Fumarate N=124
Demographic characteristics (ITT)	
Sex: n (%)	
Male	54 (43.5)
Female	70 (56.5)
Age (years)[a]	
Mean (SD)	29.0 (10.38)
Range	18 to 59
Race: n (%)	
Chinese	124 (100)
Baseline disease characteristics (ITT)	
CCMD-3 diagnosis, schizophyrenic subtype: n (%)	
Paranoid	85 (68.5)
Hebephrenic	4 (3.2)
Catatonic	1 (0.8)
Undifferentiated	34 (27.4)
PANSS total score at baseline[b]	
Mean (SD)	93.7 (16.9)
PANSS positive symptom subscale score	
Mean (SD)	24.8 (5.0)
PANSS negative symptome subscae score	
Mean (SD)	23.5 (7.3)
PANSS EC symptom score	
Mean (SD)	20.7 (6.8)
MADRS total score	
Mean (SD)	12.1 (8.4)
GAS total score	
Mean (SD)	34.7 (10.3)
PSQI total score	
Mean (SD)	10.0 (5.1)
Disposition: n	

	Quetiapine Fumarate N=124
Completed treatment	76
Premature discontinuation	48
N analysed for safety	129
N analysed for efficacy (ITT)	124
N analysed for efficacy (PP)	107

[a] At enrolment.

[b] Inclusion criteria was a PANSS total score of at least 60 and a score of 4 or greater on at least 1 of the following items: delusions (P1), conceptual disorganizations (P2), or hallucinations (P3) at both screening and allocation.

Efficacy results

A summary of efficacy results at Day 56 and Day 168 (LOCF, ITT population) is presented in Table S2.

Table S2 Summary of efficacy results at Day 56 and Day 168 (LOCF, ITT population)

	56 Days	**168 Days**
PANSS total score, LS mean change from baseline	-36.5*	-41.80*
PANSS positive symptom subscale score, LS mean change from baseline	-11.2*	-12.6*
PANSS negative symptom subscale score, LS mean change from baseline	-8.6*	-10.1*
PANSS EC symptom score, LS mean change from baseline	-9.1*	-9.6*
PANSS response rate, proportion of patients with 30% reduction from baseline (%)	75.0	77.4
MADRS total score, LS mean change from baseline	-7.6*	-
GAS total score, LS mean change from baseline	27.8*	33.8*
PSQI total score, LS change from baseline	-5.1*	-5.9*

* $p<0.0001$

Analysis of primary variable, the change from baseline in PANSS total score at Day 56, showed significant improvement ($p<0.0001$). All the analyses of secondary measures demonstrated significant improvement ($p<0.0001$) in PANSS positive symptom subscales score, negative symptom subscale score, EC symptom score, and MADRS total score at day 56 as well as GAS total score, and PSQI total score at Day 168, further supporting the robustness of the primary analyses.

Safety results

The number (%) of patients who had ata lease 1 adverse event in any catergory is summarized in Table S3. Overall quetiapine fumarate was generally safe and well tolerated at dose range of 600 mg/day to 750 mg/day tested in this study. Analysis of adverse events indicated that investigational, gastrointestinal, and psychiatric events predominated, with constipation, liver function test abnormal, tachycardia, hypersomnia, insomnia as the most common adverssee events. There was no death in the study and most adverse events were mild to moderated. SAE and discontinuations due to AEs were infrequent in the study.

Table S3 Various categories of adverse events (safety population)

	Quetiapine fumarate, n (%)
Adverse events[a]	95 (73.6)
Serious adverse events[a]	1 (0.8)
Serious adverse events leading to death	0 (0)
Serious adverse events not leading to death	1 (0.8)
Drug related adverse event[a, b]	79 (61.2)
Total number of adverse events	
Adverse events	318
Serious adverse events	1
Drug related adverse events[b]	193

[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.

[b] As judged by the investigator.

The incidence of common adverse events (occurring at an incidence of ≥5% in any treatment group) is summarized in Table S4. The pattern of common AEs observed in the study generally conformed to that which was anticipated based on the clinical experience of quetiapine fumarate in China; ie, the most common AEs associated with quetiapine fumarate were constipation and tachycardia. There were 8 nonserious AEs (white blood cell count decreased) potentially related to agranulocytosis reported during the study that did not lead to discontinuation from the study. There were no signs or symptoms of infection due to white blood cell count decreased reported. The investigators determined 4 (3 of them were mild and 1 of them was moderate)of these 8 AEs were related to study treatment.

The incidence of EPS-related adverse events was 16.3% (21 patients), moste of which were mild. Over the course of the study, there were 18 patients using anticholinergic medication for symptoms of EPS. Overall the assessment of parkinsonian and tardive dyskinesia symptomatology as assessed by mean SAS and AIMS scores indicated that an improvement or no worsening in symptomatology was noted in quetiapine fumarate treatement.

Small changes from baseline were observed at end of treatment in a number of clinical laboratory assessments, including mean hemoglobin and alkaline phosphatase values. These changes were not considered to be of clinical significance.

There were small increases in mean glucose levels and weight from baseline at end of treatment, which were not considered to be of clinical significnace.

A small increase in mean pulse rate, confirmed by ECG measurement of heart rate, was also observed in the study. The change in heart rate was well tolerated, as there were few AEs related to this change.

The most common adverse events, as summarized by preferred term, are shown in Table S4.

Table S4 Common adverse events (safety analysis set)

MedDRA Preferred Term	**Quetiapine fumarate (N=129)**
	n[b] (%)
Constipation	30 (23.3)
Liver function test abnormal	19 (14.7)
Tachycardia	16 (12.4)
Hypersomnia	14 (10.9)
Insomnia	13 (10.1)
Dizziness	12 (9.3)
Extrapyramidal disorder	12 (9.3)
Sinus tachycardia	10 (7.8)
Upper respiratory tract infection	9 (7.0)
White blood cell count decreased	8 (6.2)
Nasopharyngitis	7 (5.4)
Palpitations	7 (5.4)
Somnolence	6 (4.7)
Agitation	4 (3.1)

MedDRA Preferred Term	**Quetiapine fumarate (N=129)**
	n[b] (%)
Anxiety	4 (3.1)
Hepatic steatosis	4 (3.1)
Hypothyroidism	4 (3.1)
Orthostatic hypotension	4 (3.1)
Restlessness	4 (3.1)
Urinary tract infection	4 (3.1)

[a] Events with a total frequency of ≥3% across all treatment groups are included in this table.
[b] Number of patients in the safety population.