Clinical Study Report Synopsis	
Drug Substance	Quetiapine Fumarate XR
Study Code	D1443L00074
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A 3-Weeks, Open Label Study to Evaluate the Efficacy in Agitation and Safety of Quetiapine Fumarate (Seroquel XR) in the Treatment of Patients with Acute Schizophrenia

Study dates: First subject enrolled: 4 September 2009
Last subject last visit: 20 April 2010

Phase of development: IIIB

Objectives and criteria for evaluation

Table S1   Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective of this study was to evaluate the efficacy in agitation of quetiapine fumarate extended-release (XR) used as mono-therapy, administered once daily, in the treatment of patients with acute episode of schizophrenia.	PANSS-EC score reduction from baseline	Investigator rating

Objectives	Outcome variables	Type
Secondary Objectives:		
The secondary objectives of the study were to evaluate the following:		
• The efficacy of quetiapine fumarate XR in reducing positive, negative and general psychopathological symptoms, and aggression, hostility and depression in the treatment of acute schizophrenia.	PANSS score from baseline	Investigat or ratings
• The efficacy of quetiapine fumarate XR in improving the overall clinical status of patients with acute schizophrenia.		
• The safety and tolerability of quetiapine fumarate XR in the treatment of patients with acute schizophrenia.	Adverse event reports	

Study design

This was a 3-week, open label, single arm study to evaluate the efficacy in agitation and safety of quetiapine fumarate XR (Seroquel XR) in the treatment of patients with acute schizophrenia.

Male or female patients, 18 to 65 years of age, with Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for schizophrenia (1st episode/relapse) were eligible for inclusion if they had a total PANSS score of ≥ 75 and a PANSS-Excited Component (PANSS-EC) score of ≥ 14, and severity score of at least 4 on at least one of the five PANSS-EC items: P4 – Excitement, P7- Hostility, G4 – Tension, G8 – Uncooperativeness, or G14 – Poor Impulse Control.

The inclusion of patients with PANSS-EC score of > 14 was based on previous published clinical trials on olanzapine that have included patients with PANSS-EC score of 14 (Wright et al. 2003).

The patients were hospitalised if required for treatment and assessment based on the investigator's judgement. If patient was hospitalised, patient could be discharged from the hospital if the investigator believed that it was clinically appropriate to discharge the patient and the patient could reasonably be expected to continue in the study on an outpatient basis. This hospitalisation instruction was modified from the initial CSP.

Target subject population and sample size

For inclusion in the study, subjects had to fulfil all of the following criteria:

1. Provision of written informed consent before initiation of any study related procedures

2. In the opinion of the investigator, requirement for treatment of acute episode of schizophrenia (according to DSM-IV diagnostic criteria)

3. Male of female aged 18 to 65 years

4.   Female patients of childbearing potential must be using a reliable method of contraception and have a negative urine human chorionic gonadotropin (HCG) test at enrolment

5.   PANSS total score of ≥ 75

6.   PANSS-EC score of ≥ 14 and severity score of at least 4 on at least one of the five PANSS-EC items; P4 – Excitement P7- Hostility, G4 – Tension, G8 – Uncooperativeness or G14 – Poor Impulse Control

7.   CGI ≥ 4

8.   Able to understand and comply with the requirements of the study.

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

Quetiapine fumarate XR, the dosage regimen of 300mg/day Day 1, 600mg/day Day 2 and 400mg/day, 600mg/day or 800mg/day from Day 3 onwards.

Duration of treatment

21 days

Statistical methods

The study was exploratory and was not powered to address any pre-defined hypothesis. Sample size was not based on statistical calculations. Data was to be descriptively summarised according to the type of variables.

Descriptive statistics for continuous data include number of non-missing observations (N), number of missing observations (N missing), mean, standard deviation (SD), and minimum and maximum values, range and 95% confidence internal (95% CI).

Categorical variables were to be summarised by means of frequency table, showing number of non-missing observations (N), number of missing observations (N missing), number and percentages (%) of subjects falling into a category. Percentages were to be calculated within each group on the number of non-missing observations and displayed. In these tables, all possible categories were to be displayed.

Simple 2 sided T-test at 5% level of significant was used for efficacy evaluation. P-values associated with the test were presented, and null hypothesis was rejected if P-value is less than 0.05.

Subject population

Demographic and baseline characteristic of subjects (ITT population)

Population	Subjects (N=35)

Demographic characteristics	
Sex, n (%)	
Male	24 (68.6%)
Female	11 (31.4%)
Age, years (SD)	38.3 (11)
Race, n (%)	
Malay	12 (34.3%)
Chinese	13 (37.1%)
Indian	9 (25.7%)
Others (Pakistani)	1 (2.9%)
Height, cm (SD)	165.1 (6.9)

Baseline characteristics	
Subjects with:	
Medical history	4 (11.4%)
Surgical history	2 (5.7%)
Psychiatric history	27 (77.1%)
Subjects with schizophrenia (based on DSM-IV Diagnosis criteria)	
Disorganised type	4 (11.4%)
Paranoid type	25 (71.4%)
Undifferentiated type	6 (17.1%)
Baseline efficacy measurements, mean (SD)	
PANSS-EC score	17.8 (2.7)
PANSS-P score	26.6 (4)
PANSS-N score	25 (5.4)
PANNS-General psychopathological score	51.3 (7.6)
PANSS total score	110.8 (15.7)
CGI-S	4.6 (0.5)
CGI-I	3.9 (0.4)
Baseline EPS symptoms	
SAS score	0
BARS score	0.1 (0.5)

Baseline values for efficacy measurements and SAS and BARS scores were values at visit 2.

Summary of results

The analysis results showed that there was a steady decline in the mean PANSS-EC score over the course of the study. The magnitude of change was -2.1 ($p<0.001$) at Visit 3 (Day 2) for quetiapine fumarate XR 400mg/day, -3.6 ($p<0.001$) at visit 4 (Day 3, 600mg/day), and -5.2 ($p<0.001$), -6.5 ($p<0.001$), -7.5 ($p<0.001$) for visit 5, visit 6 and visit 7, respectively. The results indicated statistically significant improvement in patients after receiving study medication.

The variable used to assess the primary objective of the study was change from baseline in PANSS-EC score at the end of treatment (Day 21), while the variables used to evaluate the secondary objectives of the study were change from baseline in PANSS-P score, PANSS-N score, PANSS-G score, total PANSS score, PANSS aggression and hostility cluster score, PANSS depression cluster score, CGI-S and absolute CGI-I scales.

Analysis of the primary efficacy endpoint for the ITT population provided statistically significant evidence that quetiapine fumarate XR was effective in improving agitation in patients with acute schizophrenia, with a reduction of 7.5 points in PANSS-EC score from baseline at the end of treatment.

Analysis of the secondary efficacy parameters for the ITT population also showed a statistically significant treatment effect with quetiapine fumarate XR, with reduction reported in total PANSS score, and across the PANSS subscales and CGI subscales assessed.

Summary of safety results

Results from the safety population showed that quetiapine fumarate XR given once-daily to patients with acute schizophrenia is safe and well tolerated with few AEs. Adverse events were mild to moderate in intensity. One SAE occurred as hospitalisation, but was not associated to the study medication.

There were no clinically important changes in the haematological measurements, vital signs and ECG.

Statistically significant changes were observed in the levels of prolactin, triglyceride and cholesterol.