AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Quetiapine fumarate
Study Code	D1443L00009
Edition Number	1
Date	21 August 2008

FAST - A randomized, open-label, parallel, multicenter Phase IIIb Study to evaluate the Efficacy and Safety of Quetiapine IR titrated over 4 Days in Patients with Acute Psychosis (Rapid versus Conventional Titration)

Study dates: First patient enrolled: 23 May 2007
Last patient completed: 28 August 2007

Phase of development: IIIb

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

This study was conducted in Sweden comprising 14 centres. The study was on hold September 2007 - January 2008 by the notification of earlier approval process of Seroquel Depot on the Swedish market. Due to the approval, the study was not ethically acceptable to continue and therefore it was finally stopped 30 January 2008.

The Seroquel Depot formulation gives the physician the possibility of a rapid dose titration and make any study results from this study obsolescent.

Publications

None at the time of writing this report and none is planned.

Objectives

The primary objective was to compare the efficacy of quetiapine Immediate Release (IR) in patients with acute schizophrenia, schizoaffective disorder, psychosis Not Otherwise Specified (NOS) or bipolar mania with psychotic symptoms following rapid titration versus conventional titration, by assessment of Positive and Negative Syndrome Scale-Excitatory Subscale (PANSS-EC) at Day 5 compared with baseline at Day 1.

The secondary objectives were

1. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by assessment of PANSS-EC at baseline and at Day 3 and 8.

2. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by assessment of Clinical Global Impression (CGI) at baseline and at Day 5 and 8.

3. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by assessment of FAST (For Acute Seroquel Therapy) rating scale at baseline and at Day 5 and 8.

4. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by self assessment of Quality-of-Life Delighted-Terrible (QoL-DT) at baseline and at Day 5 and 8.

5. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by assessment of the sleeping pattern.

6. To compare the tolerability of quetiapine IR, following rapid titration versus conventional titration, by assessment of withdrawals/treatment failures.

7. To compare the tolerability of quetiapine IR, following rapid titration versus conventional titration, by assessment of the frequency of adverse events.

Study design

This was an open-label, randomised, multicentre, phase IIIb study to evaluate the efficacy and tolerability of quetiapine IR, following rapid titration versus conventional titration, in patients with acute schizophrenia, schizoaffective disorder, psychosis NOS or bipolar mania with psychotic symptoms, over 8 Days.

Target patient population and sample size

Male or female patients aged 18-65 years who required treatment, as judged by the Investigator, for an acute episode of schizophrenia, schizoaffective disorder, psychosis NOS or bipolar mania (according to DSM-IV criteria) were eligible for inclusion in the study. Patients were recruited from in-patient settings only. Patients should not have been taking antipsychotic medication, or other prohibited medication, such as Cytochrome P450 enzyme inducers or Cytochrome P450 enzyme inhibitors during the study period.

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

Patients randomised to quetiapine IR tablets were administered either via a rapid titration regimen over 4 Days (total daily dose: Day 1 – 200 mg, Day 2 – 400 mg, Day 3 – 600 mg; Day 4 – 800 mg) or via a conventional titration regimen over 4 Days (total daily dose: Day 1 – 50 mg, Day 2 – 100 mg, Day 3 – 200 mg, Day 4 – 300 mg). From Day 5 onwards, the dose could be adjusted depending on clinical response and tolerability as judged by the Investigator, within a total daily dose range of 300-800 mg in the rapid titration treatment arm and 300-750 mg in the conventional titration treatment arm and in increments of between 100 and 200 mg per Day. Quetiapine IR was administered orally, in divided daily doses (b.i.d.), except for the first dose which was given as a single dose. The batch numbers for the investigational product were MC4601 (25 mg), 7534K & KT4606 (both 100 mg) and 7540K & 7547K (both 200 mg).

Duration of treatment

The duration of the study treatment period was 8 Days.

Criteria for evaluation - efficacy (main variables)

Primary outcome variable: Change in PANSS-EC from baseline to Day 5.

Secondary variables: Change in PANSS-EC from baseline to Day 3 and 8. Change in CGI-S from baseline to Day 5 and 8. Value of CGI-I at Day 5 and 8. Change in FAST rating scale from baseline to Day 5 and 8. Change in QoL-DT from baseline to Day 5 and 8. Change in the sleeping pattern from baseline to subsequent days.

Criteria for evaluation - safety (main variables)

Primary safety variable: Not applicable.

Secondary safety variables: Assessment of the frequency of adverse events. Assessment of the frequency of withdrawals/treatment failures.

Statistical methods

No efficacy analysis was done due to the fact that only 5 patients were randomised.

Subject population

The randomised study population comprised 5 patients enrolled from 4 centres. Of the 5 patients 3 were randomised to conventional titration treatment and 2 to rapid titration treatment.

Of the 5 patients assigned to treatment and included in the safety analysis no patients were excluded from the Intention To Treat (ITT) population. In total 3 patients completed the study as Per Protocol (PP) criteria.

Discontinuation due to adverse events was only observed in the rapid titration treatment group.

Table S1 Patient disposition

	Rapid titration treatment (N=2)	**Conventional titration treatment (N=3)**	**Total (N=5)**
Number of patients enrolled	2	3	5
Number of patients randomised	2	3	5
Number of patients in Full Analysis Set (FAS)	2	3	5
Number of patients in Per Protocol Analysis	0	3	3
Number (%) of patients who discontinued during the study (FAS)	2 (100%)	0 (0%)	2 (40%)
Reasons for discontinuation (FAS) : n (%)			
Adverse event	1(50%)	0 (0%)	1(20%)
Subject not willing to continue study	1(50%)	0 (0%)	1(20%)
Number (%) of patients who completed the study (FAS)	0 (0%)	3 (100%)	3 (60%)

Table S2 Demographic and baseline characteristics

	Rapid titration treatment (N=2)	Conventional titration treatment (N=3)	Total (N=5)
Sex (n and % of subjects)			
Male	2 (100%)	1 (33.3%)	3(60%)
Female	0 (0%)	2 (66.6%)	2 (40%)
Age (years)			
Mean	47	46	46.4
Range	28 -66	36-53	28-66
Race (n and % of subjects			
Caucasian	2(100%)	3 (100%)	5(100%)
Weight (kg)			
Mean	84.5	73.6	78
Range	60-109	58-82	58-109
Height (cm)			
Mean	180	168.6	173.2
Range	175-185	156-177	156-185
Pulse (beats/min), standing			
Mean	101.5	80	88.6
Range	100-103	60-96	60-103
Pulse (beats/min), supine			
Mean	82.5	80	81
Range	82-83	68-88	68-88
SBP (mm Hg), standing			
Mean	117	108.3	111.8
Range	104-130	90-120	90-130
SBP (mm Hg), supine			
Mean	125.5	113.3	118.2
Range	106-145	100-120	100-145
DBP (mm Hg), standing			
Mean	85	73.3	78
Range	80-90	60-80	60-90
DBP (mm Hg), supine			
Mean	78.5	73.3	75.4
Range	67-90	70-80	67-90

Summary of safety results

In general, the study treatments were well tolerated and no new or unexpected safety findings were identified in this study. No serious adverse event occurred.

Both patients in the rapid titration treatment group discontinued; one due to adverse event during the study and one due to withdrawal of consent.

Table S3 Listing of all patients who had an AE and outcome (Safety analysis set)

Treatment	E-code	Sex (M/F)	Age (years)	Adverse event (Preferred term)	Time from start of treatment to AE onset (days)	Outcome
Conventional titration	E0101001	Female	36	Dizziness	2	AE stopped after 5 days
Conventional titration	E0101002	Male	49	Tiredness	4	AE still present at study completion. Last contact 7 days after study termination
Conventional titration	E0102001	Female	53	Bronchitis	7	AE no longer present. Last contact 3 month after study termination
Rapid titration	E0602001	Male	65	Weakness Dizziness	0 0	AEs stopped same day as occurred. Discontinued due to withdrawal of consent
Rapid titration	E0801001	Male	28	Slowed thinking	2	AE stopped after 2 days. Discontinued due to AE