Drug Product	Seroquel™	**SYNOPSIS**	
Drug Substance	Quetiapine Fumarate		
Study Code	D1443L00003		
Edition Number	1.0		
Date	13 February 2008		

RAPID – An Open-Label, Randomised, Multicentre Phase IIIb Study to Evaluate the Efficacy and Tolerability of Quetiapine IR (Immediate Release), over 14 Days, in Acute Schizophrenia / Schizoaffective Disorder (Rapid versus Conventional Titration)

Study centre(s)

Four patients were enrolled in this study at 3 investigational sites in the United Kingdom: [redacted] It was planned to enrol a total of 234 patients from 25 to 35 specialist care investigational sites.

Publications

None at the time of reporting

Study dates		**Phase of development**
First patient enrolled	18 July 2007	Therapeutic confirmatory (IIIb)
Last patient completed	1 October 2007	

OBJECTIVES

The primary objective of this study was to compare the efficacy of quetiapine IR (Immediate Release), in patients with acute schizophrenia or schizoaffective disorder, following rapid titration versus conventional titration, by assessment of Positive and Negative Syndrome Scale (PANSS) at Day 7.

The secondary objectives of the study were:

1. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by assessment of PANSS at Day 5 and 14

2. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by evaluation of PANSS excitatory subscale (PANSS-EC) at Day 5, 7 and 14

3. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by evaluation of PANSS negative, positive and general subscales at Day 5, 7 and 14

4. To compare the efficacy of quetiapine IR, following rapid titration versus conventional titration, by assessment of Clinical Global Impression – Severity (CGI-S) and Clinical Global Impression – Improvement (CGI-I) at Day 5, 7 and 14

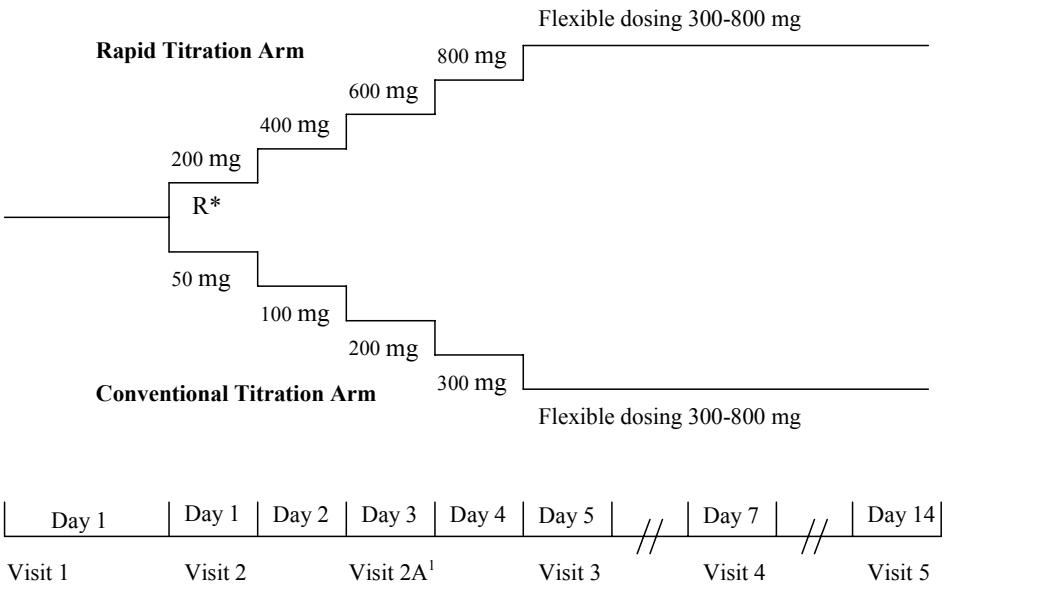
5. To compare the tolerability of quetiapine IR, following rapid titration versus conventional titration, by assessment of vital signs and the frequency and severity of adverse events (AEs).

STUDY DESIGN

This was an open-label, randomised, multicentre study to evaluate the efficacy and tolerability of quetiapine IR, following rapid titration versus conventional titration, in patients with acute schizophrenia or schizoaffective disorder over 14 days (Figure S1).

Patients were randomised with a 1:1 ratio to quetiapine IR tablets administered either via a rapid titration regimen over 4 days or via a conventional titration regimen over 4 days. From Day 5 onwards, the dose was adjusted depending on clinical response and tolerability as judged by the investigator.

Figure S1 Study flow chart



*R = Randomisation

[1]Visit 2A is for community-based subjects only

TARGET PATIENT POPULATION AND SAMPLE SIZE

Patients aged 18-65 years who required treatment, as judged by the investigator, for an acute episode of schizophrenia or schizoaffective disorder (according to DSM-IV criteria) were eligible for inclusion in the study. Patients were recruited from both in-patient and community settings.

Administration of concomitant antipsychotic medication, or other prohibited medication including cytochrome P450 inducers and inhibitors was not permitted during the study.

Sample size was calculated based on the primary efficacy variable, [redacted] With a significance level of 5% and a power of 80%, 105 evaluable patients per group were required. Assuming a 10% screen-failure / non-evaluability rate, it was planned to recruit a total of 234 patients to meet this target.

INVESTIGATIONAL PRODUCT AND COMPARATOR(S): DOSAGE, MODE OF ADMINISTRATION AND BATCH NUMBERS

Quetiapine IR tablets (Seroquel™ , manufactured by AstraZeneca) were administered orally up to a maximum daily dose of 800 mg. The following tablet strengths were used: 25 mg, 100 mg, 150 mg and 200 mg. Quetiapine IR tablets were supplied from commercial stock, and were packaged and labelled for clinical trial use, by DHP (Crickhowell, Powys, NP8 1DF). Quetiapine was given as twice daily doses (bd), except for the first dose, which was given as a single dose.

The treatment regimens for the rapid titration and conventional treatment groups are given in Table S1.

Table S1 Treatment regimen

	Rapid Titration			Conventional Titration		
	Total Daily Dose	**Morning**	**Evening**	**Total Daily Dose**	**Morning**	**Evening**
Day 1	200 mg	1 x 200 mg tablet a		50 mg	2 x 25 mg tablet a	
Day 2	400 mg	1 x 200 mg tablet	1 x 200 mg tablet	100 mg	2 x 25 mg tablet	2 x 25 mg tablet
Day 3	600 mg	2 x 150 mg tablet	2 x 150 mg tablet	200 mg	1 x 100 mg tablet	1 x 100 mg tablet
Day 4	800 mg	2 x 200 mg tablet	2 x 200 mg tablet	300 mg	1 x 150 mg tablet	1 x 150 mg tablet
Day 5-14	300-800 mg	As required	As required	300-800 mg	As required	As required

[a] The first dose of investigational product was administered as a single dose, following completion of baseline assessments at Visit 2

DURATION OF TREATMENT

The duration of study treatment was 14 days.

CRITERIA FOR EVALUATION (MAIN VARIABLES)

Efficacy

- Primary variable: Change from baseline in total PANSS score at Day 7
- Secondary variables:
  - Changes from baseline in total PANSS score at Day 5 and 14

- Changes from baseline in PANSS-EC score at Day 5, 7 and 14
- Changes from baseline in PANSS negative, positive and general psychopathology subscales at Day 5, 7 and 14
- Changes from baseline in CGI-S and absolute CGI-I at Day 5, 7 and 14.

Safety

- Secondary variables:
  - Frequency and severity of AEs
  - Changes from baseline in vital signs.

STATISTICAL METHODS

No statistical analyses were performed as only 4 patients were included in the study (105 evaluable patients per group were planned). Efficacy and safety data have been summarised descriptively.

PATIENT POPULATION

Four patients were enrolled into the study and randomised to study treatment. All 4 patients were randomised to the rapid titration group, completed the study and were analysed for efficacy and safety.

The study was closed for further patients on 19 September 2007 due to poor recruitment, despite actions taken to attempt an increase in recruitment. The study was planned to close on 31 March 2008.

The patient demographic and baseline characteristics are shown in table below. The population consisted of 3 in-patients and 1 community based patient, [redacted]

Table S2 Patient demographic and baseline characteristics, ITT analysis set

Demographic or baseline characteristic	Rapid titration (N=4)
Sex: n (%)	
[redacted]	[redacted]
[redacted]	[redacted]
Age (years)	
N	4
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Race: n (%)	
[redacted]	[redacted]
[redacted]	[redacted]
Weight (kg)	
N	4
Mean (SD)	70.5 (13.0)
[redacted]	[redacted]
[redacted]	[redacted]
Psychiatric disorder: n (%)	
Schizophrenia [a]	3 (75.0%)
Schizoaffective Disorder [a]	1 (25.0%)
Treatment setting: n (%)	
In-patient	3 (75.0%)
Community-based patient	1 (25.0%)

[a] According to DSM IV criteria

EFFICACY RESULTS

(a) PANSS

The changes from baseline in total PANSS, PANSS-EC, negative, positive and general psychopathology subscales to each visit are shown in Table S3.

Primary variable

The 4 patients treated with quetiapine in rapid titration showed an improvement in total PANSS score after 7 days (mean decrease 40.5, SD 25.6).

Secondary variables

Improvements in total PANSS scores were observed after 5 and 14 days. Improvements were also shown in all PANSS subscale scores (PANSS-EC, negative, positive and general psychopathology) after 5, 7 and 14 days.

Table S3 PANSS scores at baseline and changes from baseline to each visit, ITT analysis set

	Rapid titration (N=4)			
	Baseline	Change to Day 5	Change to Day 7	Change to Day 14
PANSS total score				
Mean (SD)	101.8 (24.4)	-30.8 (24.3)	-40.5 (25.6)	-45.8 (33.1)
Median	102.0	-20.0	-32.0	-32.5
Range	72 to 131	-67 to -16	-78 to -20	-95 to -23
PANSS-EC score				
Mean (SD)	15.5 (10.1)	-5.8 (6.9)	-6.3 (6.7)	-8.0 (10.7)
Median	12.0	-3.0	-4.0	-3.5
Range	8 to 30	-16 to -1	-16 to -1	-24 to -1
PANSS negative score				
Mean (SD)	19.8 (7.9)	-5.0 (4.7)	-6.8 (5.4)	-8.3 (5.9)
Median	21.0	-4.5	-7.5	-9.5
Range	9 to 28	-11 to 0	-12 to 0	-14 to 0
PANSS positive score				
Mean (SD)	27.0 (8.8)	-8.5 (7.9)	-12.5 (7.9)	-14.3 (11.2)
Median	23.5	-5.5	-9.5	-9.5
Range	21 to 40	-20 to -3	-24 to -7	-31 to -7
PANSS general score				
Mean (SD)	55.0 (12.2)	-17.3 (12.5)	-21.3 (14.0)	-23.3 (17.8)
Median	54.5	-11.5	-15.5	-14.5
Range	41 to 70	-36 to -10	-42 to -12	-50 to -14

PANSS Positive and Negative Syndrome Scale, EC Excitatory component
A decrease in the PANSS score indicates an improvement in symptoms

(b) CGI

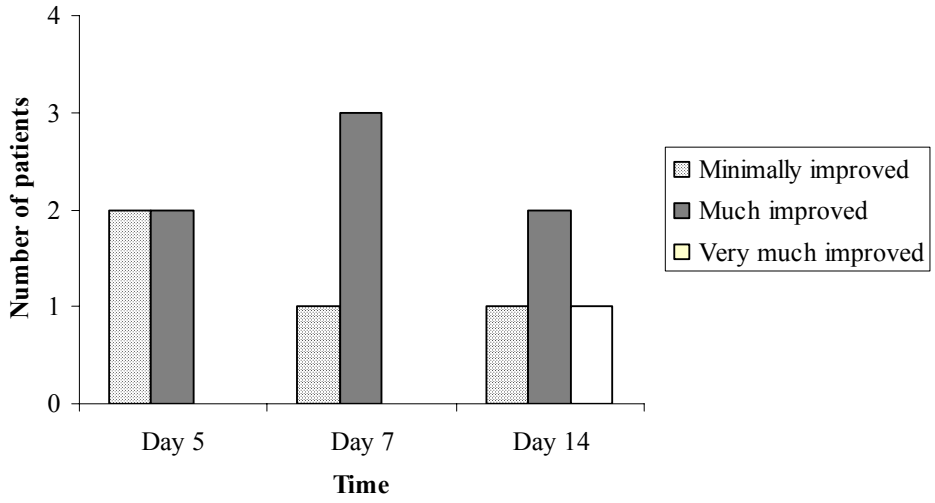
The changes from baseline in CGI-S to each visit are shown in Table S4.

Table S4 Number (%) of patients with CGI-S ratings at each visit, ITT analysis set

Clinical Global Impression – severity (CGI-S)	Rapid titration arm (N=4)			
	Baseline	**Day 5**	**Day 7**	**Day 14**
Normal, not at all ill	0	0	0	0
Borderline mentally ill	0	0	0	1 (25.0)
Mildly ill	0	0	2 (50.0)	1 (25.0)
Moderately ill	1 (25.0)	2 (50.0)	0	0
Markedly ill	0	2 (50.0)	2 (50.0)	2 (50.0)
Severely ill	3 (75.0)	0	0	0
Amongst the most extremely ill patients	0	0	0	0

All 4 patients had improved after 14 days as indicated by the CGI-I rating, and 3 of the 4 patients (75%) had a CGI-I rating of much improved or very much improved (Figure S2).

Figure S2 Number of patients with Clinical Global Impression - Improvement (CGI-I) ratings



SAFETY RESULTS

The median exposure to quetiapine IR was 14 days (range 14 to 15 days; Table S5).

The mean daily dose of quetiapine IR taken during the study was 533 mg (range 507 to 571 mg). All 4 patients were titrated up to 800 mg by Day 4 as planned.

Table S5 Overview of exposure, safety analysis set

	Rapid titration (N=4)
Duration of treatment (days)	
N	4
Mean (SD)	14.3 (0.5)
Median	14.0
Range	14 to 15
Average daily dose (mg)	
N	4
Mean (SD)	532.7 (28.4)
Median	526.2
Range	507 to 571

Quetiapine administered in rapid titration was generally well tolerated by the 4 patients. There were no serious adverse events (SAEs) or discontinuations due to adverse events (DAEs).

Three (75%) patients experienced 14 AEs during the study (14 AEs as multiple events in the same category are counted only once in that category). The most commonly reported AEs were fatigue [redacted] dizziness [redacted] dry mouth [redacted] and sedation [redacted]). Dysarthria, irritability, muscular weakness, somnolence, and tremor were also reported [redacted] All AEs other than irritability were assessed as drug related by the investigator. The AEs were of mild to moderate intensity; only sedation and irritability were of moderate intensity. The doses were changed due to AEs in 2 (50%) patients.

One patient had a potentially clinically important increase in pulse (defined as increase ≥15 bpm from baseline) and 2 patients had potentially clinically important increases in systolic blood pressure (supine and standing; defined as ≥20 mmHg increase from baseline). One patient also had a potentially clinically important orthostatic change in systolic blood pressure (defined as decrease ≥20 mmHg from supine to standing after 1 minute).