AstraZeneca

Clinical Study Report

Drug substance:	Quetiapine
EUDRACT No.:	2004-005122-45
Edition No.:	1.1
Study code:	D1441L00032
Date:	30.05.2007

RACE: Rapid Dose Escalation of Quetiapine versus Conventional Escalation in the Treatment of Patients with Acute Schizophrenia – a Multicentre, Double-blind, Parallel group, Randomized Study

Study dates: First subject enrolled: 13th June 2005
Last subject enrolled: 5th January 2006

Phase of development: II

National Co-ordinating Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

This study was performed in compliance with Good Clinical Practice.

AstraZeneca

Drug product:	Quetiapine, tablet, 50-800mg/day	**SYNOPSIS**	
Drug substance(s):	Quetiapine		
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RACE: Rapid Dose Escalation of Quetiapine versus Conventional Escalation in the Treatment of Patients with Acute Schizophrenia – a Multicentre, Double-blind, Parallel group, Randomized Study

National co-ordinating investigator

[redacted] Essen

Study centre(s)

A total of 30 patients were randomised at 6 sites [redacted].

Publications

None at the writing of this report.

Study dates		**Phase of development**
First subject enrolled	13th June 2005	Therapeutic exploratory (II)
Last subject completed	17th January 2006	

Objectives

Primary objective

The primary objective was to compare the safety and tolerability of IR (Immediate-Release) quetiapine in a rapid escalation scheme with 300 mg on day 1, 600 mg on day 2 and 800 mg on day 3 to the current approved label titration with 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, 300 mg on day 4, 400 mg on day 5, 600 mg on day 6 and 800 mg on day 7.

Secondary objectives

Safety and Tolerability

- To evaluate if the initiation with 300 mg on day 1 is safe and well tolerated in the treatment of severely ill acute schizophrenic patients.
- To evaluate if increasing the dosing up to 800 mg on day 3 is safe and has a similar tolerability to the current label titration in the treatment of severely ill acute schizophrenic patients.
- To evaluate if dosing with 800 mg from day 3 to day 7 is safe and has a similar tolerability to the current label titration in the treatment of severely ill acute schizophrenic patients.
- To evaluate if there is a comparable safety and tolerability during the 12 days of treatment.
- To evaluate if there is a comparable safety/tolerability profile between both titration schemes on EPS (measured by SAS and BARS).

Efficacy

- To evaluate if the faster titration provides a faster onset of efficacy

Study design

This was a 12-days, phase II, multicentre, double-blind, randomised, parallel-group study comparing the safety and tolerability of IR (Immediate-Release) quetiapine in a rapid escalation scheme to the current label titration. The titration phase (day 1 to 7) was double-blinded.

Target subject population and sample size

Male or female subjects, aged ≥18 to ≤65 years and hospitalized with a DSM-IV diagnosis of schizophrenia and acute agitation and psychosis were eligible for this study. Patients were severely ill, with a score ≥4 as assessed by a CGI Severity of illness.

A total of 30 patients with acute schizophrenia were enrolled into this study with 20 patients randomized to rapid escalation treatment scheme and 10 patients to the current label titration of quetiapine.

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

- Quetiapine fumarate, tablets (see Table S 1 for dosing and administration)

- Matching placebo, tablets

Table S 1 Quetiapine dose regimen for Rapid Titration and Label Titration

Group	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
Morning/ Evening dose	**M**	**E**	**M**	**E**	**M**	**E**	**M**	**E**	**M**	**E**	**M**	**E**	**M**	**E**
Rapid Titration (mg)	100	200	300	300	300	500	300	500	300	500	300	500	300	500
Label Titration (mg)	25	25	50	50	100	100	100	200	200	200	300	300	300	500

Duration of treatment

Study treatment was assigned at randomisation (day 1). During the titration phase the treatment was blinded until day 7. On day 8 the patients entered the open label continuation phase and were treated with a daily dose of 800 mg quetiapine until day 12.

Criteria for evaluation (outcome variables)

Primary variable:

- Proportion of patients who discontinued the study treatment due to adverse events (AEs) during the first week (day 1 to day 7) of treatment

Secondary variables:

Safety and Tolerability

- Number and type of adverse events
- Changes in vital signs and weight
- Clinically significant changes in ECG (reported as AE)
- Change of Simpson-Angus Scale (SAS) score
- Change of Barnes Akathisia Rating Scale (BARS) score

Efficacy

- Change of PANSS and PANSS-EC scores
- Change in CGI-Severity of Illness from baseline
- CGI-Improvement score at post-baseline visits
- Proportion of patients with a CGI-S score of 3 or less at day 12
- Proportion of patients with a CGI-I score of 1 or 2 at day 12
- Number of withdrawals due to lack of efficacy
- Number of patients who need an additional antipsychotic medication (except benzodiazepines)

Safety

Safety evaluation determined by adverse events, laboratory data and physical examination.

Statistical methods

The study was exploratory and was not powered to address any pre-defined hypothesis. No formal statistical testing was done and focus was instead on descriptive statistics.

All data collected in the study were appropriately summarized for each treatment group using tabulations, graphs and summary statistics.

The difference between treatment groups with respect to efficacy rating scales were estimated using Analysis of Covariance with the baseline score and treatment group assignment as covariates/factors, supported by appropriate 95% confidence intervals.

To evaluate the assumption that a faster titration provides a faster onset of efficacy, a response criterion was defined before the blind was broken. The time to response was analysed by means of Kaplan-Meier methods.

In case of dropouts the last available post-baseline observation was carried forward.

Safety data are presented by frequency tables together with appropriate 95% confidence.

Subject population

Table S 2 shows the relevant data describing the study population.

Table S 2 Subject population and disposition

		Rapid titration	Label titration	Total
Population				
N randomised (N planned)		20 (20)	10 (10)	30 (30)
Demographic characteristics				
Sex (n and % of subjects)	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)	Mean (SD)	33.7 (10.8)	29.8 (14.9)	32.4 (12.2)
Race (n and % of subjects)	Caucasian	19 (95.0%)	9 (90.0%)	28 (93.3%)
Baseline characteristics				
Height (cm)	Mean (SD)	175.6 (8.6)	176.4 (8.4)	175.9 (8.4)
Weight (kg)	Mean (SD)	79.0 (19.2)	75.9 (20.8)	77.9 (19.5)
Body mass index (kg/m^2)	Mean (SD)	26.0 (6.1)	24.3 (5.6)	25.4 (5.9)
Disposition				
N (%) of subjects who	Completed	14 (70%)	8 (80%)	22 (73.3%)
	Discontinued	6 30%	2 (20%)	8 (26.7%)
N analysed for safety[a]		20	10	30
N analysed for efficacy (ITT)		20	10	30

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number

Regarding comparability of the treatment groups, the analyses of demographic and baseline characteristics and compliance to treatment regimen showed no remarkable differences between the two groups. Overall, remarkably more men were included than women [redacted]

In the rapid titration group most patients who withdrew were not willing to continue with the study (20%), while two were withdrawn due to adverse events (10%). In the label titration group one of the discontinuing patients [redacted] (10%), the other was withdrawn due to an adverse event (10%).

Efficacy and pharmacokinetic results

Most results of the efficacy variables (CGI-I, CGI-S, PANSS total score, PANSS-EC at day 12) indicate that rapid titration of quetiapine provides a faster onset of efficacy and a more pronounced effect at the final visit compared to label titration. In contrast, change in PANSS-EC score from baseline was larger in the label titration group at day 2, 4, and 8, indicating a faster onset of efficacy regarding this variable. However, exploratory statistical analyses of differences between treatment groups resulted in p-values > 0.05 for all measured efficacy parameters.

Table S 3 shows the mean values of the efficacy variables over time and mean differences between baseline and final visit.

Table S 3 Efficacy parameters (CGI-I, CGI-S, PANSS-EC, PANSS)

		Rapid titration (n = 18)	Label titration (n = 10)
CGI-I			
Day 2	Mean (SD)	3.6 (0.9)	3.5 (0.7)
Day 4	Mean (SD)	3.1 (1.0)	3.3 (0.5)
Day 8	Mean (SD)	2.9 (1.2)	3.0 (0.7)
Day 12	Mean (SD)	2.4 (0.9)	3.1 (1.4)
CGI-S			
Day 2	Mean (SD)	5.2 (0.7)	5.4 (0.7)
Day 4	Mean (SD)	4.8 (0.9)	5.4 (0.7)
Day 8	Mean (SD)	4.7 (0.9)	4.9 (0.9)
Day 12	Mean (SD)	4.2 (0.9)	4.7 (1.2)
Difference between baseline and day 12	Mean (SD)	-1.0 (0.8)	-0.8 (1.1)
PANSS-EC			
Day 1	Mean (SD)	18.4 (3.8)	18.1 (2.7)
Day 2	Mean (SD)	17.9 (5.3)	16.3 (3.1)
Day 4	Mean (SD)	16.1 (5.0)	13.7 (4.0)
Day 8	Mean (SD)	13.4 (3.2)	11.1 (5.3)
Day 12	Mean (SD)	12.7 (4.4)	13.0 (6.8)
Difference between baseline and day 12	Mean (SD)	-5.9 (4.3)	-5.4 (6.6)
PANSS total score			
Day 12	Mean (SD)	82.8 (19.6)	91.9 (24.5)
Difference between baseline and day 12	Mean (SD)	-26.9 (21.1)	-19.6 (25.3)

Safety results

Discontinuation rate due to AEs during the first week, the primary safety variable, was 5% (n = 1) in the rapid titration and 0% in the label titration group. 95% CI intervals were 5.00 to 24.87 for the rapid titration group and 0 to 30.85 for the label titration group respectively (p = 1.0).

Table S 4 and Table S 5 show number and type of AEs per treatment group.

Table S 4 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	Number (%) of subjects who had an adverse event in each category[a]	
	Rapid titration (n=20)	Label titration (n=10)
Any adverse events	19 (95%)	7 (70%)
Serious adverse events	0	1 (10%)
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	0	1 (10%)
Discontinuations of study treatment due to adverse events	2 (10%)	1 (10%)
Other significant adverse event	0	0
	Total number of adverse events	
Any adverse events	59	12
Serious adverse events	0	1

a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Table S 5 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Preferred term	Rapid titration (n=20)		Label titration (n=10)	
	n	(%)	n	(%)
Somnolence	6	(30)	2	(20)
Fatigue	5	(25)	0	(0)
Dizziness	4	(20)	0	(0)
Headache	2	(10)	1	(10)
Dry mouth	2	(10)	1	(10)
Insomnia	2	(10)	1	(10)
Anxiety	2	(10)	0	(0)
Weight increased	2	(10)	0	(0)
Pharyngolaryngeal pain	2	(10)	0	(0)
Toothache	1	(5)	1	(10)

Preferred term	Rapid titration (n=20)		Label titration (n=10)	
	n	(%)	n	(%)
Restlessness	1	(5)	1	(10)
Sinus tachycardia	1	(5)	1	(10)
Akathisia	1	(5)	0	(0)
Dizziness postural	1	(5)	0	(0)
Dysarthria	1	(5)	0	(0)
Abdominal discomfort	1	(5)	0	(0)
Aphthous stomatitis	1	(5)	0	(0)
Constipation	1	(5)	0	(0)
Flatulence	1	(5)	0	(0)
Glossodynia	1	(5)	0	(0)
Nausea	1	(5)	0	(0)
Asthenia	1	(5)	0	(0)
ALAT increased	1	(5)	0	(0)
ASAT increased	1	(5)	0	(0)
Heart rate increased	1	(5)	0	(0)
Pleocytosis	1	(5)	0	(0)
Panic attack	1	(5)	0	(0)
Sleep disorder	1	(5)	0	(0)
Tachycardia	1	(5)	0	(0)
Herpes zoster infection neurological	1	(5)	0	(0)
Q fever	1	(5)	0	(0)
Rhinitis	1	(5)	0	(0)
Goitre	1	(5)	0	(0)
Accomodation disorder	1	(5)	0	(0)
Skin papilloma	1	(5)	0	(0)
Dysuria	1	(5)	0	(0)
Dysmenorrhoea	1	(5)	0	(0)
Acne	1	(5)	0	(0)
Orthostatic hypotension	1	(5)	0	(0)
Sedation	0	(0)	1	(10)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Preferred term	Rapid titration (n=20)		Label titration (n=10)	
	n	(%)	n	(%)
Contusion	0	(0)	1	(10)

[a] Events with a total frequency of ≥5% across all treatment groups are included in this table.

Overall both treatment regimens were safe and well tolerated. Most AEs were of mild to moderate intensity and resolved without further action taken within a few days. Frequency and type of AEs were comparable to the known AE-profile of quetiapine. However relatively more AEs occurred in the rapid titration group (2.95 AEs per patient) compared with the label titration group (1.2 AEs per patient).

One serious AE, which was not drug-related but led to study discontinuation, was reported in the label titration group. Two cases of study discontinuation due to AEs in the rapid titration group were drug-related.

Additionally the occurrence of EPS assessed by SAS and BARS did not change substantially between baseline and final visit in both treatment groups (see Table S 6).

Table S 6 Neurological safety parameters (SAS, BARS)

		Rapid titration (n = 18)	Label titration (n = 10)
SAS			
Baseline	Mean (SD)	0.1 (0.3)	0.7 (2.2)
Day 12	Mean (SD)	0.3 (0.6)	0.8 (1.5)
Difference between baseline and day 12	Mean (SD)	0.2 (0.5)	0.1 (0.9)
BARS			
Baseline	Mean (SD)	0.4 (0.9)	0.6 (0.8)
Day 12	Mean (SD)	0.4 (0.9)	0.1 (0.3)
Difference between baseline and day 12	Mean (SD)	0 (1.0)	-0.5 (0.7)

[redacted]

[redacted]

Date of the report

30th May 2007