AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Quetiapine Fumarate XR
Study Code	D1443L00062
Edition Number	1.1
Date	13 November 2009

A 8-week, Multi-Centre, Open-label, Non-Comparative, Phase IV Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (Seroquel XR) with daily dose 400-800mg in the Treatment of Acute Schizophrenic Patients (QUENCH)

Study dates: First patient enrolled: 04 November 2008
Last patient completed: 09 July 2009

Phase of development: IV

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

Study centre(s)

Subjects were recruited from a total of 9 centres in Korea. A total of 96 subjects were enrolled, of whom 94 were treated.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 summarises the variables of this study, and shows how they relate to the study objectives.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
1. To evaluate the efficacy of Quetiapine XR with daily dose 400mg-800mg used as mono-therapy in the treatment of acute schizophrenic patients by evaluation of the change from baseline to Day 57 in PANSS total score using the last observation carried forward (LOCF) method	1. Change from baseline to Day 57 in PANSS total score	Efficacy
Secondary	**Secondary**	
2. To treat positive symptoms in acute schizophrenic patients by evaluation of the change from baseline to Day 57 in PANSS positive scale score	2. Change from baseline to Day 57 in PANSS positive score	Efficacy
3. To treat negative symptoms in acute schizophrenic patients by evaluation of the change from baseline to Day 57 in PANSS negative scale score	3. Change from baseline to Day 57 in PANSS negative score	Efficacy
4. To treat general psychopathology in acute schizophrenic patients by evaluation of the change from baseline to Day 57 in PANSS general psychopathology score	4. Change from baseline to Day 57 in PANSS general score	Efficacy
5. To treat patients' overall clinical status in acute schizophrenic patients by evaluation of the change from baseline to Day 57 in CGI scale score	5. Change from baseline to Day 57 in CGI-S score	Efficacy
6. To treat depressive symptoms in acute schizophrenic patients by evaluation of the change from baseline to Day 57 in MADRS total score	6. Change from baseline to Day 57 in MADRS total score	Efficacy
7. To improve functional capability in acute schizophrenic patients by evaluation of the change from baseline to Day 57 in GAF score	7. Change from baseline to Day 57 in GAF score	Efficacy

Study design

This was an 8-week, multi-centre, open-label, non-comparative study to evaluate the efficacy and safety of Quetiapine XR with daily dose 400mg-800mg used as mono-therapy in the treatment of acute schizophrenic patients. The eligible patients were

assigned to study treatment with Quetiapine XR on Day 1.

Target subject population and sample size

Male and female patients aged from 18 to 65 years old for the treatment of acute schizophrenia. Approximately 100 patients from 9 centres were be assigned to study treatment.

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

Quetiapine XR was administered orally once daily beginning on Day 1. The dose was started at 300mg/day on Day 1 and was increased to 600mg/day on Day 2 and 800mg/day on Day 3 in line with the prescription information. On Day 4, either 800mg dose was maintained or if the 800mg dose was not tolerated the dose was decreased within 400mg-800mg /day.

Duration of treatment

56 days (8 weeks)

Statistical methods

Analysis on efficacy endpoints was performed using the modified intent-to-treat population (MITT) as primary analysis and the per-protocol population (PP) for consistency check. Safety endpoints were performed in the safety population. The MITT population consisted of all patients who received at least one dose of study treatment and who had measurements at baseline and at least one on treatment assessment. PP population was defined as all MITT patients with no major protocol violations and/or deviations. The safety population consisted of all patients who received at least one dose of study treatment. If patients discontinued the study prior to Day 57, the last-visit observations were carried forward (LOCF).

The changes from baseline to Day 57 in PANSS total score were analysed using paired t-test. The results were presented in terms of mean changes and associated 95% confidence intervals.

The changes from baseline to Day 57 in PANSS positive scale score, PANSS negative scale score, PANSS general psychopathology score and GAF score were analysed using paried t-test and GCI scale score, MADRS total score were analysed using Wilcox's signed rank test. No other correction to the reported p-values wasmade 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 rates was based on the safety population. An event that occurred one 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 to Day 57 in prolactin level, SAS, AIMS and BARS total score were also analysed using Wilcoxon's signed rank test. 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 and weight were analysed using descriptive statistics for raw numbers and change from baseline. The proportions of patients with normal/abnormal ECG were compared to baseline. The proportions of patients who had a ≥7% weight gain compared with baseline was tabulated.

Subject population

The subject population and disposition are presented in Table S2. A total of 96 were screened for participating in this study. Of them, 94 took part in the treatment period and took at least one dose of study medication. Sixty-seven (67) subjects completed this study and 27 were dropped out during the treatment period. Five subjects were excluded from the MITT analysis set on the grounds of having no recorded post-dose efficacy results. The MITT set thus comprised 89 subjects and 82 subjects were included in PP set.

Table S2 Subject population and disposition

		N
All enrolled subjects		96
All treated subjects		94
N(%) of subjects who	Completed	67
	Discontinued	27
Safety analysis set		94
Modified analysis set (MITT)		89
Per-protocol set (PP)		82

The demographic and background characteristics of study subjects are summarised in Table S3. There were more men(58.4%) than women(41.6%), and all subjects were Korean. The mean age was 39.7 years, and ages ranged from 19 to 63. But male group was older than female group. The mean weight and height at baseline were 63.5kg and 164.2cm, respectively. Weight ranged from 35 to 103kg for all MITT subjects. Mean BMI was 23.5kg/m^2. BMI ranged from 16.2kg/m^2 to 39.1kg/m^2. Mean BMI was comparable between male group and female group.

Current medical history that were ongoing at enrolment were reported in 41(46.1%) of the 89 MITT subjects. 71 (79.8%) of all MITT subjects before the start of the study and during the course of the study took at least one concomitant medication with study medication.

Table S3 Demographic and baseline characteristics (MITT set)

		Male N=52	Female N=37	Total N=89
Age(years)	Mean (SD)	42.4(9.8)	35.8(13.0)	39.7(11.6)
	Range	23 to 60	19 to 63	19 to 63
Origin	Korean	52(100.0%)	37(100.0%)	89(100.0%)
(n and % of subjects)	Other	0	0	0
Weight(kg)	Mean (SD)	66.6(11.4)	59.1(13.0)	63.5(12.6)
	Range	45 to 103	35 to 94	35 to 103
Height(cm)	Mean (SD)	168.7(6.6)	158.0(5.9)	164.2(8.2)
	Range	153 to 181	147 to 174	147 to 181
BMI(kg/m^2)	Mean (SD)	23.4(3.5)	23.7(5.4)	23.5(4.4)
	Range	17.6 to 31.8	16.2 to 39.1	16.2 to 39.1

Summary of efficacy results

The mean change in PANSS total score was -26.8 (95% CI: -31.0, -22.6) and the PANSS total score value at endpoint was significantly lower than at baseline.

The PANSS positive score, negative score, and general score were showed statistically significant reduction at end of study (mean change in PANSS positive score: -7.4, mean change in PANSS negative score: -6.2, and mean change in PANSS general score: -13.2)

And there were statistically significant changes in CGI-S score, MADRS total score, and GAF score.

Quetiapine XR affected significantly changes in PANSS total and subscale score, CGI-S score, MADRS total score, and GAF score.

Table S4 Summary of major efficacy results (MITT set)

Efficacy variables		N	Mean (95% CI)	Median (95% CI)	p-value*
PANSS total score	Change	89	-26.8 (-31.0, -22.6)	-27.0 (-30.0, -21.0)	<0.0001
PANSS positive score	Change	89	-7.4 (-8.6, -6.1)	-8.0 (-9.0, -6.0)	<0.0001
PANSS negative score	Change	89	-6.2 (-7.5, -5.0)	-6.0 (-8.0, -4.0)	<0.0001

PANSS general score	Change	89	-13.2 (-15.5, -10.9)	-13.0 (-15.0, -10.0)	<0.0001
CGI-S score	Change	89	-1.46 (-1.71, -1.21)	-1.0 (-2.0, -1.0)	<0.0001
MADRS total score	Change	89	-9.44 (-11.44, -7.43)	-8.0 (-12.0, -4.0)	<0.0001
GAF score	Change	81**	17.9 (15.0, 20.8)	16.0 (15.0, 21.0)	<0.0001

* Paired t-test or Wilcoxon's signed rank test
** 8 patients had no post-baseline GAF score

Summary of safety results

The proportions of subjects reporting at least one Adverse event was 69.1%. During treatment period, 221 Adverse events in 65 subjectsin safety set were reported. 53 Treatment-related AEs occurred in 29 subjects (30.9%). Only 4 adverse events were severe and 4 subjects discontinued permanently due to AE.

There was no SAE(Serious AE) and death due to AE.

Table S5 Number (%) of subjects who had at least one adverse event in any category, and total number of adverse events (safety set)

	N=94 n(%)	events
Adverse event	65(69.1)	221
Treatment-related AE	29(30.9)	53
Severe AE	4(4.3)	4
SAE(Serious adverse event)	0	0
Study permanently discontinuation due to AEs	4(4.3)	5
Died during the treatment period due to AEs	0	0

Quetiapine XR affected significantly reductions in prolactin level, BARS total score, SAS total score, and AIMS total score.

Table S6 Summary of major safety results (Safety set)

Safety variables	N	Mean (95% CI)	Median (95% CI)	p-value*

Prolactin level [ng/mL]	Change	79**	-14.4 (-22.0, -6.7)	-8.3 (-13.8, -2.6)	<0.0001
BARS total score	Change	89	-0.69 (-1.10, -0.27)	0.0 (0.0, 0.0)	<0.0001
SAS total score	Change	89	-2.63 (-3.63, -1.63)	0.0 (-1.0, 0.0)	<0.0001
AIMS total score	Change	89	-1.34 (-2.18, -0.50)	0.0 (0.0, 0.0)	<0.0001

* Wilcoxon's signed rank test
** 10 patients had no post-baseline prolactin level