AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Quetiapine Fumarate XR
Study Code	D1444C00008
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A 6-Week, Multi-centre, Double-blind, Double-dummy, Chlorpromazine-Controlled Randomised Study to Evaluate the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL) Extended-Release (XR) in the Treatment of Schizophrenic Patients with Acute Episode

Study dates: First subject enrolled: 1 Apr 2009
Last subject last visit: 21 July 2010

Phase of development: Phase III

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

Study centre(s)

This study was conducted at 11 centres in China.

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the efficacy of Quetiapine fumarate extended-release (XR) used as mono-therapy, administered once daily, in the treatment of schizophrenic patient with acute episode	Change from baseline of the PANSS total score at the end of treatment at Day 42	**Efficacy**
Secondary	**Secondary**	
To evaluate the efficacy of Quetiapine fumarate XR in reducing positive, negative and general psychopathological symptoms, and aggression, hostility, depression in the treatment of schizophrenic patient with acute episode	Change from baseline in PANSS positive, negative, general psychopathological subscale score at the end of treatment at Day 42	**Efficacy**
	Change from baseline in PANSS aggression, hostility and depression clusters score at the end of treatment at Day 42	
To evaluate the response rate of Quetiapine fumarate XR in the treatment of schizophrenic patient with acute episode	Proportion of patients achieving a reduction of at least 30% from baseline PANSS total score at the end of treatment at Day 42	
	Proportion of patients with CGI Global Improvement rating ≤3 at the end of treatment at Day 42	
To evaluate the efficacy of Quetiapine fumarate XR in improving overall clinical status of schizophrenia in the treatment of schizophrenic patients with acute episode	Change in the CGI Severity of Illness score from baseline at the end of treatment at Day 42	
To evaluate the safety and	The incidence of adverse events (AEs)	**Safety**

Objectives	Outcome variables	Type
tolerability of Quetiapine fumarate XR in the treatment of schizophrenic patients with acute episode	Clinically significant changes in hematology, clinical chemistry (including thyroid function test, glycosylated hemoglobin (HbA1c), fasting plasma glucose, fasting lipid levels and prolactin levels), vital signs (including blood pressure, pulse and weight) and electrocardiogram (ECG) results. Extrapyramidal symptoms (EPS), adverse events related to EPS, changes in EPS related scales i.e., Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS), and the proportion of patients using anticholinergic medication.	

Study design

This is a 6-week, multi-centre, double-blind, double-dummy, chlorpromazine-controlled randomised study to evaluate the efficacy and safety of Quetiapine fumarate (SEROQUEL) extended-release (XR) in the treatment of patients hospitalised for an acute schizophrenic episode.

Target subject population and sample size

Male or female patient, 18 to 65 years of age, inclusive, with a diagnosis of schizophrenia by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (Schizophrenia [DSM-IV]: disorganised [295.10]; catatonic [295.20]; paranoid [295.30]; undifferentiated [295.90]) will be enrolled. The patients should also have a PANSS total score of ≥ 70 and at least 4 on one or more of the following PANSS items: P1 - delusions; P2 - conceptual disorganization; P3 - hallucinatory behaviour; P6 - suspiciousness/persecution at Visit 1 (screening) and 2 (randomisation). Approximate 380 patients from 11 sites were randomised into Quetiapine XR group or chlorpromazine group.

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

All eligible patients on Day 1 will be randomly allocated to 6 weeks of treatment with Quetiapine fumarate XR or chlorpromazine.

Quetiapine XR was administered orally, once daily in the evening. The initial dose was 300 mg. This dose was to be adjusted on Day 2 to 600 mg, from Day 3 to Day 42, the dose of Quetiapine fumarate XR could be adjusted to 400 mg/day, 600 mg/day, or 800 mg/day at the investigator's discretion.

Chlorpromazine was be administered orally, twice daily. The initial dose was 50 mg to 100 mg. This dose was to be adjust on Day 2 from 100 to 200 mg, on Day 3 from 150 to 300 mg,

and Day 4 from 200 to 400 mg. From Day 5, the dose of chlorpromazine could be adjusted to 300 mg/day, 400 mg/day, 500 mg/day, or 600 mg/day at the investigator's discretion.

The dose of investigational products in each arm (active drug and placebo respectively) should be increased or decreased at the same time according to corresponding dose unit.

Batch numbers for Quetiapine XR and matching placebos were 6728.10/1 and 6728.12/1, and 6728.11/1 and 6728.13/1 for chlorpromazine and matching placebo.

Duration of treatment

42 days (6 weeks)

Statistical methods

The primary objective of the statistical analysis was to demonstrate non-inferior efficacy of Quetiapine XR compared to chlorpromazine. All statistical tests were 2-sided with a significance level of 5%; ie, α=0.05. Where appropriate, 95% confidence intervals were presented. Patients with post baseline data (PP population) had their observed cases (OC) data as the final assessment for primary analyses (MMRM). Missing data resulting from patient dropouts will be imputed using a Last Observation Carried Forward (LOCF) approach (for ANCOVA model). The primary statistical analysis utilized a mixed-effect model repeated measure (MMRM) for the change from baseline at the end of treatment in the PANSS total score. The model include the independent variables for treatment and centre, the model also considered the visit time as a factor variable and interaction effect of treatment to visit time. Fixed effects in the model were treatment and baseline PANSS, whereas centre was regarded as a random effect. The results were presented in terms of Least Square (LS) means and the difference between LS means, with associated 95% confidence intervals. If the upper limit of 95% confidence intervals for the difference between Quetiapine XR and chlorpromazine was less than 6, non-inferiority would be claimed. All the secondary analyses used LOCF data in the full analysis set (FAS). The reported confidence levels and p-values were nominal, thus, no adjustment for multiplicity was made. Descriptive statistics were used for safety assessments.

Patient population

Baseline patient characteristics are presented in Table S2. The randomized study population included 388 patients enrolled from 11 centers. The number of patients discontinuing early ranged from 38 (19.4%) in the Quetiapine XR group to 44 (22.8%) in the chlorpromazine group, most commonly because of lack of efficacy, withdrawal of consent, or AEs. A total of 306 patients completed study treatment (80.6% Quetiapine XR patients and 77.1% chlorpromazine patients). The FAS included a similar percentage of men (47.4%) and women (52.6%), and the mean age was 32.5 years for the total population. All the patients were Chinese mainland citizens. Overall, the treatment groups were comparable with respect to demographic characteristics and baseline disease characteristics.

Of the 388 patients assigned to treatment and included in the safety analyses, 4 were excluded from the FAS because post-baseline PANSS scores were missing. The proportion of patients excluded from the FAS was evenly distributed across the treatment groups. Of the 384 patients included in the FAS analyses, 75 were excluded from the per protocol (PP) analysis set, with few differences among treatment groups in reasons for exclusion. Most of these exclusions were due to use of prohibited concomitant medications. Patient disposition and analysis sets please are shown in Table S3.

Table S2 Demographic and baseline characteristics—FAS population

	Quetiapine XR (N=194)	**Chlorpromazine (N=190)**	**Overall (N=384)**
Demographic or baseline characteristics			
Age (yrs)a			
Mean(SD)	32.9(10.70)	32.0(10.33)	32.5(10.52)
Range	18-60	18-58	18-60
Sex			
male	92 (47.4%)	90 (47.4%)	182(47.4%)
female	102 (52.6%)	100 (52.6%)	202(52.6%)
Race			
Asian(China Mainland)	194(100.0%)	190(100.0%)	384(100.0%)
DSM-IV diagnosis, schizophrenic subtype			
Disorganized	6 (3.1%)	13 (6.8%)	19 (4.9%)
Catatonic	1 (0.5%)	1 (0.5%)	2 (0.5%)
Paranoid	116(59.2%)	103(53.6%)	219(56.4%)
Undifferentiated	73 (37.2%)	75 (39.1%)	148(38.1%)
PANSS total score at randomizationb			
Mean(SD)	93.4(14.19)	92.9(14.51)	93.1(14.34)
Range	71-143	64-137	64-143
CGI Severity of Illness at randomizationc			
Mean(SD)	5.3(0.68)	5.2(0.70)	5.2(0.69)
Range	4-7	4-7	4-7

a At enrollment.
b Inclusion criteria was PANSS score at randomization ≥70.
c Inclusion criteria was CGI score at randomization ≥4.

CGI Clinical Global Impression. DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition. FAS full analysis set. N Number of patients in treatment group. n Number of patients. PANSS Positive and Negative Syndrome Scale. PP Per protocol.

Table S3 Summary of analysis population all patients randomized

	Quetiapine XR	Chlorpromazine	Overall
Disposition (randomized patients): n			
Completed randomized treatment	158	148	306
Premature discontinuation	38	44	82
N analyzed for safety	196	192	388
N analyzed for efficacy (FAS)	194	190	384
N analyzed for efficacy (PP)	159	150	309

Summary of efficacy results

Primary efficacy result at Day 42 (OC, PP population) is presented in Table S4.

Table S4 Primary efficacy result at Day 42(OC, PP population)

			MMRM: Adjusted means or Difference between groups		
Group	N	Baseline Mean(SD)	Estimate(SE)	CI.95%	P value
Quetiapine XR group	134	93.1(13.71)	-33.4(1.45)	-36.2,-30.5	
Chlorpromazine group	122	92.9(13.85)	-35.9(1.35)	-38.6,-33.3	
Intergroup			2.6(1.56)	-0.50,5.63	0.1011

Change from baseline=post baseline-baseline

The difference between the two groups (LS means of Quetiapine XR group minus that of chlorpromazine group) was 2.6(1.56) and its 95% CI was (-0.50 to 5.63). The upper limit of 95% CI is within the non-inferiority margin 6. This was supported by the results in ANCOVA analysis in the FAS (the difference of two groups was 2.9± 1.66 due to the LS means estimates -28.7(1.61) and -31.6(1.55), the 95% CI of difference is -0.37 to 6.14, with upper limit near margin 6.

A summary of secondary efficacy results at Day 42 (LOCF, FAS) is presented in Table S5.

Table S5 Summary of efficacy results at Day 42 (LOCF, FAS)

	Quetiapine XR (N=194)	Chlorpromazine (N=190)
PANSS positive subscale score, LS mean change from baseline (SE)	-9.9(0.53)	-11.1(0.51)
	Intergroup difference: 1.2(95%CI: 0.15, 2.30)	
PANSS negative subscale score, LS mean change from baseline (SE)	-5.9(0.50)	-6.7(0.48)
	Intergroup difference: 0.8(95%CI: -0.24,1.77)	
PANSS psychopathology subscale score, LS mean change from baseline (SE)	-12.9(0.74)	-13.9(0.71)
	Intergroup difference:1.1(95%CI: -0.45, 2.55)	
PANSS aggression and hostility clusters scores, LS mean change from baseline (SE)	-4.8(0.33)	-5.4(0.32)
	Intergroup difference: 0.6(95%CI: -0.06,1.30)	
PANSS depression cluster scores, LS mean change from baseline (SE)	-1.8(0.18)	-1.7(0.18)
	Intergroup difference: -0.1(95%CI: -0.47,0.27)	
Response rate: Proportion of ≥30% reduction in the PANSS total score from baseline, n (%)	112 (57.7%)	126 (66.3%)
	OR: 0.60; 95%CI: 0.38,0.95	
CGI-BP severity of illness score, LS mean change from baseline (SE)	-1.8(0.12)	-2.1(0.11)
	Intergroup difference: 0.3(95%CI: 0.04,0.51)	
Proportion of "very much improved", "much improved" "minimally improved" in the CGI Global Improvement score, n (%)	170 (87.6%)	169 (88.9%)
	OR: 0.88; 95%CI: 0.47,1.64	

No obvious differences between the two groups were demonstrated in most secondary variables: PANSS subscales (negative, psychopathological, aggression and hospitality, depression) and CGI scale (CGI global improvement). Improvements in terms of PANSS positive subscale, PANSS responder and CGI severity of illness were more pronounced in the chlorpromazine group.

Summary of safety results

The number (%) of patients who had at least 1 adverse event in any category is summarized in Table S6. There was no death in the study. SAEs were only seen in the chlorpromazine group (2 patients). Discontinuations due to AEs were infrequent in both treatment groups, but more common in the chlorpromazine group. The overall incidence of AEs was higher in the chlorpromazine group (86.5%) than in the Quetiapine XR group (72.4%). Most adverse events were mild to moderate. The incidence of drug-related AEs was higher in the chlorpromazine group compared to Quetiapine XR group (67.2 vs. 55.1%).

Table S6 Various categories of adverse events (safety population)

	Quetiapine XR N=196 n (%)	Chlorpromazine N=192 n (%)
Adverse eventsa	142(72.4%)	166(86.5%)
Serious adverse eventsa	0	2 (1.0%)
Serious adverse events leading to deatha	0	0
Serious adverse events not leading to deatha	0	2 (1.0%)
Drug-related adverse eventsa, b	108(55.1%)	129(67.2%)
Adverse events leading to discontinuationa	9 (4.6%)	18 (9.4%)

[a] Patients with multiple events in the same category are counted only once in that category.
[b] As judged by the investigator.
N Number of patients in treatment group. n Number of patients.

The common AEs (≥5%) (see Table S7) in both treatment groups were constipation, dizziness, insomnia, agitation, extrapyramidal disorder, palpitations, upper respiratory tract infection and diarrhoea. However, extrapyramidal disorder was higher in the chlorpromazine group (30.2%) than in the Quetiapine XR group (8.7%).

The pattern of common AEs observed in the Quetiapine XR treatment group generally conformed to that which was anticipated based on the pharmacological profile of Quetiapine IR and Quetiapine XR. Extrapyramidal disorder was the most commonly reported individual AE during the study treatment period. It was reported by 30.2% of the patients in the chlorpromazine group and by 8.7% of the Quetiapine XR patients. Orthostatic hypotension (9.4 vs. 2.0%), tachycardia (8.9 vs. 4.6%), increased heart rate (7.8 vs. 4.1%), akathisia (7.3 vs. 1.5%) and nasopharyngitis were also more commonly reported in the chlorpromazine group. Constipation (25.0 vs. 16.1%) and somnolence (7.7 vs. 2.1%) were more common in the Quetiapine XR group than in the chlorpromazine group. The safety profile of Quetiapine XR was consistent with previous studies and no new safety findings were recorded.

There other AEs reported by ≥ 5% of the patiens in any treatment group were reported by similar number of patients in the two treatment groups.

In the first week of treatment dizziness was the most common seen AE, 9.7% in the Quetiapine XR group and 6.8% in the chlorpromazine group. A higher incidence of EPS was found in the chlorpromazine group 7.3% than in the Quetiapine XR group 2.6% in the first week. There were 5.6% patients reporting constipation, 3.6% patients reporting somnolence, and only 0.5% patients reporting orthostatic hypotension in the Quetiapine XR group in the first week.

Table S7 Common adverse events (safety population)

Preferred Term	Quetiapine XR (N=196)	Chlorpromazine (N=192)
CONSTIPATION	49 (25.0%)	31 (16.1%)
EXTRAPYRAMIDAL DISORDER	17 (8.7%)	58 (30.2%)
DIZZINESS	28 (14.3%)	27 (14.1%)
INSOMNIA	25 (12.8%)	28 (14.6%)
AGITATION	24 (12.2%)	21 (10.9%)
PALPITATIONS	12 (6.1%)	16 (8.3%)
UPPER RESPIRATORY TRACT INFECTION	12 (6.1%)	14 (7.3%)
DIARRHOEA	11 (5.6%)	15 (7.8%)
TACHYCARDIA	9 (4.6%)	17 (8.9%)
HEART RATE INCREASED	8 (4.1%)	15 (7.8%)
ORTHOSTATIC HYPOTENSION	4 (2.0%)	18 (9.4%)
HEPATIC FUNCTION ABNORMAL	11 (5.6%)	9 (4.7%)
SOMNOLENCE	15 (7.7%)	4 (2.1%)
NASOPHARYNGITIS	5 (2.6%)	13 (6.8%)
AKATHISIA	3 (1.5%)	14 (7.3%)

One patient was counted at most once per category.
One patient may be counted in multiple categories.
Items are sorted by descending total patient number of system organ class and preferred term.
For subject data listing refer to Appendix 12.2.7.1.

Small changes from baseline were observed at end of treatment for both groups in clinical laboratory assessments, including mean hemoglobin, ALT, AST, and insulin levels values. Two patients recorded clinically important treatment-emergent fasting glucose values in the Quetiapine XR group, and 9 patients in the chlorpromazine group. A mean increase in prolactin levels were observed in the chlorpromazine group (291.62 mIU/L), while a decrease was observed in the Quetiapine XR group (-282.13 mIU/L). Increases in triglycerides and total cholesterol and changes in FT4 and TSH were consistent with the known safety profile for Quetiapine XR.

A small increase in mean pulse rate and QTc interval were noted in both treatment groups with more patients with clinically important decrease of supine SBP value in the chlorpromazine group than in the Quetiapine XR group at last follow-up, 17(11.5%) and 8(5.1%), respectively. Similar percentages of patients with weight increases of ≥7% were noted in the Quetiapine XR group and in the chlorpromazine group, 29(15.3) and 26(14.1), respectively.