AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Seroquel™
ACTIVE INGREDIENT: Quetiapine Fumarate

Study No: D1443L00023
An Open Label, 4-Week, Randomised, Multi-Centre, Phase IV Study to Compare the Efficacy and Safety of Quetiapine Fumarate (Seroquel™) as Mono-Therapy or adjunct to lithium in the Treatment of Patients with Acute Mania in Bipolar Disorder

Developmental phase: Phase IV
Study Completion Date: 3 July 2009
Date of Report: 10 Dec 2009

OBJECTIVES:

Primary objective

The primary objective of this study is to test the efficacy of quetiapine fumarate used as mono-therapy not inferior to adjunct therapy to lithium in the treatment of patient with acute mania in bipolar disorder by evaluation of change from baseline in the YMRS total score to Day 28.

Secondary objectives

Efficacy

1. To evaluate efficacy of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in the treatment of patients with acute mania in bipolar disorder with YMRS at all time points and CGI-BP

2. To evaluate the response rate of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in the treatment of patients with acute mania in bipolar disorder

3. To evaluate the remission rate of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in the treatment of patients with acute mania in bipolar disorder

4. To evaluate the efficacy of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in the treatment of psychotic symptoms in patients with acute mania in bipolar disorder

5. To evaluate the efficacy of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in the treatment of agitation in patients with acute mania in bipolar disorder

6. To evaluate the efficacy of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in the treatment of aggression in patients with acute mania in bipolar disorder

7. To evaluate the efficacy of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in the treatment of depressive symptoms in patients with acute mania in bipolar disorder

8. To evaluate the efficacy of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in improving sleep quality in the treatment of patients with acute mania in bipolar disorder

Safety

To evaluate the safety and tolerability of quetiapine fumarate used as mono-therapy compared to adjunct therapy to lithium in the treatment of patients with acute mania in bipolar disorder

METHODS:

This is a 4-week, multi-centre, open label, parallel group, active-controlled, randomised study to compare the efficacy and safety of quetiapine fumarate given as mono-therapy or adjunct therapy to lithim in the treatment of patients with acute mania in bipolar disorder. Eligibility for the study will be assessed at enrolment and randomisation. The patient will be randomised to treatment groups at Visit 2 after fulfilling all inclusion criteria and none of the exclusion criteria. All visits allow a visit window of ±1 day calculated from randomisation, except for Day 28 with an allowed visit window of ±2 days. The handling of assessments outside the allowed visit windows is described in the statistical section The study comprises 2 periods: an enrolment period of up to 7 days and a 4-week randomised treatment period.

Target subject population and sample size

Male or female patients, 18 to 60 years old, with a DSM-IV diagnosis of manic episode in bipolar disorder (296.4X Bipolar Disorder I, Most Recent Episode Manic; 296.0X Bipolar I Disorder, Single Manic Episode). The patients should also have a YMRS total score ≥20 to be eligible for the study.

Duration of treatment

28 days (4 weeks)

Statistical methods

Data were summarized using descriptive statistics including number of patients, mean, standard deviation, median, minimum and maximum for continuous variables, and

frequency counts and percentages for categorical variables. The results of comparison between two groups will primarily be presented as model based point estimates and their two-sided 95% confidence intervals. Nevertheless, p-values will also be presented in order to aid the interpretation of the results. All secondary objectives will be tested in 2-sided, with a significance level of 5%, i.e., α=0.05 unless otherwise specified.
The primary outcome variable, the change from baseline in the YMRS total score to Day 28, will be analysed for PP as the primary analysis set and for FAS as the secondary analysis set using an analysis of covariance (ANCOVA) model including treatment and centre as explanatory variables and baseline YMRS total score as covariate. Centre will be treated as a random effect while all other explanatory variables will be treated as fixed effects. Treatment differences will be estimated from the model and a two-sided 95% confidence interval for the expected difference in change from baseline will be calculated and used as the primary test statistically. Non-inferiority will be claimed if the lower limit of two sided 95% confidence interval for the expected difference between quetiapine mono-therapy and adjunct therapy is totally above $-\Delta$(adjunct therapy- mono-therapy). In this study, the non-inferiority margin Δ is defined as 3.5.
MMRM (Mixed Model Repeated Measurement) analysis will be performed for changes from baseline in YMRS total scores (OC) to assess the robustness of the primary analysis. Changes from baseline to each assessment in the YMRS total score as well as changes from baseline to each assessment in CGI-BP severity of illness subscale scores, PANSS total scores, PANSS activation subscale score, PANSS supplemental aggression risk subscale score, MADRS total score, and YMRS item 4 scores will be analysed using ANOVA model.
Response, remission at Day 28, defined from YMRS scores, as well as the dichtomized CGI-BP Global improvement score at Day 28 will be analysed utilising logistic regression models.
ANCOVA analysis will be performed separately for change from baseline to Day 28 in AIMS total score, BARS total score, and SAS total score. Changes from baseline to Day 28 for weight as well as the number and proportion of patients with weight increase $\geq$7% during treatment phase from baseline will be presented by descriptive statistics.
Incidence rates will be calculated for AEs (including serious adverse events, AEs leading to withdrawals and deaths if any) and reasons for premature discontinuation. Other safety variables that evaluate physical examinations: laboratory assessments, vital signs, ECGs and selected AEs will be conducted by means of descriptive statistics and frequency tabulations.
There were three changes of statistical methods before data lock: 1)The primary analysis population for the efficacy analysis was changed from MITT (FAS) population to PP population. This is in line with ICH E9 recommendation. In non-inferiority setting, PP population is more conservative than MITT population (FAS). 2) ANCOVA analysis will be performed separately for change from baseline to Day 28 in AIMS total score, BARS total score, and SAS total score.3) MMRM (Mixed Model Repeated Measurement) analysis will be performed for changes from baseline in YMRS total scores (OC).

RESULTS:

Patient population

Baseline patient characteristics are presented in Table S1. The total study population comprised 430 patients enrolled from 21 centers. Of those, 378 qualified and were

randomised to quetiapine fumarate mono-therapy group (n=188) or quetiapine fumarate adjunct therapy to lithium group (n=190) on Day 1. Of the 52 patients who did not qualify, 69% (36 patients) were not eligible to receive treatment because eligibility criteria were not fulfilled. Discontinuations were more frequent in the adjunct therapy group (17.4%) than in the mono-therapy group (13.3%). Discontinuations due to voluntary quit were similar between the mono-therapy group (4.8%) and the adjunct therapy group (5.3%). The rates of discontinuation due to AEs were less in the mono-therapy group (2.7%) than in the adjunct therapy group (4.2%). Approximately 86.7% patients in the mono-therapy group and 82.6% in the adjunct therapy group completed the study. There was no difference in gender and age distribution between two groups at baseline.

Table S1 Baseline demography and other features- FAS

Index	Mono-therapy (N=187)	Adjunct therapy (N=189)
Age[1]		
Mean(Std)	34.3(12.16)	32.43(11.14)
Median	31	31
Min-Max	17-63	18-60
Gender		
Male	93(49.73%)	102(53.97%)
Female	94(50.27%)	87(46.03%)
Race		
White	1(0.53%)	0(0%)
Oriental	186(99.47%)	189(100%)
Weight(Kg)		
N	187	187
Mean (Std)	62.07(11.17)	64.33(12.38)
Median	60	62
Min-Max	39-93	42-102
Baseline of YMRS total score		
Mean(Std)	37.12(6.86)	37.32(5.83)
Median	36	37
Min to Max	25 to 58	23 to 53
Baseline of PANSS total score		
Mean (Std)	52.88(11.39)	53.95(11.43)
Median	52	54
Min to Max	30 to 83	30 to 92
Baseline of MADRS total score		
Mean (Std)	4.32(3.94)	4.54(4.16)
Median	4	4
Min to Max	0 to 18	0 to 32
Total frequency of Prior Manic/Mixed Episode Over Life		

Index	Mono-therapy (N=187)	Adjunct therapy (N=189)
Mean (Std)	3.04 (4.12)	2.77(3.12)
Median	2	2
Min to Max	0 to 30	0 to 24
Total frequency of Depressed Episode Over Life		
N	144	144
Mean(Std)	1.56(2.39)	1.45(1.9)
Median	1	1
Min to Max	0 to 20	0 to 10
DSM-IV		
296.0X	42(22.46%)	44(23.28%)
296.4X	145(77.54%)	145(76.72%)

[1] Age is the period between DICF date and birthday.

Of the 378 randomized patients, 187 subjects of mono-therapy group and 189 subjects of adjunct therapy group were analyzed as safety set and full analysis set, 1 patient in each group were excluded because of not administrating the study medication. Of the 376 patients included in the FAS analyses, 20 (9 of mono-therapy group and 11 of adjunct therapy group) were fully excluded from the PP analysis set, because of violated eligibility criteria, drug compliance less than 70%, median serum lithium level in lithium arm <0.6mmol/l and concomitant medication of protocol deviations. See Table S2.

Table S2 Analysis sets-All randomized subjects

	Mono-therapy (N=188)	Adjunct therapy (N=190)
Subjects in SFS	187(99.5%)	189(99.5%)
Subjects not in SFS	1(0.5%)	1(0.5%)
Reason for absent from SFS		
Not administrate the study medication	1(0.5%)	1(0.5%)
Subjects in FAS	187(99.5%)	189(99.5%)
Subjects not in FAS	1(0.5%)	1(0.5%)
Reason for absent from FAS		
Not administrate the study medication	1(0.5%)	1(0.5%)
Subjects in PP	178(94.7%)	178(93.7%)
Subjects not in PP	10(5.3%)	12(6.3%)
Reason for absent from PP		
Violated eligibility criteria	3(1.6%)	2(1.1%)
Not administrate the study medication	1(0.5%)	1(0.5%)
Drug compliance less than 70%	2(1.1%)	0(0.0%)

	Mono-therapy (N=188)	Adjunct therapy (N=190)
Median serum lithium Level in Lithium arm is <0.6mmol/L	0(0.0%)	6(3.2%)
Concomitant medication of protocol deviations	4(2.1%)	3(1.6%)

[1] The meaning of SFS is randomized subjects received study drug at least one.
[2] The meaning of FAS is randomized subjects received study drug at least one with assessable record.
[3] The meaning of PP is FAS subjects without primary protocol deviation and violation

Efficacy results

Primary efficacy result at Day 28(LOCF, PP population) is presented in Table S3.

Table S3 Primary efficacy result at Day 28(LOCF, PP population)

				ANCOVA: Adjusted means or Difference between groups			
Group	**N**	**Baseline Mean(SD)**	**Change Mean(SD)**	**Estimate(SE)**	**CI.95%**	**F**	**P**
Mono-therapy group	178	37.2(6.8)	-25.7(13.7)	-23.72(0.969)	-25.627 to -21.814		
Adjunct therapy group	178	37.5(5.8)	-26.1(13.4)	-23.9(0.978)	-25.823 to -21.977		
Intergroup				-0.18(1.174)	-2.489 to 2.131	0.020	8789

ANCOVA model include baseline and treatment, centre is random effect.

The difference between two groups (LS means of Adjunct therapy group minus that of Mono-therapy group) is -0.18±1.174 and its 95% CI is (-2.489 to 2.131). The low limit of 95% CI is within the non-inferiority margin -3.5. This consequence was also confirmed by the results in ANCOVA analysis in FAS (the difference of two groups is -0.92±1.177 due to the LS means estimates -23.44±0.954 and -24.36±0.941, the 95% CI of difference is -3.236 to 1.395, with low limit larger than -3.5), and MMRM analysis in both FAS and PP (p values of treatment in day 28 are larger than 0.05).

The overall conclusion as defined in protocol, it is reasonable to say that quetiapine mono-therapy is non-inferior
to lithium plus adjunct quetiapine in the treatment of patients with acute mania in bipolar disorder.

A summary of secondary efficacy results at Day 28(LOCF, FAS) is presented in Table S4.

Table S4 Summary of efficacy results at Day 28 (LOCF, FAS)

	Mono-therapy (N=187)	Adjunct group (N=189)	P value
Proportion of ≥50% reduction in the YMRS total score from baseline, n (%)	139(74.332%)	153(80.952%)	0.0844
	OR:1.592; 95%CI: 0.939 to 2.698		
Proportion of ≤12 in the YMRS total score, n (%)	117(62.567%)	123(65.079%)	0.5279
	OR:1.173; 95%CI:0.714 to 1.927		

	Mono-therapy (N=187)	Adjunct group (N=189)	P value
CGI-BP severity of illness score, LS mean change from baseline (SE)	-2.48(0.116)	-2.65(0.115)	0.2277
	Intergroup difference: -0.17(0.144)		
Proportion of "much improved" or "very much improved" in the CGI-BP Global improvement score, n (%)	92(49.198%)	91(48.148%)	0.8567
	OR: 0.959; 95%CI: 0.612 to 1.504		
PANSS total score, LS mean change from baseline (SE)	-16.12(0.285)	-16.44(0.28)	0.3003
	Intergroup difference: 0.32(0.305)		
PANSS activation subscale score, LS mean change from baseline (SE)	24.97(0.746)	24.32(0.738)	0.4795
	Intergroup difference: 0.65(0.923)		
PANSS Supplement Aggression Risk subscale score, LS mean change from baseline (SE)	22.71(0.766)	22.2(0.759)	0.5891
	Intergroup difference: 0.51(0.947)		
MADRS total score, LS mean change from baseline (SE)	-2.99(0.181)	-3.02(0.179)	0.9072
	Intergroup difference: 0.03(0.223)		
YMRS item 4 score, LS mean change from baseline (SE)	-36.65(0.071)	-36.65(0.07)	0.9999
	Intergroup difference: 0(0.088)		

All the analyses of secondary measures demonstrated no difference ($p>0.05$) between two groups in YMRS response rate, YMRS remission rate, CGI-BP severity of illness score, Proportion of "much improved" or "very much improved" in the CGI-BP Global improvement score, PANSS total score, PANSS activation subscale score, PANSS Supplement Aggression Risk subscale score, MADRS total score, and YMRS item 4 score at Day 28, further supporting the robustness of the primary analyses.

Safety results

The number (%) of patients who had at least 1 adverse event in any catergory is summarized in Table S5. Overall quetiapine fumarate was generally safe and well tolerated at mean dose of 569.18 mg/day as mono-therapy and 484.05 mg/day as adjunct to lithium (mean exposure dose 1107.45 mg/day) therapy. Analysis of adverse events indicated that dizziness, constipation, somolence, weight gain and upper respiratory tract infection in mono-therapy and adjunct to lithium occurring as the most common adverse events. Nausea, tremor, extrapyramidal disorder and vomiting were additional most common AEs in adjunct therapy to lithium. Gastrointestinal disorders and hypothyroidism were more seen in adjunct therapy to lithium. There was no death in the study and most adverse events were mild to moderate. SAE and discontinuations due to AEs were infrequent in the study.

Table S5 Various categories of adverse events (SFS)

AE Levels	Mono-therapy (N=187)	Adjunct therapy (N=189)	Total (N=376)
AEs frequency	278	318	

AE Levels	Mono-therapy (N=187)	Adjunct therapy (N=189)	Total (N=376)
Number of subject with at least one AE	120(64.2%)	125(66.1%)	245(65.2%)
Number of subject with at least one SAE	0	1(0.5%)	1(0.3%)
Number of Death	0	0	0
Number of subject with at least one drug related AE	84(44.9%)	99(52.4%)	183(48.7%)
Number of subject with at least one severe AE	2(1.1%)	1(0.5%)	3(0.8%)
Number of subject discontinuations of IP due to an AE(DAE)	5(2.7%)	8(4.2%)	13(3.5%)

AEs calculation only base on AE happened after treatment.

The incidence of common adverse events (occurring at an incidence of ≥5% in any treatment group) is summarized in Table S6. The pattern of common AEs observed in the study generally conformed to that which was anticipated based on the clinical experience of quetiapine fumarae; ie, dizziness, constipation, somolence, weight gain and upper respiratory tract infection. There was no new safety concern that arose from quetiapine treatment. Nausea, tremor, extrapyramidal disorder and vomiting were additional most common AEs in adjunct therapy to lithium. 60(31.74%) patients in adjunct group were reported as AE of gastrointestinal disorders associated with investigation drugs, more than 21(11.22%) patients in quetiapine mono-therapy group.

There were no unexpected observations in laboratory measurements (clinical chemistry, hematology and urinalysis) with quetiapine mono-therapy treatment. However, T3, T4, fT3 and fT4 decrease were more seen in adjunct therapy to lithium. 8 patients were reported as AE of hypothyroidism in the adjunct group, while no patients in mono-therapy group.

There were no unexpected observations with quetiapine treatment whether in mono-therapy or adjunct to lithium. 5 patients in mono-therapy and 11 patients in adjunct therapy were found QTc interval ⩾ 450 ms in ECG measurement at Day 28, but no patient was reported as AE.

Small changes from baseline were observed in vital signs (blood pressure and pulse rate) with quetiapine treatment (eg, increased pulse rate, hypotension) whether in mono-therapy or adjunct to lithium. 1 patient in mono-therapy was reported as hypotension of AE. 4 patients in mono-therapy group and 3 patients in adjunct group were reported as heart rate increased of AE. 7 patients in mono-therapy group and 4 patients in adjunct group were reported as palpitations of AE.

There was no difference in EPS symptoms as assessed by means of SAS, AIMS and BARS scores between two groups. 11 (5.88%) patients in mono-therapy group and 25(13.23%) patients in adjunct group were reported as AE associated with EPS (EPS and tremor).

There was no relationship shown between new emergence of diabetes and quetiapine mono-therapy treatment or adjunct to lithium. Only 1 patient reported as AE of blood glucose increased was considered to be associated with investigation drugs in each group.

The most common adverse events, as summarized by preferred term, are shown in Table S6.

Table S6 Common adverse events (SFS)

PT	Mono-therapy (N=187)	Adjunct therapy (N=189)
Number of subject with at least one AE	120(64.2%)	125(66.1%)
Dizziness	21(11.2%)	14(7.4%)
Upper respiratory tract infection	14(7.5%)	12(6.3%)
Constipation	13(7.0%)	24(12.7%)
Weight gain	12(6.4%)	16(8.5%)
Somnolence	10(5.3%)	10(5.3%)
Nausea	4(2.1%)	15(7.9%)
Tremor	5(2.7%)	13(6.9%)
Extrapyramidal disorder	6(3.2%)	12(6.3%)
Vomiting	1(0.5%)	10(5.3%)

AEs calculation only base on ae happened after treatment.
For those subjects reported various AEs in same SOC term, calculation should be once