AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Seroquel XR
Study Code	D1443L00086
Edition Number	1.0
Date	30 May 2013

A comparison of the effectiveness of Seroquel XR and Seroquel XR plus lithium in patients with acute bipolar mania:

An open-label, randomized, parallel groups, rater-blinded, 4 week, multicenter, comparative, phase IV study (STAR)

Study dates: First subject enrolled: 7 December 2010
Last subject last visit: 31 October 2012

Phase of development: Therapeutic use (IV)

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

Study centre(s)

Total 13 centres participated in Korea.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

This study was designed to compare the efficacy of Seroquel XR monotherapy compared with Seroquel XR plus lithium in the treatment of acute bipolar mania.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To compare the efficacy of Seroquel XR monotherapy compared with Seroquel XR plus lithium in the treatment of acute bipolar mania by evaluation of the changes from baseline in YMRS total score to Day 29 using the last observation carried forward method.	Young Mania Rating Scale (YMRS)
Secondary	Efficacy	The percentage of patients with a ≥50% reduction from baseline in the YMRS total score at study endpoint	Young Mania Rating Scale (YMRS)
	Efficacy	The percentage of patients with YMRS remission (defined as a YMRS score ≤ 12) at Day 29	Young Mania Rating Scale (YMRS)
	Efficacy	The change from baseline to each assessment (observed cases) in the YMRS total score	Young Mania Rating Scale (YMRS)
	Efficacy	The change from baseline to each assessment (observed cases) and final assessment in the CGI-I and the CGI-S	Clinical Global Impression-Improvement of Illness/Severity of Illness (CGI-I/S)
	Efficacy	Reporting Treatment Emergent Adverse Events(TEAEs)	Treatment Emergent adverse Events

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
	Efficacy	Medication Satisfaction Questionnaire (MSQ) Score Change From Baseline to the Week 4 Endpoint	Medication Satisfaction Questionnaire (MSQ)
	Efficacy	Medication Satisfaction Questionnaire (MSQ) - Categorical Summary - Dichotomized Categories - Week 4 LOCF	Medication Satisfaction Questionnaire (MSQ)
	PRO	Patients' satisfaction with their medication	Medication Satisfaction Questionnaire (MSQ)
	Safety	The tolerability and safety profile between the two groups (especially metabolic side effects)	The incidence and severity of TEAEs, Other significant Adverse Event (OAE)
	Safety	The mean change from baseline to week 4 in SAS total score	Simpson-Angus Scale (SAS)
	Safety	The mean change from baseline to week 4 in BARS total score	Barnes Akathisia Rating Scale (BARS)
	Safety	The mean change from baseline to week 4 in PSQI total score	Pittsburgh Sleep Quality Index (PSQI)
	Safety	The mean change from baseline to week 4 in ACES score	Agitation-Calmness Evaluation Scales (ACES)
	Safety	Vital signs including ECG	

Study design

An open-label, randomized, parallel groups, rater-blinded, 4 weeks, multicenter, comparative, phase IV study of Seroquel XR and Seroquel XR plus lithium in the treatment of acute bipolar mania.

The subjects were randomized to treatment group (monotherapy or in combination with lithium).

Target subject population and sample size

Male and female in-or out-patients aged over 18 years and under 65 years for the treatment of acute bipolar mania. Approximately 220 patients from 13 centres were randomized to the study treatment.

When the sample size in each group is 100, a two group 0.025 one-sided t-test had 80% power to reject the null hypothesis that the seroquel+lithium and seroquel were not equivalent in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0.0, the common standard deviation is 10, and non-inferiority acceptance limit is 4. The sample size estimate was based on data from in which the difference in YMRS total score with respect to a short-term study was 18.8 with a standard deviation of 10.07. Considering the rate of non-evaluable patients being approximately 10%, the total sample size was planned to be 220 patients.

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

In 4 weeks, the dose of Seroquel XR was started at 300mg/day on Day 1 and was increased to 600mg/day on Day 2 in line with the prescription information. From Day 3, the dose could be adjusted from 400mg/day to 800mg/day in both treatment groups. Seroquel XR tablet 50mg, 200mg, 300mg, 400mg were used

Lithium was started with 300mg tid on Day 1 then adjusted between the 900mg/day and 1200mg/day from Day 2 within lithium concentration [0.8~1.2mEq/L].

Duration of treatment

28 days (4 weeks)

Statistical methods

The primary variable is the changes in YMRS total score from baseline to Day 29 was analysed using ANCOVA. Covariates included centre and baseline YMRS total score.

If patients discontinued the study prior to Day 29, the last-visit observation was carried forward (LOCF).

The statistical test for primary variable was two-sided with a significance level of 5%, i.e., α=0.05. Where appropriate, 95% confidence intervals was presented.

Analysis on efficacy endpoints was performed using the intent-to-treat population (ITT) as primary analysis and the per-protocol population (PP) for consistency check. Safety endpoints were performed in the safety population. The ITT population consisted of all patients who receive at least one dose of study treatment and who have measurements at baseline and at least one on treatment assessment. PP population was defined as all ITT patients with no major protocol violations and/or deviations. The safety population consisted of all patients

who receive at least one dose of study treatment. If patients discontinue the study prior to Day 29, the last-visit observation was carried forward (LOCF).

The results were presented in terms of mean changes and associated 95% confidence intervals.

Adverse events were reported as TEAEs. Numbers of events and crude incidence rates was 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.

Other safety variables including all laboratory test results, vital signs and weight was analyzed using descriptive statistics for raw numbers and change from baseline. The proportions of patients with normal/abnormal ECG was compared to baseline. The proportions of patients who have a ≥7% weight gain compared with baseline was tabulated.

Non-inferiority was claimed if the lower limit of two-sided 95% confidence interval for the expected difference between seroquel XR mono-therapy and seroquel XR added on lithium is totally above $-\Delta$.

In this study, the non-inferiority margin Δ was defined as 4.0

Subject population

The first and last patients were enrolled on 7 December 2010 and 24 September 2012, respectively, and the last patient's last study visit was on 31 October 2012. A total of 141 patients were enrolled and 131 patients were randomized at 13 centers in Korea. 130 patients received at least 1 dose of study medication.

Of the 131 randomized subjects, 1 subject terminated before start study treatment and 130 subjects received at least 1 dose of study medication. 37 subjects were discontinued and 94 patients were completed study treatment.

The reasons for discontinuation were subject not willing to continue study (19 patients), lack of therapeutic response (6 patients), adverse event (5 patients), subject lost to follow-up (4 patients), death (1 patient) and other (1 patient).

Summary of efficacy results

It was found that the mean change in YMRS total score from baseline to Day 29, which was the primary variable of this study, was -13.7 (the adjusted mean change was -13.7) for the Seroquel XR monotherapy arm and -15.4 (the adjusted mean change was -15.5) for the Seroquel XR + Lithium arm. Based on these results, the difference between the adjusted means for two arms was -1.7, with two-sided 95% confidence interval of (-6.4, 2.9). Considering the lower limit of the two-sided 95% confidence interval which could not exceed

-4.0 defined as the non-inferiority margin, non-inferiority could not be claimed (Table 1 and Table 2).

Table 1 Summary of YMRS total score: descriptive statistics (ITT set)

Treatment		N	Mean	SD	Median	Min	Max
Seroquel XR Mono	Baseline	63	28.3	7.4	26.0	20.0	49.0
	Day 29 (LOCF)	63	14.5	13.1	10.0	0.0	49.0
	Change	63	-13.7	13.8	-18.0	-40.0	19.0
	% Change	63	-47.4	46.8	-60.0	-100.0	70.8
Seroquel XR + Lithium	Baseline	58	28.1	6.2	27.0	18.0	44.0
	Day 29 (LOCF)	58	12.7	12.7	8.5	0.0	44.0
	Change	58	-15.4	13.3	-17.0	-40.0	21.0
	% Change	58	-54.0	44.8	-67.0	-100.0	91.3

Table 2 Change in YMRS total score from baseline after 4 weeks: ANCOVA analysis (ITT set)

YMRS total score at baseline (t-test)	Adjusted mean change (Baseline to Week 4)		Difference between adjusted means	95% CI for the LSMean difference**
	Seroquel XR Mono	Seroquel XR + Lithium		
p=0.9258	-13.7	-15.5	-1.7	(-6.4*, 2.9)

* Lower limit of two-sided 95% confidence interval -6.4 < -4.0 (non-inferiority margin): Inferior.
** From ANCOVA model with covariate of baseline YMRS total score.

It was indicated that the change from baseline to Day 29 in CGI-Severity score was -1.37 (the adjusted mean change was -1.36) for the Seroquel XR montherapy arm and -1.58 (the adjusted mean change was -1.59) for the Seroquel XR + Lithium arm. The difference between the adjusted means for two arms was -0.23, which was not statistically significant (p=0.3785) (Table 3 and Table 4).

Table 3 Summary of CGI-Severity score: descriptive statistics (ITT set)

Treatment		N	Mean	SD	Median	Min	Max
Seroquel XR Mono	Baseline	63	4.84	0.81	5.0	3.0	6.0
	Day 29 (LOCF)	63	3.48	1.38	3.0	1.0	6.0
	Change	63	-1.37	1.52	-1.0	-5.0	2.0
Seroquel XR + Lithium	Baseline	57	4.82	0.78	5.0	3.0	6.0
	Day 29 (LOCF)	57	3.25	1.44	3.0	1.0	6.0
	Change	57	-1.58	1.56	-2.0	-5.0	2.0

Table 4 Change in CGI-Severity score from baseline after 4 weeks: ANCOVA analysis (ITT set)

CGI-Severity score at baseline (t-test)	Adjusted mean change (Baseline to Week 4)		Difference between adjusted means (ANCOVA)*	95% CI for the LSMean difference
	Seroquel XR Mono	Seroquel XR + Lithium		
P=0.9087	-1.36	-1.59	-0.23 p=0.3785	(-0.74, 0.28)

* From ANCOVA model with covariate of baseline CGI-Severity score.

Summary of safety results

In this study, treatment-emergent adverse events were reported in 52 of 68 subjects (76.5%) of the Seroquel XR monotherapy arm and 49 of 62 subjects (79.0%) of the Seroquel + Lithium arm (p=0.8337, Fisher's test). Among them, the most common treatment-emergent adverse events indicating at least 5% of the incidence rate in total subjects included constipation reported in 20 of 68 subjects (29.4%) in the the Seroquel XR monotherapy arm and 20 of 62 subjects (32.3%) of the Seroquel + Lithium arm, followed by headache, dyspepsia, dry mouth, nasopharyngitis, insomnia, akathisia, tremor and dizziness (Table 5).

4 subjects had 1 SAE for each, manic symptoms aggravation(1), bipolar mania(1), mood elevation(1) and death(1), all were unrelated to study drug.

Table 5 Summary of Most common Treatment emergent adverse events

Preferred term	**Seroquel XR Mono N=68**		**Seroquel XR + Lithium N=62**		**Total N=130**	
	n(%)	**events**	**n(%)**	**events**	**n(%)**	**events**
Constipation	20(29.4)	21	20(32.3)	21	40(30.8)	42
Headache	6(8.8)	6	6(9.7)	10	12(9.2)	16
Dyspepsia	8(11.8)	9	3(4.8)	4	11(8.5)	13
Dry mouth	3(4.4)	4	7(11.3)	7	10(7.7)	11
Nasopharyngitis	5(7.4)	6	5(8.1)	5	10(7.7)	11
Insomnia	8(11.8)	8	2(3.2)	2	10(7.7)	10
Akathisia	4(5.9)	4	5(8.1)	5	9(6.9)	9
Tremor	3(4.4)	3	6(9.7)	6	9(6.9)	9
Dizziness	6(8.8)	6	2(3.2)	2	8(6.2)	8