Clinical Study Report Synopsis

Drug Substance	Quetiapine Fumarate
Study Code	D1443L00055
Edition Number	3.0
Date	15 February 2012

A Randomised, Multi-Centre Study to Compare the Efficacy and Safety of Extended Release Quetiapine Fumarate (Seroquel XR™) Tablets as Mono-Therapy or in Combination with Lithium in the Treatment of Patients with Acute Bipolar Depression

Study dates: First subject enrolled: *22 April 2009*
Last subject last visit: *01 March 2011*

Phase of development: Therapeutic confirmatory (III)

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

Study centre(s)

This study was performed at 29 centers in Turkey, Argentina, Mexico, Brazil, Guatemala, Chile, Venezuela, Peru and Colombia.

COUNTRY (CENTER)	Quetiapine XR N (%)	Quetiapine XR + Lithium N (%)	TOTAL N (%)
ARGENTINA (4)	13 (6,13)	12 (5,74)	25 (5,94)
BRASIL (4)	48 (22,64)	50 (23,92)	98 (23,28)
CHILE (2)	10 (4,72)	10 (4,78)	20 (4,75)
COLOMBIA (3)	19 (8,96)	21 (10,05)	40 (9,50)
GUATEMALA (2)	29 (13,68)	31 (14,83)	60 (14,25)
MEXICO (6)	47 (22,17)	40 (19,14)	87 (20,67)
PERU (1)	2 (0,94)	4 (1,91)	6 (1,43)
TURKEY (6)	14 (6,60)	8 (3,83)	22 (5,23)
VENEZUELA (1)	30 (14,15)	33 (15,79)	63 (14,96)
TOTAL (29)	212 (100,00)	209 (100,00)	421 (100,00)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1: Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	The efficacy of quetiapine fumarate monotherapy with quetiapine fumarate in combination with lithium in the treatment of a major depressive episode in patients with bipolar disorder after receiving treatment for 8 weeks as assessed by comparing the change from baseline to final assessment in the Montgomery-Asberg Depression Rating Scale (MADRS) total score	MADRS total score. Non-inferiority of treatment arm (quetiapine alone) was sought versus quetiapine+lithium arm over the change of MADRS total score from baseline to the end of treatment for 8 weeks.
Secondary	Efficacy	Response rate defined as the percentage of patients with a $\geq$50% reduction from baseline in the MADRS total score at the final assessment	MADRS Total Score
Secondary	Efficacy	The change in the MADRS total score from baseline in each assessment	MADRS Total Score

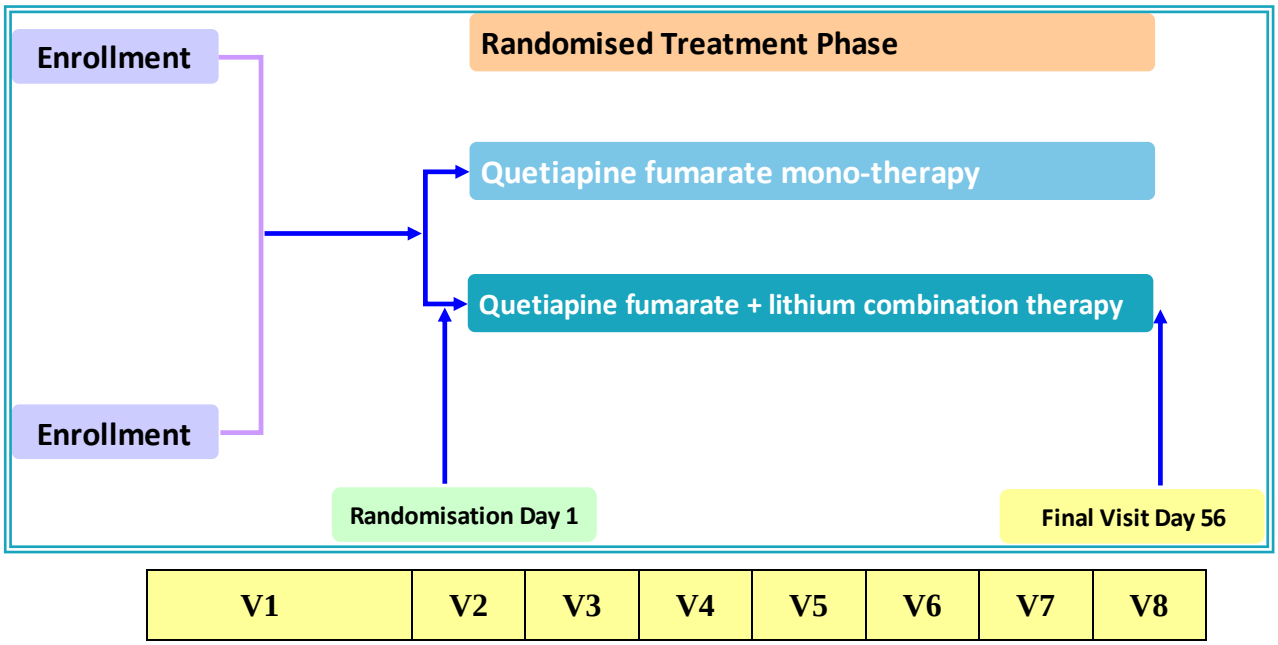
Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	The change from baseline to each assessment in the Hamilton Rating scale for Depression (HAM-D), HAM-D Item 1, the Clinical Global Impression - Severity (CGI-S), and the Clinical Global Impression - Improvement (CGI-I)	Changes in the following scoring at each visit when compared to baseline: HAM-D HAM-D, item 1 CGI-Severity and Improvement
Secondary	Efficacy	To evaluate the effect on anxiety by comparing the change from baseline either in each assessment or for the final assessment in the Hamilton Rating Scale for Anxiety (HAM-A) total score	HAM-A Total score
Secondary	Safety	To evaluate the safety and tolerability	• The incidence of treatment-emergent mania defined as the percentage of patients in each group who had a YMRS total score of 16 or greater on any 2 consecutive visits, or at the final assessment or an adverse event of mania or hypomania. Treatment emergent mania on the basis of YMRS • Adverse events (incidence and nature), all, drug-related and withdrawals if any
Secondary	Efficacy	Effects of treatment on sleep quality, overall quality of life, productivity in social and family life	PSQI,Q-Les-Q-Short Form, SDS and TSQM

Study design

This study was performed as an 8-week, multi-centre, rater-blind, parallel group, active-controlled, randomized study to compare the efficacy and safety of quetiapine fumarate as monotherapy or in combination with lithium in the treatment of a major depressive episode in patients with bipolar disorder. Eligibility of patients was assessed at enrolment and randomization. The patients were randomized to treatment groups at Visit 2 after fulfilling all inclusion criteria and none of the exclusion criteria. All visits allow a visit window of ± 2 days calculated from randomization. The handling of assessments outside the allowed visit windows is described in the statistical section.

The study comprises 3 periods, i.e., an enrolment period of up to 7 days, a washout period of 7-28 days, and an 8-week randomized treatment period.

Figure 1: Study Flow chart and visits (V1 to V8)



V1	V2	V3	V4	V5	V6	V7	V8

Target subject population and sample size

The target population for this study was patients from both genders, aged 18 to 65 years, with a diagnosis of DSM-IV-TR bipolar I or bipolar II disorder with a current major depressive episode of duration less than one year but greater than 2 weeks with the following criteria at screening:

a) The HAM-D (17-item scale) score ≥20,
b) The HAM-D item 1 (depressed mood) score ≥2, and
c) The YMRS score ≤12

The sample size of this study was calculated on the basis of previous studies performed with quetiapine versus placebo in patients with bipolar I or bipolar II disorder. The average change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score, from baseline to 8 weeks after treatment was 10-12 in placebo and 16-17 points in quetiapine group and standard deviations of the average changes in MADRS total score were calculated as 8-10 points in both groups. Thus an assumption of standard deviations as 9 points was made for the calculation of the sample size and a minimum difference in overall change in MADRS total score was assumed as 4 points as a clinically significance difference in change in MADRS total score with a non-inferiority limit set as 3.5 points.

The protocol hypothesis was planned as a non-inferiority hypothesis with a type I error level set at 0.05 as a “one-sided” error. For avoiding a risk of missing valid equivalency, power of the study was set as 0.90 (therefore type II error level was 0.10) and with such assumptions

(equivalency limit: 3.5 points, standard deviations: 9 points, type I error level: 0.05 (one-sided) and type II error: 0.10), the sample size was calculated as 288 patients in overall and 144 patients at each treatment group. The drop-out rate was estimated as 30%, and a total of 412 patients were planned to be randomized into two treatment arms (1:1 ratio).

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

The investigational products were supplied as solid dosage forms (tablets or capsules whenever applicable) for oral use. There were two investigational products, Quetiapine XR (quetiapine fumarate) which was provided by the study sponsor with the following strengths and product descriptions/batch numbers were described as follows:

QuetiapineXR™

Study Drug	Manufacturer	Strengths	Presentation	Batch Number
Quetiapine fumarate	AstraZeneca England	50 mg	Peach colored oval tablets	F13219
Quetiapine fumarate	AstraZeneca England	300 mg	Cream colored oval tablets	F12527

Lithium Carbonate

Study Drug	Manufacturer	Strengths	Presentation	Batch Number
Lithium carbonate	Various	300 mg	Capsules/tablets	N/A

Lithium carbonate which was an additive treatment to quetiapine fumarate comparator arm was provided by local teams of the sponsor. Individual batch numbers and further information are included in the CSR. All patients were randomized to treatment with either monotherapy or combination therapy and monotherapy arm received QUETIAPINE XR (SEROQUEL XR™, extended release), once daily at bedtime in oral tablet form, bay the following escalating dosage schedule: Day 1: 50 mg, Day 2: 100 mg, Day 3: 200 mg, Day 4 onwards: 300 mg.
In the combination arm, QUETIAPINE XR (SEROQUEL XR™, extended release) was administered at a similar schedule with lithium carbonate twice daily (morning and evening) throughout the treatment period (from Day1 to Day 56). The lithium carbonate dosage was 300 mg/day in the first 7 days, gradually increasing within the dose range of 300-1800 mg/day after Day 7, as judged by the investigator. Dose adjustment for lithium was at the discretion of the investigator to achieve symptom control and minimizing side effects along with achieving serum concentrations within the target range of 0.8 – 1.2 mmol/L.

Duration of treatment

The overall treatment duration was 8-weeks. However, the study was formed of 3 periods, an enrolment period of up to 7 days, a wash-out period if deemed necessary by the investigator (up to 28 days) and an 8-week randomized treatment period. Qualifying patients was planned to undergo a washout period before randomization (7-28 days) depending on the previous medications (antidepressants, antipsychotics or mood stabilizers). Thus, theoretically a per-protocol patient with a maximum duration of washout and enrollment, the duration of study was 13 weeks.

Statistical methods

Efficacy analysis

Descriptive statistics including frequency tables (including number of patients, mean, median, standard deviation, interquartile range, minimum and maximum for numeric variables and number of patients, frequency and percentage for categorical values) and graphs were provided for all variables, as well as for the changes from baseline within each treatment and the differences between the treatment groups at each visit, for both actual values and LOCF values, as appropriate.

The results of comparison between two groups primarily presented as point estimates and their two-sided 90% confidence intervals. If the lower limit of the confidence interval for the difference between groups is above –3.5 points, non-inferiority was claimed. P-values were presented for the interpretation of the results. All hypotheses, including the primary hypothesis, were tested as one-sided with a significance level of 5%, i.e., α=0.05.

The primary analysis was based on an analysis of covariance (ANCOVA) model for the change from baseline to final assessment for MADRS total score. The ANCOVA model included factors for treatment and center, with the baseline MADRS total score as a covariate. The primary analysis was performed in the PP population. Analysis of ITT population served as a consistency check for analysis of the primary objective.

The following secondary analyses were performed mainly in PP population:

a. Comparison of study groups with regards to response rate defined as the percentage of patients with a $\geq$ 50% reduction from baseline in the MADRS total score at final assessment as well as changes in the MADRS total score from baseline in each assessment. In this method study groups were compared at each assessment visit for the change in the MADRS total score from baseline by repeated measures of covariance (RM-ANCOVA) model.

b. Comparison of study groups with regards to the change from baseline to each assessment in the Hamilton Rating scale for Depression (HAM-D), HAM-D Item 1, the Clinical Global Impression - Severity (CGI-S), and the Clinical Global Impression - Improvement (CGI-I).

c. Study groups were compared at each assessment visit for the change in the HAM-D and HAM-D Item 1, CGI-S and CGI-I scores from baseline by separate repeated measures of covariance (RM-ANCOVA) models.

d. Comparison of study groups with regards to the effect on anxiety on the basis of the change from baseline in the final assessment in the Hamilton Rating Scale for Anxiety (HAM-A) total score.

e. Comparison of study groups with regards to the change in the PSQI, Q-Les-Q Short Form, SDS, TSQM score from baseline to Day 56:

The ANCOVA method was also implemented for PSQI, Q-Les-Q Short Form, SDS, TSQM changes from baseline.

Safety analysis

The safety analysis were made by tabulating data such as vital signs, weight, and body mass index by means of descriptive statistics at baseline, final assessment, and for change from baseline. For laboratory assessments, patients with clinically important values emerging during treatment phase were presented for each treatment arm.

All adverse events were coded using the MedDRA dictionary, adverse events and incidence rates were summarized by preferred terms and system organ class in each treatment group. Descriptive statistics of incidence rates were implemented for the evaluation adverse events (including serious adverse events). For safety analysis areas of special interest were sexual dysfunction, nausea, vomiting, EPS, QT prolongation, depression, suicidality, diabetes mellitus, neutropenia and syncope.

The incidence of treatment-emergent mania, all adverse events and drug-related adverse events and proportion of subjects withdrawn due to adverse events during treatment were planned to be compared by contingency table methods, i.e. chi-square test or Fisher's exact test.

Patient Populations

The study outcomes were evaluated on the basis of per-protocol and intention-to treat population:

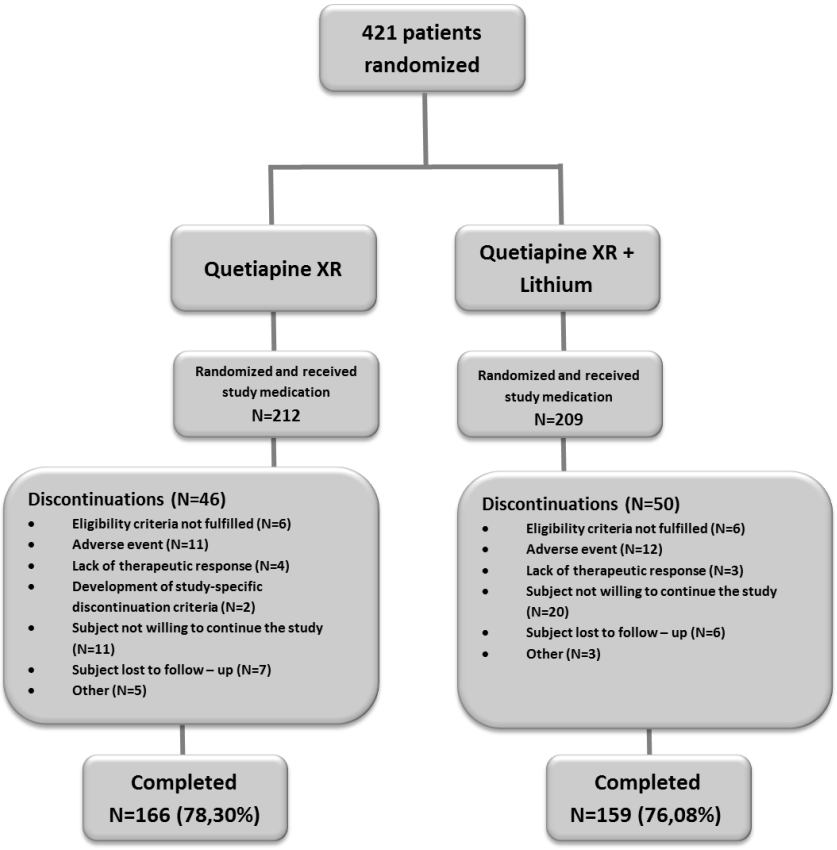
- **Per-protocol (PP) population:** Since the primary hypothesis was taken as a non-inferiority hypothesis, the efficacy analyses were based on the per-protocol (PP) population. PP population included patients who completed the study treatment with no major protocol violations or deviations affecting efficacy. The reason for preference for PP protocol for the primary analysis was to avoid to missing true equivalency that could be obtained with intention-to-treat (ITT) population.

- **Intention-to-treat (ITT) population:** ITT population included all randomized patients, classified according to randomized treatment, who took study medication and who had MADRS assessments at baseline and at least one post-randomisation period, which could be carried forward, regardless of any major protocol violation or deviation. Data from this population was analyzed as a consistency check for analysis of the primary objective.

Subject population

A total of 421 patients were randomized to the study to receive either monotherapy with QUETIAPINE XR (SEROQUEL XR™, extended release) or combination therapy with lithium and QUETIAPINE XR (SEROQUEL XR™). All randomized patients were included in the safety evaluation. Disposition of patients enrolled to the study is illustrated in Figure 1.

Figure 2: Disposition of subjects, treated at both arms (n=421, randomized)



Summary of efficacy results

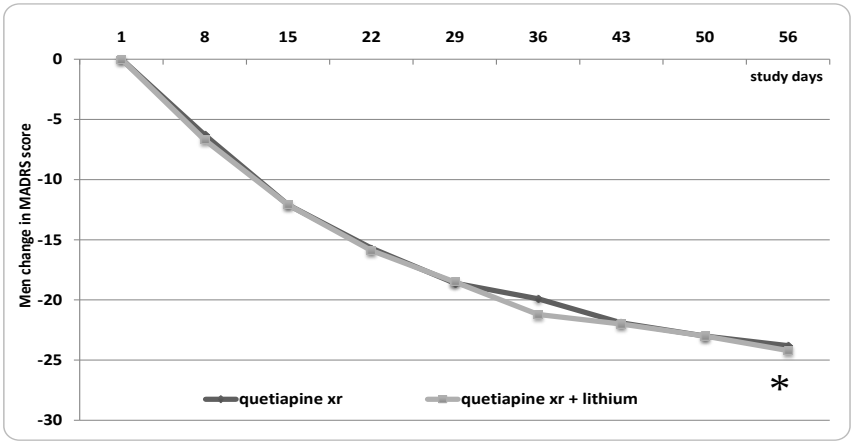
Both treatment groups were comparable in relation with baseline demographic characteristics and disease presentation. The percentage of women enrolled was very high when compared to men presenting with the same disease. Almost 70% of all patients were women. MADRS and HAM-D scores were almost identical in both groups, so was YMRS and HAM-A and CGI total score.

Table S2:

	Quetiapine XR	Quetiapine XR + Lithium
Gender, n (%)		
Male	57 (27,9)	57 (29,2)
Female	147 (72,1)	138 (70,8)
Mean age (years), mean (SD)	40,6 (10,8)	39,9 (12,1)
Mean weight (kg), mean (SD)	72,8 (16,3)	72,3 (15,4)
Pulse (beats/min), mean (SD)	77,3 (8,8)	75,5 (8,7)
Systolic Blood Pressure (mm/Hg), mean (SD)	116,9 (13,2)	115,4 (12,7)
Diastolic Blood Pressure (mm/Hg), mean (SD)	75,9 (9,3)	75,3 (8,9)
HAM-D total score, mean (SD)	26,1 (4,6)	26,0 (4,3)
MADRS total score, mean (SD)	29,7 (5,9)	29,5 (6,1)
YMRS total score, mean (SD)	3,2 (2,6)	3,2 (2,3)
HAM-A total score, mean (SD)	23,2 (6,8)	23,1 (7,2)
CGI-S TOTAL SCORE, mean (SD)	4,9 (0,9)	5,0 (0,8)

Efficacy evaluation: The primary efficacy criteria was comparison of change of Montgomery-Asberg Depression Rating Scale (MADRS) total score assessed by comparing the change from baseline to final assessment. A significant reduction in both treatment groups was observed after one week of treatment and continued until end of treatment (8 weeks of treatment). No statistically significant change was observed between groups for the change of MADRS score from baseline to final assessment when the baseline MADRS score acted as a covariate (p=0.334).

Figure 3: Mean changes in MADRS Scores



***p<0,001, for both treatment arms.**

Table S3: Primary analysis for MADRS (ANCOVA)

Descriptive statistics for change from baseline to final assessment	**Mean**	**SD**	**N**	
Quetiapine XR	23,7	8,4	162	
Quetiapine XR + lithium	24,3	7,9	155	
Tests of Between Subject Effects	**F**	**p**	**90% CI**	
Baseline MADRS total score	257,707	< 0,001	Lower	Upper
Group	0,937	0,334	-0,463	1,779
Estimated marginal means	**Mean**	**Std. Error**	**90% CI**	
			Lower	Upper
Quetiapine XR	23,7	0,5	22,9	24,5
Quetiapine XR + lithium	24,3	0,5	23,5	25,1

The mean changes in MADRS total score (Per Protocol population), from baseline to week 8 (Visit 10) was -22.3 and -22.6 in the QUETIAPINE XR and QUETIAPINE XR+lithium treatment arms, respectively ($p<0.001$). LOCF analysis from baseline to week 8 was -21.6 and -21.9, respectively ($p<0.001$). Quetiapine extended release monotherapy at a dose of 300 mg/day was non-inferior to combination therapy with quetiapine extended release formulation with lithium.

When a non-inferiority analysis was performed with dependent factor being the change of MADRS score from baseline to final assessment, whereas covariate was baseline MADRS score for both groups, the non-inferiority was claimed and ensured. Besides non-significant difference between treatment groups, analysis of treatment to time interaction indicated a clear parallelism with Hotelling's trace F=1.456 (p: 0.173).

As a secondary efficacy endpoint, response rate defined as the percentage of patients with a $\geq$ 50% reduction from the baseline in MADRS Total Score at the final assessment was evaluated and no significant difference was shown (p: 0.950). All outcomes in this study synopsis were given on the basis of PP (Per Protocol) population as ITT (Intent-to-Treat) population analysis were performed only for consistency check for the analysis of the primary objective.

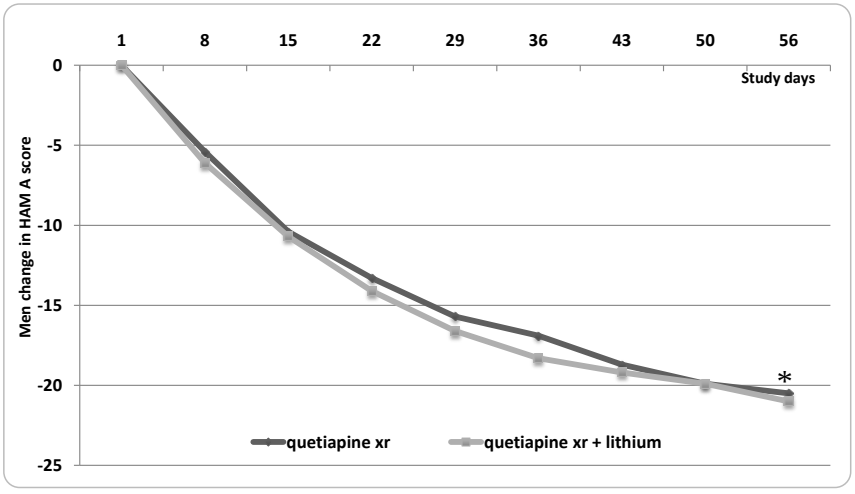
Table S4: Response rate for MADRS (Percentage of patients with ≥50% reduction from baseline in the MADRS total score at each assessment)

Day 1 vs. LOCF	<%50		≥ %50		Total		Chi square (p)
	N	%	N	%	N	%	
Quetiapine XR	33	16,2	171	83,8	204	100,0	0,950
Quetiapine XR + lithium	32	16,4	163	83,6	195	100,0	
Total	**65**	**16,3**	**334**	**83,7**	**399**	**100,0**	

Other efficacy parameters (secondary) were HAM-D Total score, Anxiety (HAM-A) and Young Mania Rating Scale (YMRS) scores as investigated on the basis of changes fom baseline to end of treatment (8 weeks of treatment, Visit 0 to Visit 10).

The mean changes for HAM-D total score was -20.5 and 21.0 in the QUETIAPINE XR and QUETIAPINE XR+lithium treatment arms, respectively (p<0.001). On the other hand, the mean changes for HAM-A was -17.5 and 17.7 in the QUETIAPINE XR and QUETIAPINE XR+lithium treatment arms, respectively (p<0.001).

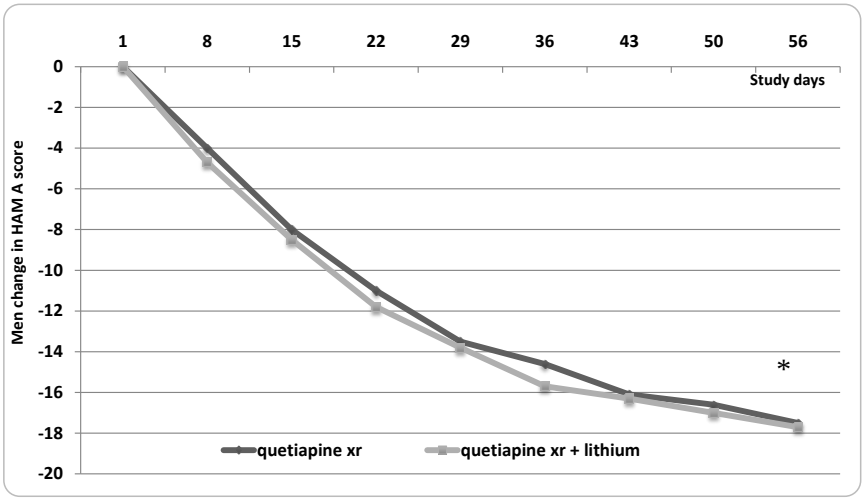
Figure 4: Mean changes in HAM-D Scores



***p<0,001, for both treatment arms.**

Comparisons of study groups with regards to the change from baseline to each assessment were performed for YMRS and CGI severity and improvement as well. The YMRS changes for QUETIAPINE XR group was -2.3 and -2.2 for the QUETIAPINE XR+lithium group, both changes from baseline as being significant (p<0.001). GCI sores also indicated similar significant changes.

Figure 5: Mean changes in HAM-A Scores



***p<0,001, for both treatment arms.**

The study protocol was amended for the addition of four significant Quality of Life (QoL) tests to be performed during the study run. Although comparatively around 25-30% of randomized patients responded (64 to 85 patients at baseline depending on the test) to these QoL evaluations, final comparison of study groups with regards to the change in the PSQI, Q-Les-Q Short Form, SDS, TSQM score were performed from baseline to Week 8 (Visit 10). Interestingly, results indicated a better scored in the QUETIAPINE XR treatment arm (Table 4).

Summary of pharmacokinetic results

Not applicable

Summary of pharmacodynamic results

Not applicable

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Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable

Summary of pharmacogenetic results

Not applicable

Table S5: Outcomes of Patient Questionnaires (PSQI,Q-LES-Q,SDS and TSQ-M)

Patient Questionnaires	Quetiapine XR	Quetiapine XR + Lithium
PSQI _Week 1, mean (SD)	13,7 (5,1)	13,6 (4,9)
PSQI _Week 56, mean (SD)	10,2 (8,9)	8,8 (6,4)
Q-LES _ Week 1, mean (SD)	31,6 (10,0)	29,8 (7,8)
Q-LES _ Week 56, mean (SD)	49,8 (10,9)	48,5 (11,1)
SDS _ Week 1, mean (SD)	20,9 (7,0)	21,8 (6,9)
SDS _ Week 56, mean (SD)	6,5 (8,0)	7,4 (8,3)
TSQ-M _ Week 1, mean (SD) – effectiveness	42,7 (20,2)	36,7 (23,7)
TSQ-M _ Week 56, mean (SD) – effectiveness	68,7 (24,9)	66,7 (21,8)
TSQ-M _ Week 1, mean (SD) – side effects	41,7 (25,9)	44,4 (24,9)
TSQ-M _ Week 56, mean (SD) – side effects	58,2 (26,7)	50,4 (17,0)
TSQ-M _ Week 1, mean (SD) – convenience	53,8 (21,5)	52,8 (21,8)
TSQ-M _ Week 56, mean (SD) – convenience	73,6 (17,1)	72,9 (17,2)
TSQ-M _ Week 1, mean (SD) – global satisfaction	37,4 (26,1)	35,0 (27,7)
TSQ-M _ Week 56, mean (SD) – global satisfaction	69,4 (19,4)	70,7 (18,9)

Summary of safety results

In general, study medication at both treatment arms was very well tolerated. The adverse events which required special interest were sexual dysfunction, nausea, vomiting, EPS, QT prolongation, depression, suicidality, diabetes mellitus, neutropenia and syncope. There were only few cases of adverse events occurred.

Sexual dysfunction occurred in in 6 incidences for patients in QUETIAPINE XR arm, whereas QUETIAPINE XR+lithium arm had only two cases of such occurrences. Nausea was more frequent in the QUETIAPINE XR+lithium arm (29 versus 14), however, cardiac rhythm problems occurred only in the QUETIAPINE XR arm (5 cases versus nil). There were only one case of diabetes mellitus, and one case of depression, both occurring in the QUETIAPINE XR+lithium arm.

Discontinuation due to adverse events was also low, only 11 patients in the QUETIAPINE XR arm and 12 patients in the QUETIAPINE XR+lithium arm discontinued the study due to adverse events (5.1% and 5.7%). The most frequent adverse event was dry mouth and somnolence, both occurring at a rate more frequent than 30%. There were no differences between treatment arms. Most frequently recorded adverse events and adverse event intensity data were summarized in Tables 5 and 6.

Table S5: Most frequently recorded adverse events

Adverse Events, n (%)	Quetiapine XR	Quetiapine XR + Lithium
Dry mouth	50 (34,0)	47 (31,5)
Somnolence	46 (31,3)	49 (32,9)
Headache	28 (19,0)	25 (16,8)
Anxiety	21 (14,3)	14 (9,4)
Constipation	20 (13,6)	17 (11,4)
Dizziness	16 (10,9)	32 (21,5)
Diarrhea	14 (9,5)	13 (8,7)
Nausea	14 (9,5)	29 (19,5)
Increased appetite	13 (8,8)	5 (3,4)
Tremor	11 (7,5)	28 (18,8)
Insomnia	10 (6,8)	9 (6,0)
Sedation	9 (6,1)	11 (7,4)
Tachycardia	8 (5,4)	6 (4,0)
Weight gain	8 (5,4)	11 (7,4)

Table S6: Adverse event intensities at both treatment arms

Adverse Events Intensity, n (%)	Quetiapine XR	Quetiapine XR + Lithium
Mild	315 (62,5)	388 (67,0)
Moderate	145 (28,8)	160 (27,6)
Severe	44 (8,7)	31 (5,4)
TOTAL	**504 (100,0)**	**579 (100,0)**

Table S7: The number and proportion of patients with at least 7 % weight increase

	Quetiapine XR	Quetiapine XR + Lithium
Weight increase, n (%)		
<7 %	102 (87,2)	75 (76,5)
≥ 7 %	15 (12,8)	23 (23,5)

Weight increase during treatment was a protocol specified item for follow-up and strictly recorded. Results showed that patients with more than 7% weight increase was significantly higher in the combination arm, when compared to QUETIAPINE XR only arm.