Drug product:	Seroquel™	**SYNOPSIS**	
Drug substance(s):	quetiapine fumarate		
Study code:	D1447C00127		
Date:	19 June 2007		

A Multicenter, Randomized, Parallel-group, Double-blind, Phase III Comparison of the Efficacy and Safety of Quetiapine Fumarate (Oral Tablets 400 mg to 800 mg Daily in Divided Doses) to Placebo when Used as Adjunct to a Mood Stabilizer (Lithium or Valproate) in the Maintenance Treatment of Bipolar I Disorder in Adult Patients

Study centre(s)

This study was conducted in 127 centers in the United States and Canada.

Publications

None at report time

Study dates		**Phase of development**
First patient enrolled	02 March 2004	Therapeutic confirmatory (III)
Last patient completed	18 September 2006	

Primary objective:

The primary objective was to evaluate the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in increasing time to recurrence of a mood event.

Recurrence was defined as (1) initiation of an antipsychotic, antidepressant, mood stabilizer other than the assigned mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic, depressed or mixed event, (2) hospitalization for a manic, depressed or mixed event, (3) Young Mania Rating Scale (YMRS) score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or Montgomery-Asberg Depression Rating Scale (MADRS) score ≥20 at 2 consecutive assessments or at the final

assessment if the patient discontinues, or (4) discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a manic, depressed or mixed event.

Secondary objectives:

1. To evaluate the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in increasing time to recurrence of a manic event. Recurrence was defined as (1) initiation of an antipsychotic, mood stabilizer other than the assigned mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic event or mixed event with predominantly manic symptoms, (2) hospitalization for a manic event or mixed event with predominantly manic symptoms, or (3) YMRS score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or (4) discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a manic event or mixed event with predominantly manic symptoms.

2. To evaluate the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in increasing time to recurrence of a depressed event. Recurrence was defined as (1) initiation of an antidepressant, mood stabilizer other than the assigned mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a depressed event or mixed event with predominantly depressed symptoms, (2) hospitalization for a depressed event or mixed event with predominantly depressed symptoms, or (3) MADRS score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or (4) discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a depressed event or mixed event with predominantly depressed symptoms.

3. To evaluate the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in decreasing the severity of manic and depressive symptoms between mood events as assessed by the YMRS, the MADRS and the Clinical Global Impression-Bipolar (CGI-BP).

4. To evaluate the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in decreasing the severity of psychotic symptoms between mood events as assessed by the Positive and Negative Syndrome Scale-Positive Subscale (PANSS-P).

5. To evaluate the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in improving level of functioning between mood events as assessed by the Sheehan Disability Scale (SDS).

6. To explore the efficacy of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) in improving Quality of Life (QOL) as assessed by the Psychological General Well-being Scale (PGWB).

7. To explore the level of patient acceptance of quetiapine versus placebo when used as adjunct to mood stabilizer (lithium or valproate) as assessed by time to all-cause discontinuation.

8. To determine whether quetiapine when used as adjunct to mood stabilizer (lithium or valproate) is safe and well-tolerated as assessed by adverse events (AEs), laboratory values, vital signs, extrapyramidal symptoms (EPS) scales including Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS); physical examinations, and electrocardiograms (ECGs).

Study design

This was a multicenter, randomized, parallel-group, double-blind study to compare quetiapine with placebo when used as adjunct to lithium or valproate in the maintenance treatment of adult patients with Bipolar I Disorder (both mania and depression) for up to 104 weeks. The study consisted of enrollment and 2 phases, the initial open-label treatment phase and the subsequent randomized treatment phase. To be eligible for randomization, a patient must have been treated with quetiapine within the range of 400 to 800 mg/day and mood stabilizer (lithium or valproate) for at least 12 weeks during the open-label treatment phase. To be randomized, a patient also had to have a YMRS total score ≤12, and a MADRS total score ≤12 assessed at a minimum of 4 consecutive visits spanning at least 12 weeks, with the allowance of a single excursion with a YMRS and/or MADRS score of 13 or 14 (unless this occurred on the last of the 4 consecutive visits).

Target patient population and sample size

Male or female patients, aged 18 years or older, with Bipolar I Disorder, who had experienced an acute manic, depressed or mixed episode at enrollment; or a past manic, depressed or mixed episode within 26 weeks, as documented by medical records, treated with quetiapine and mood stabilizer (lithium or valproate). The patients should have had at least 1 manic, depressed or mixed episode in the 2 years prior to the index episode.

Assuming a hazard ratio of 0.65 for quetiapine versus placebo and proportional hazards, 227 patients were needed to have recurrence of a mood event (with a two-tailed test of significance level of 0.05 and power of 90%). To observe a total of 227 mood events, it was originally estimated in the study protocol that approximately 1420 patients should be enrolled in order to provide approximately 710 randomized patients, assuming that approximately 50% of the enrolled patients would fulfill the criteria for randomization. The final number of enrolled and randomized patients was increased during the study, based on observed randomization and event rates: 1953 patients were enrolled, which provided a total of 628 randomized patients (32.2% randomization rate) and 226 patients with recurrence of a mood event.

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

Patients began or continued on an oral dose of open-label quetiapine, 400 to 800 mg daily in divided doses, with a recommended target dose of 600 mg/day, after meeting all inclusion and none of the exclusion criteria for entering the open-label treatment phase. Doses could be adjusted within this range to maximize efficacy and tolerability. After meeting all inclusion criteria and none of the exclusion criteria for randomization, patients were randomized either to quetiapine, or placebo, twice daily. After randomization, open-label 100-mg quetiapine tablets (from a specific visit pack for this phase) were titrated down and replaced with 100-mg tablets of blinded investigational product (provided by the investigator or a designee) at a rate of 1 tablet per every 2 days. The dose of blinded investigational product (quetiapine or placebo) could be adjusted as clinically indicated within the dose range of 400 to 800 mg/day all through the randomized treatment phase. The strengths of study treatment from the following batches used in this study were: open label quetiapine 100 mg tablets, batch numbers: 2000053927, 2000054095, 2000062056, 2000063335, 2000065204, 2000069552, 2000073537, 2000076334, 2000079259, 2000080873, 2000084822, 2000086364; randomized quetiapine 100 mg tablets, batch numbers: 2000053929, 2000054252, 2000065207, 2000068245, 2000077806, 2000085520, 2000093377, 2000098206; and randomized placebo, tablets, batch numbers: 2000054027, 2000054250, 2000065206, 2000070332, 2000078228, 2000085522, 2000096643.

Adjunct treatment, dosage and mode of administration

Patients began or continued on an oral dose of open-label lithium or valproate (valproate is a general term, and used in this CSR referring to a family of medications including the various formulations of divalproex) chosen by the investigator according to his or her clinical judgment, after meeting all inclusion and none of the exclusion criteria for entering the open-label treatment phase. Dose adjustments for lithium or valproate were made at the discretion of the investigator to achieve symptom control, to minimize side effects, and to achieve target trough serum concentrations of 0.5 mEq/L to 1.2 mEq/L for lithium and 50µg/ml to 125 µg/ml for valproate during the entire length of the study.

Duration of treatment

The study consisted of enrollment and 2 phases: open-label treatment phase (12 weeks to 36 weeks), and randomized treatment phase (up to 104 weeks).

Criteria for evaluation (main outcome variables)

Efficacy

- Primary outcome variable: time to recurrence of a mood event
- Secondary outcome variables related to mood events: proportion of patients with a mood event prior to Week 28 and Week 52; recurrence of a manic event; recurrence of a depressed event; time to all-cause discontinuation.
- Secondary outcome variables related to symptoms between mood events: YMRS total score; MADRS total score; CGI-BP scores; PANSS-P score. For the listed symptom rating scales, results from between mood events are presented, ie, from randomization up to final assessment but excluding assessment associated with a mood event.

Patient Reported Outcomes

Secondary outcome variables: SDS total score (a secondary outcome variable of particular interest) and PGWB total score; for both scales results between between mood events are presented, ie, from randomization up to final assessment but excluding assessment associated with a mood event.

Safety

Standard safety assessments included adverse events; laboratory test results; vital signs; weight and body mass index (BMI); ECG results; physical examination results; and extrapyramidal symptoms (EPS), assessed by means of SAS, BARS, and AIMS scores

Statistical methods

All hypotheses were 2-sided. A stepwise sequential procedure was used for the confirmatory part of this study to ensure a multiple level of significance of 0.05. The four outcome variables time to a mood event, time to a manic event, time to a depressed event and mean change in SDS total score were tested sequentially.

The primary outcome variable, time to recurrence of a mood event, and the secondary outcome variables of time to recurrence of a manic event and time to recurrence of a depressed event were analyzed using a Cox-proportional hazard model to estimate the hazard ratio of recurrence between treatment groups. The mixed model was used for repeated measures analysis of the YMRS, MADRS, CGI-BP, PANSS-P, and PGWB total scores across all assessments between randomization and up to, but excluding, the assessments associated with a mood event. The outcome variable of the SDS total score was analyzed using analysis of covariance (ANCOVA). Cochran-Mantel-Haenszel test (CMH) was used for categorical comparisons. Descriptive statistics were provided for all efficacy and safety variables.

Patient population

There were 1953 patients enrolled into the study, 1938 received open-label treatment with quetiapine, and thus were included in the open-label safety population. Of the 1953 enrolled patients, 1324 patients were discontinued during open-label treatment, and 1 patient finished the 12- to 36-week open-label treatment phase but was not randomized. Thus, 628 patients were randomized to treatment with quetiapine or placebo used as adjunct to a mood stabilizer (lithium or valproate), 5 of whom did not receive any randomized study medication, so 623 patients were included in the randomized safety population (310 receiving quetiapine and 313 receiving placebo). Of those, all 623 were included in the ITT population, the primary population for analyses of efficacy results.

Although the randomization rate (32%) was lower than the original estimate (50%), the demographics and baseline characteristics of the open-label population and the randomized population were similar. The most common reasons for discontinuation during the open-label phase were "adverse event" (404 patients, 20.7%) and "subject lost to followup" (329 patients,16.8%).

Of the 623 randomized patients in the ITT population, 226 experienced a mood event (63 in quetiapine group and 163 in placebo group) during maintenance treatment, and 176 patients (110 in quetiapine group and 66 in placebo group) were treated in the randomized treatment phase without having a mood event for the maximum 104 weeks or until the termination of the study. Due to the efficacy of quetiapine at preventing or delaying mood events, exposure to study drug was considerably greater in quetiapine patients than in the placebo group. Total randomized exposure was 34% greater in the quetiapine group (74323 days in the quetiapine group compared to 55570 days in the placebo group). The greater randomized exposure in the quetiapine group resulted in the quetiapine patients having greater potential for discontinuation for reasons other than a mood event. Of the 247 remaining patients in the quetiapine group, 35 were discontinued due to "Adverse event" and 32 were discontinued due to "Subject not willing to continue". Of the 150 remaining patients in the placebo group, 26 were discontinued due to "Subject not willing to continue" and 25 were discontinued due to "Subject lost to follow up".

The 2 treatment groups were well matched in number, demographic and baseline disease characteristics. Patients had an overall mean age of approximately 40 years, and 53% were female. The YMRS total score and MADRS total score at randomization were similar in the 2 treatment groups. At enrollment, more patients (44%) had a mixed episode as the most recent bipolar episode, compared to 34% with a depressive episode, and 22% with a manic episode. The randomization rate was similar with regard to type of most recent (index) episodes: the randomized population included 46% of patients with a mixed index episode, 31% with a depressive index episode, and 24% with a manic index episode.

Total randomized exposure was about 34% greater in the quetiapine-treated group (74323 days in the quetiapine group compared to 55570 days in the placebo group).

The demographic characteristics of the study population at randomization are described in Table S 1.

Table S 1 Patient population (ITT population)

		QTP + LI/VAL N = 310		PLA + LI/VAL N = 313		Total 623	
Demographic characteristics							
Sex (n and % of patients)	Male	151	(48.7)	145	(46.3)	296	(47.5)
	Female	159	(51.3)	168	(53.7)	237	(52.5)
Age (years)[a]	Mean (SD)	40.6	(11.698)	39.6	(11.718)	40.1	(11.709)
	Range	18 to 75		19 to 74		18 to 75	
Race (n and % of patients)	Caucasian	248	(80.0)	261	(83.4)	509	(81.7)
	Black	46	(14.8)	34	(10.9)	80	(12.8)
	Oriental	4	(1.3)	3	(1.0)	7	(1.1)
	Other	12	(3.9)	15	(4.8)	27	(4.3)
Weight (kg)[a]	Mean (SD)	94.3	(22.055)	91.1	(19.471)	92.7	(20.839)
	Range	46 to 182		50 to 170		46 to 182	
Disease characteristics							
YMRS total score at randomization	Mean (SD)	3.6	(3.143)	3.5	(3.148)	3.5	(3.636)
	Range	0 to to 15		0 to 13		0 to 15	
MADRS total score at randomization	Mean (SD)	5.0	(3.677)	4.6	(3.588)	4.8	(3.636)
	Range	0 to 18		0 to 12		0 to 18	
Assigned mood stabilizer: n (%)	Lithium	131	(42.3)	134	(42.8)	265	(42.5)
	Valproate	179	(57.7)	179	(57.2)	358	57.5)
DSM-IV diagnosis of bipolar I disorder, most recent episode: n (%)	Manic	63	(20.3)	84	(26.8)	147	(23.6)
	Depressed	104	(33.5)	87	(27.8)	191	(30.7)
	Mixed	143	(46.1)	142	(45.4)	285	(45.7)
With rapid cycling course: n (%)	Unknown	1	(0.3)	1	(0.3)	2	(0.3)
	No	156	(50.3)	147	(47.0)	303	(48.6)
	Yes	153	(49.4)	165	(52.7)	318	(51.0)

[a] At enrollment

ITT=Intention to treat; N=Number

Efficacy results

The main efficacy results, the analysis of time to recurrence of a mood event, are summarized in Table S 2. The primary analysis is based on time to first recurrence of a mood event, and the statistical model used in this analysis is a Cox regression model. This model uses the primary variable (time to mood event) to estimate a hazard ratio, which is the outcome of the model. Therefore, even though it is called "Analysis of time to recurrence of a mood event", no actual measure of time is presented in the primary analysis. The results of the primary analysis of time to recurrence of a mood event were confirmed in sensitivity analyses using a stratified Cox model and Log-rank test stratified by the assigned mood stabilizer. As a complement, Kaplan-Meier estimates and plots are provided in order to infer the time to mood events.

In patients with bipolar I disorder, quetiapine as adjunct with a mood stabilizer (lithium or valproate) significantly increased the time to recurrence of a mood event (manic or depressed) compared to placebo adjunct with a mood stabilizer. Kaplan-Meier estimates of time to 20 percent of the patients experiencing recurrence of a mood event was 220 days for the quetiapine treatment group and 29 days for the placebo treatment group. The demonstrated efficacy of quetiapine did not show restriction to any specific subgroup (assigned mood stabilizer, sex, age, race, index episode, or episode cycling frequency) and the results in the primary ITT population were supported by the results in the PP population. Likewise, quetiapine significantly increased the time to recurrence of a manic episode and a depressed episode, compared to placebo. The time to all-cause discontinuation from the study was increased in the quetiapine treatment group. The symptom scales were analysed from randomization up to final assessment but excluding assessments associated with a mood event. Quetiapine was more effective in suppressing manic and depressive symptoms, as assessed by YMRS and MADRS scores, but not not psychotic symptoms, as assessed by the PANSS-P score. The analyses of the results from the CGI-BP scale provided evidence that maintenance treatment with quetiapine was more efficacious than placebo in suppressing overall bipolar symptoms on the Severity of Overall Bipolar Illness scale, but not on the Global Improvement scale. Quetiapine had no conclusive effect on the patients' level of functioning in the period from randomization (with patients stabilized in their bipolar symptomatology from open-label treatment with quetiapine and an assigned mood stabilizer) to recurrence of a mood event, as demonstrated in the analyses of the SDS total score as well as in the analysis of the domain scores for work/school, social life/leisure, and family life/home.

The main efficacy results are summarized in Table S 2 and Table S 3.

Table S 2 Efficacy results, randomized treatment phase (ITT population)

Outcome variable	QTP + LI/VAL vs PLA + LI/VAL N_{QTP} =360 / N_{PLA} =400 Hazard ratio (95% CI)	P-value
Time to recurrence of a mood event	0.32 (0.24, 0.42)	<0.0001
Time to recurrence of a manic event	0.30 (0.18, 0.49)	<0.0001
Time to recurrence of a depressed event	0.33 (0.23, 0.48)	<0.0001

Analysis using Cox's proportional hazards model with the assigned mood stabilizer and region within study included as covariates.

ITT Intention-to-Treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. CI Confidence interval.

Table S 3 Summary of efficacy results prior to mood events, LS means and treatment comparisons of rating scales (ITT population)

Outcome variable	LS mean (SE)		Difference in LS means	95% CI	P-value
	QTP + LI/VAL (N = 310)	PLA + LI/VAL (N = 313)			
SDS total score, mean change[a]	0.3 (0.329)	0.3 (0.357)	-0.5	-1.45, 0.45	0.3017
Additional rating scales[b]					
PGWB total score	97.2 (0.564)	96.1 (0.822)	1.1	-0.86, 3.09	0.2664
YMRS total score	4.1 (0.119)	4.9 (0.145)	-0.8	-1.14, -0.41	<0.0001
MADRS total score	5.9 (0.164)	6.8 (0.196)	-0.9	-1.36, -0.36	0.0008
CGI-BP Severity of Illness	1.8 (0.023)	1.9 (0.032)	-0.1	-0.22, -0.06	0.0003
CGI-BP Global Improvement	3.5 (0.065)	3.6 (0.069)	-0.1	-0.24, 0.13	0.5650
PANSS-P score	8.3 (0.065)	8.4 (0.068)	-0.2	-0.37, 0.00	0.0521

[a] Analysis of the mean change from randomization across all assessment after randomization and up to, but excluding the first mood event, using an ANCOVA model

[b] Analysis of all assessments between randomization and up to, but excluding the first mood event, using a repeated measures mixed model

ITT Intention-to-Treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. SD Standard deviation. SDS Sheehan Disability Scale. PGWB Psychological General Well-being Scale. CGI-BP Clinical Global Impression – Bipolar. MADRS Montgomery-Asberg Depression Rating Scale. PANSS-S Positive and Negative Syndrome Scale-Positive Subscale. YMRS Young Mania Rating Scale.

Safety results

The number (and percentage) of patients who had at least 1 adverse event in any category is summarized in Table S 4. Quetiapine was generally safe and well tolerated in the dose range of 400-800 mg when used as adjunct with lithium or valproate for maintenance treatment in patients with bipolar I disorder. The overall incidence of adverse events (AE) was similar in the quetiapine group (78.4%) and in the placebo group (76.7%) and more AEs in the quetiapine group were considered by the investigator to be causally related to the study drug. There were 2 deaths reported in the study, 1 during open label treatment and 1 during randomized treatment in the quetiapine group. The death during open label treatment was due to severe trauma (patient hit by train), and the death during randomized treatment was a completed suicide which occurred 24 days after the patient discontinued from the study. During randomized treatment, the incidence of serious adverse events (SAE) ongoing at randomization or reported during randomized treatment in the quetiapine group was higher than the placebo group, and 35 (11.3%) of the patients in the quetiapine group were prematurely discontinued from the study due to an AE compared to 12 (3.8%) patients in the placebo group. However, the total randomized exposure was 34% greater in the quetiapine group than in the placebo group.

Table S 4 Number (%) of patients who had at least 1 adverse event in any category (randomized safety population)

Category of adverse event	QTP + LI/VAL (N=310)		PLA + LI/VAL (N=313)	
	n	(%)	n	(%)
Any adverse events reported during randomized treatment[a]	243	(78.4)	240	(76.7)
Serious adverse events ongoing at randomization or reported during randomized treatment[a]	18	(5.8)	7	(2.2)
Serious adverse events leading to death[a]	1	(0.3)	0	
Serious adverse events not leading to death[a]	17	(5.5)	7	(2.2)
Drug-related adverse event reported during randomized treatment[b]	124	(40.0)	101	(32.3)
Discontinuations of study treatment due to adverse events ongoing at randomization or reported during randomized treatment[a]	35	(11.3)	12	(3.8)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As judged by the investigator.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate.

The incidence of common AEs (occurring at an incidence of ≥5% in any treatment group) is summarized in Table S 5 for the randomized treatment period. The most common AEs in the

quetiapine treatment group were upper respiratory tract infection, headache, insomnia, and nausea. The incidence rate in the quetiapine group for upper respiratory tract infection AEs was higher than in the placebo group, but the incidence for the other three AE types were higher in the placebo group. The incidences of individual and composite EPS-related AEs were similar in each treatment group with a majority reported as mild or moderate. The incidence of AEs potentially related to suicidality was low in both treatment groups.

Small changes from baseline were observed during treatment for quetiapine patients in a number of clinical laboratory assessments. These changes were well tolerated. There were small increases in mean glucose, $HbA1_C$, and insulin levels in the quetiapine treatment group compared to the placebo group during randomized treatment, and clinically important values for glucose regulation measures were more common in the quetiapine treatment group. Lipid measurements of total cholesterol, HDL, and LDL changed little during open-label treatment and in the quetiapine group during randomized treatment; while each improved somewhat in the placebo group during randomized treatment. The change from randomization to end of treatment in thyroid laboratory data was small. Changes in TSH levels were similar in both treatment groups: mean change 0.62 in the quetiapine treatment group and –0.60 in the placebo group. Free T4 and T3 levels were similar in both quetiapine and placebo treatment groups. However, during randomized treatment more patients had clinically important TSH values in the quetiapine treatment group compared to the placebo group, but there were few clinically important free T3 and T4 values in either treatment group. Finally, there were very few patients who had the combination of clinically important high TSH and clinically important low T4.

Weight increased by 3.11 kg during open-label treatment, and attenuated in the placebo group by –1.95 kg during randomized treatment. There was a minimal increase in weight (0.46 kg) in the quetiapine treatment group throughout the randomized treatment phase. Accumulation of metabolic risk factors during randomized quetiapine treatment was similar to placebo. At randomization, 158 patients (51.0%) in the quetiapine group and 171 patients (54.6%) had fewer than 3 metabolic risk factors. Of these patients, 38 patients (24.1%) in the quetiapine group and 34 patients (19.9%) in the placebo group developed additional risk factors to result in ≥ 3 concurrent risk factors at the end of the randomized treatment phase.

Overall the assessment of parkinsonian, akathisia, and dyskinesia symptomatology as assessed by mean SAS, BARS, and AIMS scores indicated that quetiapine treatment was similar to placebo.

Table S 5 Number (%) of patients with the most commonly reported (≥5%) adverse events (randomized safety population)

Adverse event (preferred term)	QTP + LI/VAL n (%)	PLA + LI/VAL n (%)
ANY ADVERSE EVENT	174 (56.1)	184 (58.8)
UPPER RESPIRATORY TRACT INFECTION	36 (11.6)	25 (8.0)

Table S 5 Number (%) of patients with the most commonly reported (≥5%) adverse events (randomized safety population)

Adverse event (preferred term)	QTP + LI/VAL n (%)	PLA + LI/VAL n (%)
HEADACHE	31 (10.0)	42 (13.4)
NAUSEA	30 (9.7)	36 (11.5)
INSOMNIA	29 (9.4)	61 (19.5)
NASOPHARYNGITIS	28 (9.0)	29 (9.3)
TREMOR	27 (8.7)	26 (8.3)
SEDATION	22 (7.1)	3 (1.0)
WEIGHT INCREASED	21 (6.8)	8 (2.6)
HYPOTHYROIDISM	20 (6.5)	4 (1.3)
VOMITING	19 (6.1)	19 (6.1)
BACK PAIN	18 (5.8)	21 (6.7)
INFLUENZA	18 (5.8)	19 (6.1)
COUGH	18 (5.8)	12 (3.8)
DIARRHOEA	16 (5.2)	26 (8.3)
ARTHRALGIA	16 (5.2)	13 (4.2)

[a] Events with a total frequency of ≥5%in any treatment group are included in this table. Events are ordered according to decreasing incidence in the QTP + LI/VAL treatment group.

PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate.