Drug product:	Seroquel™	**SYNOPSIS**	
Drug substance(s):	quetiapine fumarate		
Study code:	D1447C00126		
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 177 centers in 18 countries.

Publications

None at report time

Study dates		**Phase of development**
First patient enrolled	6 April 2004	Therapeutic confirmatory (III)
Last patient completed	31 October 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) (Young et al 1978) score ≥20 at 2 consecutive assessments or at the final assessment if the patient discontinues, or

Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) 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 total 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 total 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) (Spearing et al 1997).

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) (Kay et al 1987).

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) (Sheehan 1983, Sheehan et al 1996).

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) (Dupuy 1984).

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 (Simpson Angus Scale [SAS] [Simpson and Angus 1970], Barnes Akathisia Rating Scale [BARS] [Barnes 1989], and Abnormal Involuntary Movement Scale [AIMS] [Guy 1976]), 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 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 total 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 (most recent episode according to DSM-IV).

Assuming a hazard ratio of 0.65 for quetiapine versus placebo in a Cox proportional hazards model, the model required at least 227 patients with recurrence of a mood event (with a 2-tailed test of significance level of 0.05 and power of 90%). To observe a total of 227 mood events, it was estimated that approximately 1700 patients should be enrolled, giving approximately 710 randomized patients, assuming that approximately 42% of the enrolled patients fulfilled the criteria for randomization.

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: quetiapine 100 mg tablets batch numbers: 12962A03, 12964F03, 12965C03, 21035E04, 30947E05, 30131A05, 30943F05, 31747H05, 31370K05, LK4603, 41277C06, 30131A05, 30947E05, 30130D05. Placebo, tablets, batch numbers: 12961D03, 21038G04, 30133F05, 23826G04, 30944C05, 30945K05, LC4634, 31745C05, 30133F05, 31748E05.

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 judgement, 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. During the randomized treatment phase, more stringent criteria for dose adjustments were applied. In the case of intolerability, the dose of the mood stabilizer could be decreased as long as the serum level remained above the lower limit (0.5mEq/L for lithium or 50 µg/ml for valproate), and dose could also be adjusted if serum level was outside the predefined range (ie, 0.5mEq/L to 1.2 mEq/L for lithium or 50 µg/ml to 125 µg/ml for valproate).

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 from 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 4 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 3 secondary outcome variables, time to recurrence of a manic event, time to recurrence of a depressed event, and time to all-cause discontinuation 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 1461 patients enrolled into the study, 1433 received open-label treatment with quetiapine, and thus were included in the open-label safety population. Of the 1461 enrolled patients, 706 patients were randomized to treatment with quetiapine or placebo used as adjunct to a mood stabilizer (lithium or valproate), 3 of whom did not receive any randomized study medication, so 703 patients were included in the randomized safety population

(336 receiving quetiapine and 367 receiving placebo). Of those, all 703 were included in the ITT population, the primary population for analyses of efficacy results.

Although the randomization rate was somewhat higher in patients with a manic index episode (58.3%), possibly due to a lower incidence of adverse events, than in patients with a depressed (42.0%) or a mixed index episode (41.5%), 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" (219 patients, 15.0%) and "subject not willing to continue" (162 patients, 11.1%).

Of the 703 randomized patients, 242 experienced a mood event (62 in quetiapine group and 180 in placebo group) during maintenance treatment, and 347 patients (213 in quetiapine group and 134 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. Of the patients remaining in the study, 61 patients in quetiapine group and 53 in placebo group were discontinued for reasons other than a mood event during randomized maintenance treatment. Of the patients discontinuing for reasons other than a mood event, "subject not willing to continue" was the most common reason for discontinuation in both treatment groups; 26 out of 61 quetiapine patients and 16 out of 53 placebo patients.

The 2 treatment groups were well matched as to demographic and baseline disease characteristics. Patients had an overall mean age of approximately 42 years, and 53% were female. The YMRS total score and MADRS total score at randomization were similar in the 2 treatment groups. At randomization, more patients (48.5%) had a manic episode as the most recent bipolar episode, compared to 28.9% with a depressive episode, and 22.6% with a mixed episode.

The mean exposure during the randomized period was about 44% longer to quetiapine than to placebo (189 and 130 days respectively).

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 =750		**PLA + LI/VAL N = 748**		**Total 1498**	
Demographic characteristics							
Sex (n and % of patients)	Male	144	(42.9)	172	(46.9)	316	(45.0)
	Female	192	(57.1)	195	(53.1)	387	(55.0)
Age (years)[a]	Mean (SD)	42.26	(12.59)	41.93	(12.82)	42.09	(12.66)
	Range	18 to 75		18 to 84		18 to 84	
Race (n and % of patients)	Caucasian	321	(95.5)	358	(97.5)	679	(96.6)
	Black	8	(2.4)	3	(0.8)	11	(1.6)

		QTP + LI/VAL N =750		PLA + LI/VAL N = 748		Total 1498	
	Oriental	2	(0.6)	1	(0.3)	3	(0.4)
	Other	5	(1.5)	5	(1.4)	10	(1.4)
Weight (kg)[a]	Mean (SD)	84.6	(18.03)	83.7	(18.53)	84.10	(18.29)
	Range	45 to 145		46 to 165		45 to 165	
Disease characteristics							
YMRS total score at randomization	Mean (SD)	2.47		2.24		2.53	
	Range	0 to 12		0 to 12		0 to 12	
MADRS total score at randomization	Mean (SD)	3.38		3.68		3.54	
	Range	0 to 17		0 to 30		0 to 30	
Assigned mood stabilizer: n (%)	Lithium	143	(42.6)	153	(41.7)	296	(42.1)
	Valproate	193	(57.4)	214	(58.3)	407	(57.9)
DSM-IV diagnosis of bipolar I disorder, most recent episode: n (%)	Manic	163	(48.5)	174	(47.4)	337	(47.9)
	Depressed	97	(28.9)	109	(29.7)	206	(29.3)
	Mixed	76	(22.6)	84	(22.9)	160	(22.8)
With rapid cycling course: n (%)	Yes	74	(22.0)	94	(25.6)	168	(23.9)
	No	262	(78.0)	270	(73.6)	532	(75.7)

[a] At enrollment
ITT=Intention to treat; N=Number; PP=Per-protocol

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. 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 (estimated hazard ratio 0.28, corresponding to a risk reduction of 72%). Kaplan-Meier estimates of time to 20% of the patients experiencing recurrence of a mood event was 211 days for the quetiapine treatment group and 30 days in the placebo treatment group. The demonstrated efficacy of quetiapine did not show restriction to any specific subgroup (assigned mood stabilizer, age, sex, race, index episode, or precence of rapid cycling) 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 (estimated hazard ratio 0.30, corresponding to a risk reduction of 70%) and a depressed episode (estimated hazard ratio 0.26, corresponding to a risk reduction of 74%), respectively, compared to placebo. The time to all-cause discontinuation from the study was greater in the quetiapine treatment group.

Quetiapine was superior to placebo in improving quality of life between mood events assessed by PGWB, but had no conclusive effect on the patients' level of functioning according to the analyses of the SDS scores. In addition, from randomization up to final assessment but excluding assessments associated with a mood event, quetiapine was more effective in suppressing manic, depressed, and psychotic symptoms, as assessed by YMRS, MADRS and PANSS-P total scores. 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 and Global Improvement scale.

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

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

	QTP + LI/VAL vs PLA + LI/VAL QTP N=336 / PLA N=367
Analysis of time to recurrence of a mood event	
Hazard ratio	0.28
95% CI	0.21, 0.37
p-value	<.0001
Analysis of time to recurrence of a manic event	
Hazard ratio	0.30
95% CI	0.20, 0.44
p-value	<.0001
Analysis of time to recurrence of a depressed event	
Hazard ratio	0.26
95% CI	0.17, 0.41
p-value	<.0001

ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.
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Table S 3 Summary of efficacy results between mood events, LS means and treatment comparisons of rating scales (ITT population)

Outcome variable	LS mean (SE)		Difference in LS means (SE)	95% CI	P-value
	QTP + LI/VAL (N =)	PLA + LI/VAL (N =)			
SDS total score, mean change[a]	-0.55 (0.302)	0.13 (0.312)	-0.68 (0.432)	-1.53, 0.17	0.1149
Additional rating scales[b]					
PGWB total score	102.46 (0.601))	100.54 (0.697)	1.92 (0.834)	0.28, 3.55	0.0218
YMRS total score	2.44 (0.093)	3.34 (0.148)	-0.90 (0.161)	-1.21, -0.58	<0.0001
MADRS total score	3.55 (0.129)	4.28 (0.154)	-0.73 (0.175)	-1.07, -0.39	<0.0001
CGI-BP Severity of Illness	1.53 (0.022)	1.67 (0.028)	-0.14 (0.031)	-0.20, -0.08	<0.0001
CGI-BP Global Improvement	3.91 (0.039)	4.08 (0.045)	-0.18 (0.051)	-0.28, 0.08	0.0006
PANSS-P score	7.68 (0.049)	7.90 (0-054)	-0.22 (0.063)	-0.35, -0.10	0.0005

[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

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) emerging during the randomized period was similar in the quetiapine group (54.8%) and in the placebo group (55.3%) (Table S 4). The overall incidence of AEs considered by the investigator to be causally related to the study drug was similar in the 2 treatment groups.

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

	Randomized treatment		Assigned mood stabilizer			
	QTP+ LI/VAL (N=336)	PLA+ LI/VAL (N=367)	QTP+ LI (N=143)	PLA+ LI (N=153)	QTP+ VAL (N=193)	PLA+ VAL (N=214)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ANY ADVERSE EVENT	184 (54.8)	203 (55.3)	79 (55.2)	93 (60.8)	105 (54.4)	110 (51.4)
DRUG-RELATED ADVERSE EVENT [a]	78 (23.2)	80 (21.8)	28 (19.6)	32 (20.9)	50 (25.9)	48 (22.4)

[a] As judged by the investigator.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients.
Note: Events reported during randomized treatment phase. Patients with multiple events in the same category are counted only once.
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There were 7 deaths reported in the study, 3 during open-label treatment (2 suicide and 1 pneumonia) and 1 during randomized treatment in the quetiapine group (suicide), and 3 in the placebo group (cardiac failure, suicide and a death of unknown cause at the time of report). The incidence of serious adverse events (SAE) during the randomized period was higher in the placebo group (5.4%) than in the quetiapine group (1.5%). In the quetiapine group, 2.4% of the patients were prematurely discontinued from the study during the randomized phase due to an AE ongoing at randomization or emerging during randomized treatment, compared to 3.0% of the patients in the placebo group.

Table S 5 Patients in various categories of adverse events ongoing at randomization or reported during randomized treatment (Randomized safety population)

	Randomized treatment		Assigned mood stabilizer			
	QTP+ LI/VAL (N=336)	PLA+ LI/VAL (N=367)	QTP+ LI (N=143)	PLA+ LI (N=153)	QTP+ VAL (N=193)	PLA+ VAL (N=214)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
SERIOUS ADVERSE EVENT	5 (1.5)	20 (5.4)	4 (2.8)	6 (3.9)	1 (0.5)	14 (6.5)
SERIOUS ADVERSE EVENT LEADING TO DEATH	1 (0.3)	3 (0.8)	1 (0.7)	2 (1.3)	0	1 (0.5)
SERIOUS ADVERSE EVENT NOT LEADING TO DEATH	4 (1.2)	17 (4.6)	3 (2.1)	4 (2.6)	1 (0.5)	13 (6.1)
ADVERSE EVENTS LEADING TO DISCONTINUATION	8 (2.4)	11 (3.0)	4 (2.8)	6 (3.9)	4 (2.1)	5 (2.3)

[a] As judged by the investigator.

PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients.
Note: Events ongoing at randomization or reported during randomized treatment phase.
Patients with multiple events in the same category are counted only once.
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The most common adverse events by preferred term emerging during the randomized treatment phase in the quetiapine treatment group were "somnolence", "nasopharyngitis", and "headache". "Insomnia" was more common in the placebo group than in the quetiapine treatment group.

Table S 6 Number (%) of patients with the most commonly reported (≥5%) adverse events (randomized safety population)

	Randomized treatment		Assigned mood stabilizer			
	QTP+LI/VAL (N=336)	PLA+LI/VAL (N=367)	QTP+LI (N=143)	PLA+LI (N=153)	QTP+VAL (N=193)	PLA+VAL (N=214)
MEDDRA PREFERRED TERM[a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ANY ADVERSE EVENT	60 (17.9)	90 (24.5)	26 (18.2)	44 (28.8)	34 (17.6)	46 (21.5)
SOMNOLENCE	19 (5.7)	8 (2.2)	8 (5.6)	4 (2.6)	11 (5.7)	4 (1.9)
NASOPHARYNGITIS	18 (5.4)	20 (5.4)	8 (5.6)	8 (5.2)	10 (5.2)	12 (5.6)
HEADACHE	17 (5.1)	21 (5.7)	8 (5.6)	9 (5.9)	9 (4.7)	12 (5.6)
INSOMNIA	13 (3.9)	52 (14.2)	7 (4.9)	29 (19.0)	6 (3.1)	23 (10.7)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. n Number of patients.
MedDRA Medical Dictionary of Regulatory Activities.
Note: Common adverse event: occurring at an incidence of >=5% in any randomized treatment group.
Note: Events reported during randomized treatment phase sorted by decreasing frequency in the QTP + LI/VAL treatment group.
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The incidence of AEs potentially related to suicidality was low in both treatment groups (0.6 vs 0.8%). The incidences of AEs potentially associated with EPS emerging during randomized treatment were similar in the 2 treatment groups (5.1 vs 4.6%) and there were no mean increases from baseline in parkinsonian symptomatology or akathisia in the quetiapine group as assessed by mean SAS, BARS, and AIMS scores.

Quetiapine was not associated with treatment-emergent neutropenia or agranulocytosis during randomized treatment. There were no adverse events potentially related to neutropenia or agranulocytosis reported during randomized treatment with quetiapine. During the open-label phase 3 patients (0.2%) had "neutrophil count decreased" and 2 patients (0.1%) had "neutropenia". Neutrophil counts were low ($<1.5 \times 10^9$ cells/L) in 7 patients (2.3%) in the quetiapine treatment group, compared to 2 patients (0.6%) in the placebo group. None of the patients had neutrophil counts below 1.0×10^9 cells/L.

The mean body weight increased by 2.87 kg during open-label treatment in the open-label safety population. During the randomized treatment phase there was a mean weight increase

of 0.51 kg in the quetiapine group and a mean decrease of –1.88 kg in the placebo group. Mean HDL and triglycerides showed an increase during both the open-label treatment and during randomized treatment with quetiapine.

There were small increases in mean glucose, HbA_{1C}, and insulin levels in the quetiapine treatment group compared to placebo. Clinically important values for glucose regulation measures were more common in quetiapine-treated patients. The incidence of patients with a shift from ≤2 to ≥3 metabolic risk factors during randomized treatment was somewhat higher in quetiapine group (41 patients, 17.9%) than in the placebo group (29 patients, 12.2%). Some differences between the treatment groups were noted in BMI, triglycerides and glucose.