AstraZeneca

Drug product:	Seroquel™	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate		
Study code:	D1447C00144		
Date:	1 April 2008		

Multicenter, Randomized, Parallel-group, Double-blind, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate and Lithium as Monotherapy for up to 104 Weeks Maintenance Treatment of Bipolar I Disorder in Adult Patients

Study centres: The study was conducted in 128 centers in 15 countries in Asia, Europe, Central/South America and US.

Publications: None at report time

Study dates		**Phase of development**
First patient enrolled	29 March 2005	Therapeutic confirmatory (III)
Last patient last visit	5 July 2007	

End of study was defined as date of database lock: 6 December 2007.

Primary objective: The primary objective of the study was to evaluate the efficacy of quetiapine versus placebo in increasing time from randomization to recurrence of a mood event in patients with Bipolar I Disorder. Recurrence of a mood event was defined as fulfilling at least 1 of the following: (a) initiation of an antipsychotic, antidepressant, mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic, depressed or mixed event, (b) hospitalization for a manic, depressed or mixed event, (c) 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 (d) 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:
The secondary objectives of the study were

1. To evaluate the efficacy of quetiapine versus placebo in increasing time from randomization to recurrence of a manic event. Recurrence of a manic event was defined as fulfilling at least 1 of the following: (a) initiation of an antipsychotic,

mood stabilizer, anxiolytic other than lorazepam, or any other medication to treat a manic event or a mixed event with predominantly manic symptoms, (b) hospitalization for a manic event or a mixed event with predominantly manic symptoms, (c) YMRS score ≥20 for 2 consecutive assessments, or YMRS score ≥20 at final assessment if the patient discontinues, or (d) discontinuation from the study by the patient if, in the opinion of the investigator, the discontinuation was due to a manic event or a mixed event with predominantly manic symptoms.

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

3. To evaluate the efficacy of quetiapine versus placebo in decreasing the severity of manic and depressed symptoms between mood events as assessed by YMRS total score, MADRS total score and Clinical Global Impression-Bipolar (CGI-BP) score.

4. To evaluate the efficacy of quetiapine versus placebo in decreasing the severity of psychotic symptoms between mood events as assessed by Positive and Negative Syndrome Scale- Positive Subscale (PANSS-P) score.

5. To evaluate the efficacy of quetiapine versus placebo in improving level of functioning between mood events as assessed by Sheehan Disability Scale (SDS).

6. To explore the level of patient acceptance with quetiapine as assessed by time to all-cause discontinuation.

7. To explore the efficacy of quetiapine versus placebo in cognitive symptoms between mood events as assessed by Medical Outcomes Study Cognitive Scale (MOS-Cog) and Trail Making Test (TMT).

8. To explore the effect of quetiapine on work productivity between mood events as assessed by Work Productivity and Activity Impairment Questionnaire (WPAI).

9. To determine whether quetiapine is safe and well-tolerated as assessed by adverse events (AEs), laboratory values, vital signs, weight, waist circumference, extrapyramidal symptoms (EPS) scales (Simpson Angus scale [SAS]; Barnes Akathisia Rating Scale [BARS]; Abnormal Involuntary Movement Scale [AIMS]), physical examinations including eye examination, and electrocardiograms (ECGs).

Study design: This was a multicenter, randomized, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of quetiapine and lithium (active comparator in the study) for up to 104 weeks of recurrence prevention treatment in adult patients with bipolar I disorder. The study consisted of enrollment and 2 phases, the initial open-label treatment phase and the subsequent randomized treatment phase. The study was originally planned to be stopped when a total of 600 recurrences of mood events had occurred. An interim analysis was added to the study design in an Amendment to the Clinical Study Protocol (CSP), dated 18 January 2007. The interim analysis was conducted when recurrence of approximately 150 manic events and 150 depressed events had been observed. Details of the interim analysis are given in the Statistical methods part of the Synopsis.

Lithium was included in the study design in order to allow an assessment of assay sensitivity (if needed) and to provide data for assessing the benefits and risks of continuing quetiapine treatment versus switching to lithium for recurrence prevention. An optional part of the study included the collection of a blood sample for future genetic research. The sampling was optional at patient, center, and country level.

Target patient population and sample size

For enrollment into the study male or female patients aged 18 years or older, had to have a diagnosis of Bipolar I Disorder as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association 2002). Patients were to have an acute manic, depressed or mixed episode at enrollment; or had experienced a past manic, depressed or mixed episode within 26 weeks, as documented by medical records. If the patient had the index episode within 26 weeks prior to enrollment, the episode should have been treated with quetiapine, which must not have been interrupted for more than 2 weeks continuously since the start of treatment. Patients should have had at least 1 additional manic, depressed, or mixed episode in the 2-year period prior to the index episode.

To be eligible for randomization, a patient had to be treated with quetiapine within the range of 300 to 800 mg/day for at least 4 weeks during the open-label treatment phase. Also, a patient had to be stabilized in remission, defined as having a YMRS total score ≤12, and a MADRS total score ≤12 during the last 4 weeks of open-label treatment.

It was originally assumed that 2100 randomized patients were required to ensure an adequate number of randomized patients to observe 300 recurrences of mania and 300 recurrences of depression, within the given time frame. To meet this, the target for enrollment was 3500 patients, with approximately 3000 expected to enter the open-label treatment phase. An interim analysis was added to the study, and is described in the Statistical methods section of the Synopsis.

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

In the initial open-label treatment phase, patients began or continued on an oral dose of open-label quetiapine, 300 mg 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 the open-

label treatment phase. Doses could be adjusted within this range to optimize efficacy and tolerability. After meeting all inclusion criteria and none of the exclusion criteria for randomization, patients were randomized to quetiapine, placebo, or lithium. Following randomization, open-label quetiapine tablets were replaced with 100-mg or 200-mg tablets of blinded quetiapine or placebo, and with capsules containing 300 mg lithium or placebo during 2 weeks. The dose of blinded quetiapine (or placebo) could be adjusted as clinically indicated within the dose range of 300 mg to 800 mg/day and the dose of blinded lithium (or placebo) could be adjusted within the dose range of 600 mg to 1800 mg/day all through the randomized treatment phase. Dose adjustments for lithium were made to achieve target trough serum concentrations of 0.6 mEq/L to 1.2 mEq/L.

A total of 52 batches of quetiapine and 16 batches of lithium were used in this study. Individual batch numbers, strength, and formulation numbers are included in Clinical Study Report (CSR) Appendix 12.1.6.

Duration of treatment

The study consisted of enrollment and 2 phases, the open-label treatment phase (4 to 24 weeks) and the placebo-controlled blinded randomized treatment phase (up to 104 weeks). As the study was terminated after a positive interim analysis, no patients were treated in the randomized treatment phase for 104 weeks. In the intent-to-treat (ITT) population, the mean duration of treatment with quetiapine in the double-blind, randomized treatment period was 191 days and the maximum duration was 715 days. The mean duration of treatment with placebo was 118 days and the maximum duration was 569 days. The mean duration of treatment with lithium was 130 days and the maximum duration was 553 days. During the whole study, including both open-label and randomization periods, 335 patients were treated with quetiapine for at least 26 weeks and 115 of these patients were treated for at least 52 weeks.

Criteria for evaluation - Main variables

Efficacy variables	
Primary outcome variable:	time to recurrence of a mood event
Secondary outcome variables related to mood events:	time to recurrence of a manic event; time to recurrence of a depressed event; time to all-cause discontinuation, time to recurrence of a mood event, manic event and depressed event per rating scale criteria only
Secondary investigator rated outcome variables related to symptoms:	YMRS total score; MADRS total score; CGI-BP score; PANSS-P total 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.
Other secondary efficacy variable	Time required to complete TMT Parts A and B: results from between mood events are presented, ie, from randomization up to final

	assessment but excluding assessment associated with a mood event.
Secondary patient reported outcome variables:	SDS total score, MOS-Cog score, and WPAI score. For all 3 scales, results from between mood events are presented, ie, from randomization up to final assessment but excluding assessment associated with a mood event.
Safety variables:	- Adverse events (AE); - laboratory test results; - vital signs; - weight; waist circumference - electrocardiogram (ECG) results; - physical examination including eye examinations. - for EPS, the extended analyses also included some specially designed rating scales, ie, SAS, BARS, and AIMS. For 6 predefined safety areas of specific interest to this compound or class of drugs, more thorough evaluations of AE potentially associated with these areas were made: suicidality; extrapyramidal symptoms (EPS); QT prolongations; diabetes mellitus; neutropenia, somnolence. In addition, the overall evaluation also included lab data, ECGs, and concomitant medications, as relevant.

Statistical methods

The primary analysis of time to recurrence of a mood event, and the secondary analyses of time to recurrence of a manic event and time to recurrence of a depressed event, in the comparison between quetiapine and placebo were based on the interim ITT population. The statistical model used in this analysis was a Cox proportional hazards regression model. The primary objective of the study was to evaluate the efficacy of quetiapine versus placebo in increasing time from randomization to recurrence of a mood event. Therefore, patients in the lithium arm of the study were not included in the interim analyses. Supportive analyses were performed on the ITT and per protocol (PP) population, including the lithium arm. An additional approach to define time to event (mood, manic, and depressed) was applied where definition of event is based on the MADRS and YMRS rating scales, and analyzed using the Cox proportional hazard model. All statistical tests in this study were performed for two-sided hypotheses. Where appropriate, two-sided 95% confidence intervals (CIs) were presented.

Emerging data from Studies 126 and 127 suggested that the assumptions made in the original powering of Study 144 were conservative. It was believed that the study could be conclusive at a lower number of mood events than it was initially estimated. Therefore, it was considered ethical to conduct an interim analysis when 50% of the planned total number of mood events had been attained. To account for the possibility of early closure of the study due to an

observed treatment difference between quetiapine and placebo in the interim analysis, the significance level was adjusted according to the Pocock method (Pocock 1977, Jennison and Turnbull 2000), to assure an overall significance level of 0.05. In the interim analysis, the observed p-value was compared with the boundary significance level instead of the overall alpha significance level. As a result of the analysis of the time to recurrence of a mood event, manic event and depressed event after approximately 300 events, carried out by the external independent statistical group (EISG), the study was stopped. The data collected after AstraZeneca's decision to stop the study and up to the actual termination of the study were collected under blinded condition as well.

A stepwise semi-sequential procedure was used as a confirmatory strategy. The null hypothesis that there is no difference between quetiapine and placebo was tested semi-sequentially for the following outcome variables: 1) time to a mood event, 2) time to a manic event, 3) time to a depressed event, and 4) mean change in SDS total score. Time to a manic event and time to a depressed event were independent of each other in the semi-sequential procedure.

The outcome variable SDS total score was analyzed to evaluate the efficacy of quetiapine versus placebo, in improving level of functioning between mood events, using analysis of covariance (ANCOVA). A mixed model was used for repeated measures analysis of the YMRS, MADRS, and PANSS-P total scores as well as the MOS-Cog and WPAI score, the time to complete the TMT, and the CGI-BP domain scores, to evaluate the efficacy of quetiapine versus placebo, in improving symptoms between mood events. Descriptive statistics were provided for all efficacy and safety variables.

Data analyses were based on the 5 patient populations: the interim ITT, ITT and PP populations, randomized safety population and open-label safety population.

Patient population

The number of patients included in the study populations were: 730 patients in the interim ITT population (quetiapine and placebo); 1172 patients in the ITT population (quetiapine, placebo and lithium); 966 patients in the PP population (quetiapine, placebo and lithium); 2428 patients in the open-label safety population; and 1226 patients in the randomized safety population.

The first patient entered the study on 29 March 2005 and the last patient completed the study on 5 July 2007. In total, 2438 patients were enrolled to open-label treatment at 128 study sites and 1226 patients (50.3% of the enrolled) were randomized. 237 of the 375 patients (63.2%) in the "Other" category discontinuing the open-label treatment did so, because the study was terminated by AstraZeneca after the positive interim analysis. Considering this, the actual randomization rate (ie, patients that had the opportunity to enter the randomization phase) was 55.7% (1226 randomized patients divided by 2438 enrolled patients minus 237 patients who discontinued open-label treatment due to early termination of the study).

Of the 1226 randomized patients, 378 (32.3%) in the ITT population had the treatment reported to be discontinued due to a mood event. 247 ITT patients had the randomized treatment discontinued for other reason than a mood event. 547 patients (46.7%) completed the randomized treatment, up to the time the study was terminated by AstraZeneca, due to the positive results of the interim analysis (note that "completed" patients were actually discontinued when the study was stopped). 54 patients randomized to lithium were excluded from the ITT population, due to not having their serum concentrations monitored according to the CSP and meeting certain criteria for exclusion based on low serum concentration.

Patients entering the randomized phase were clinically stable during the last 4 weeks of the open-label phase. Mean YMRS and MADRS scores in the randomized ITT population fell from 15.3 and 13.14, respectively at enrollment and to 3.77 and 3.44 respectively at randomization.

During this study, 2438 patients with bipolar I disorder were enrolled to the open-label stabilization phase with a flexible dose of 300 to 800 mg/day of quetiapine (the mean of open-label safety patients' median daily dose was 497 mg). For 404 patients who were randomized for quetiapine, the mean median dose during randomized treatment phase was 546 mg/day. The mean median serum concentration in lithium patients was 0.63 mEq/L in the ITT population and 0.77 mEq/L in patients in the PP population.

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 treatment group. Total exposure in the randomized safety population was 62% higher (mean of 191 days) in the quetiapine treatment group than in the placebo treatment group (mean of 118 days), and was 30% higher than in the lithium treatment group (mean of 147 days). The overall number of discontinuations other than due to a mood event in the randomized treatment phase was 68 patients in the quetiapine treatment group, 80 patients in the placebo treatment group and 99 patients in the lithium treatment group. "Patient not willing to continue" was the main reasons for premature discontinuations in all treatment groups. There was no apparent difference between the quetiapine (22 patients) and placebo (28 patients) treatment groups in the number of patients who had important protocol deviations leading to exclusion from the PP analysis. However, the number of patients with important protocol deviations leading to exclusion from the PP analysis was higher in the lithium treatment group (156 patients), due to the fact that their median serum concentrations were outside the therapeutic range. In total, 206 patients in the ITT population were excluded from the PP analysis.

The mean age in the ITT population was 39.5 years old and the population was well balanced with regard to gender. The ITT population was predominantly Caucasian (63.1%), 16.9% were Other race (121 of the 198 patients in this category were Hispanic), 14.9% were Oriental and 5.0% were Black. Overall, the mean weight of the ITT population at enrollment was 71.6 kg.

A similar use of sleep medication and lorazepam was observed across the treatment groups, both during the last 4 weeks prior to randomization and during randomized treatment. The use of anticholinergic drugs was similar and low in all treatment groups. The variety of

psychoactive drugs used by the patients entering the open-label treatment period are commonly seen in the bipolar population. 1507 patients (62.1%) received treatment with at least 1 psychoactive drug. 1262 patients (52.0%) took antipsychotics, the majority of which were atypical antipsychotics (34.8%), quetiapine being used by 494 patients (20.3%). Of the mood stabilizers, valproate was the most commonly used, taken by 25% of the patients, followed by lithium taken by 18.9% of the patients. Psychoactive medication use in the ITT population at enrollment was similar across the 3 randomized treatment groups and similar to the use at enrollment in all open-label patients.

The demographic and disease characteristics of the ITT population are described in Table S 1.

Table S 1 Patient population (ITT population)

		Quetiapine (N =404)	Placebo (N =404)	Lithium (N=364)	Total (N=1172)
Demographic characteristics					
Sex (n and % of patients)	Male	182 (45.0)	210 (52.0)	155 (42.6)	547 (46.7)
	Female	222 (55.0)	194 (48.0)	209 (57.4)	625 (53.3)
Age (years)[a]	Mean (SD)	39.93 (12.29)	39.96 (12.86)	38.43 (12.48)	39.48 (12.55)
	Range	18 to 73	18 to 75	18 to 70	18 to 75
Race (n and % of patients)	Caucasian	259 (64.1)	260 (64.4)	221 (60.7)	740 (63.1)
	Black	17 (4.2)	20 (5.0)	22 (6.0)	59 (5.0)
	Oriental	61 (15.1)	58 (14.4)	56 (15.4)	175 (14.9)
	Other	67 (16.6)	66 (16.3)	65 (17.9)	198 (16.9)
Weight (kg)[a]	Mean (SD)	72.22 (18.88)	71.71 (17.69)	70.74 (19.66)	71.58 (18.72)
	Range	39 to 165	40 to 150	34 to 159	34 to 165
Disease characteristics					
YMRS total score at enrollment	Mean (SD)	15.34 (9.80)	15.32 (10.25)	15.24 (9.84)	15.30 (9.96)
	Range	0 to 44	0 to 46	0 to 47	0 to 47
YMRS total score at randomization	Mean (SD)	3.88 (3.66)	3.69 (3.55)	3.74 (3.48)	3.77 (3.56)
	Range	0 to 14	0 to 13	0 to 12	0 to 14
MADRS total score at enrollment	Mean (SD)	13.07 (10.24)	13.22 (10.52)	13.14 (10.50)	13.14 (10.41)
	Range	0 to 40	0 to 44	0 to 44	0 to 44
MADRS total score at randomization	Mean (SD)	3.55 (3.48)	3.41 (3.41)	3.34 (3.47)	3.44 (3.45)
	Range	0 to 12	0 to 14	0 to 19	0 to 19
DSM-IV diagnosis of bipolar I disorder, most recent episode: n (%)	Manic	212 (52.5)	223 (55.2)	193 (53.0)	628 (53.6)
	Depressed	114 (28.2)	115 (28.5)	99 (27.2)	328 (28.0)
	Mixed	78 (19.3)	66 (16.3)	72 (19.8)	216 (18.4)
With rapid cycling course: n (%)	Yes	61 (15.1)	47 (11.6)	55 (15.1)	163 (13.9)
	No	343 (84.9)	357 (88.4)	308 (84.6)	1008 (86.0)
	Unknown	0	0	1 (0.3)	1 (0.1)

[a] At enrollment

ITT Intent to treat; N Number; YMRS Young Mania Rating scale; MADRS Montgomery-Asberg Depression Rating Scale; DSM-IV Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
Table derived from: Table 11.1- 10 and Table 11.1- 21

Efficacy results

The results of the primary efficacy analysis in the interim ITT population are summarized in Table S 2.

Table S 2 Summary of efficacy results (interim ITT population)

	Quetiapine vs Placebo **$N_{Quetiapine}$ =366/ $N_{Placebo}$ =364**
Analysis of time to recurrence of a mood event	
Hazard ratio	0.26
95% CI	0.19, 0.35
p-value	<0.0001
Analysis of time to recurrence of a manic event	
Hazard ratio	0.27
95% CI	0.19, 0.39
p-value	<0.0001
Analysis of time to recurrence of a depressed event	
Hazard ratio	0.25
95% CI	0.15, 0.41
p-value	<0.0001

Analysis using Cox's proportional hazards model with region included as covariates.
ITT Intent-to-Treat. N Number of patients in treatment group. CI Confidence interval.
Table corresponds to: Table 11.2- 1

Quetiapine significantly increased the time to recurrence of a mood event (hazard ratio [HR] 0.26, corresponding to a risk reduction of 74% [ie, (1-HR) x 100] p<0.0001), as well as the time to recurrence of a manic event and a depressed event, compared with placebo, as shown in the interim ITT population. The total number of patients with mood events was 60 (16.4%) and 156 (42.9%) in the quetiapine and placebo treatment groups, respectively.

The primary analysis (comparison of quetiapine and placebo in the interim ITT) showed positive results, thus, based on the pre-defined stopping criteria, the study was stopped by AstraZeneca. After this, a number of analyses were performed to support the robustness in the comparison of quetiapine and placebo, as well as to include lithium.

The results of the efficacy analysis in the ITT population are summarized in Table S 3, Table S 4, Table S 5, and Table S 6.

Table S 3 Summary of efficacy results (ITT population)

	Quetiapine vs Placebo $N_{Quetiapine}$ =404/ $N_{Placebo}$ =404	Lithium vs Placebo $N_{Lithium}$ =364/ $N_{Placebo}$ =404	Quetiapine vs Lithium $N_{Quetiapine}$ =404/ $N_{Lithium}$ =364
Analysis of time to recurrence of a mood event			
Hazard ratio	0.29	0.46	0.66
95% CI	0.23, 0.38	0.36, 0.59	0.49, 0.88
p-value	<0.0001	<0.0001	0.0050
Analysis of time to recurrence of a manic event			
Hazard ratio	0.29	0.37	0.78
95% CI	0.21, 0.40	0.27, 0.53	0.53, 1.16
p-value	<0.0001	<0.0001	0.2264
Analysis of time to recurrence of a depressed event			
Hazard ratio	0.30	0.59	0.54
95% CI	0.20, 0.44	0.42, 0.84	0.35, 0.84
p-value	<0.0001	<0.0037	0.0055

Analysis using Cox's proportional hazards model with region included as covariates.
ITT Intent-to-Treat. N Number of patients in treatment group. CI Confidence interval.
Table corresponds to: Table 11.2- 2

The results seen in the primary analysis of the interim ITT population were confirmed in the ITT population: quetiapine significantly increased the time to recurrence of a mood event, manic event and depressed event compared with placebo ($p<0.0001$).

Lithium significantly increased the time to recurrence of a mood event ($p<0.0001$), compared with placebo, thereby confirming the assay sensitivity of the study that was demonstrated by quetiapine being superior to placebo. In the comparison between quetiapine and lithium, the estimated risk of patients experiencing a mood and depressed event was generally lower in the quetiapine-treated group compared with that in the lithium-treated group. No significant difference was noted in the analysis of time to recurrence of a manic event between quetiapine and lithium.

The demonstrated efficacy of quetiapine in the ITT population was not restricted to any specific subgroup (age, sex, race, episode cycling frequency, or region) and the results were supported by the results in the PP population.

In the quetiapine treatment group, the significantly increased time to recurrence of a mood event, as well as manic event and depressed event was irrespective of index episode in the ITT population (Table S 4).

Table S 4 Time to recurrence of a mood event by index episode, quetiapine vs placebo (ITT population)

	Manic index episode (N_{QTP}=212 / N_{PLA}=223)			Depressed index episode (N_{QTP}=114 / N_{PLA}=115)			Mixed index episode (N_{QTP}=78 / N_{PLA}=66)		
	n_{QTP} / n_{PLA}	HR	95% CI	n_{QTP} / n_{PLA}	HR	95% CI	n_{QTP} / n_{PLA}	HR	95% CI
Mood event	50 / 108	0.31	0.22, 0.44	27 / 63	0.29	0.18, 0.46	14 / 37	0.26	0.14, 0.48
Manic event	39 / 82	0.33	0.22, 0.48	11 / 26	0.26	0.12, 0.53	5 / 15	0.18	0.06, 0.53
Depressed event	11 / 26	0.26	0.13, 0.54	16 / 37	0.32	0.18, 0.58	9 / 22	0.32	0.14. 0.70

Analysis using Cox's proportional hazards model with region included as covariates.
ITT Intent-to-Treat. N Number of patients in treatment group. n number of patients with event in subgroup. PLA Placebo.
QTP Quetiapine CI Confidence interval. HR: Hazard ratio
Table is derived from Table 11.2.1- 10, Table 11.2.2- 6, Table 11.2.3- 6

The analysis of time to recurrence of a mood event by rating scale criteria only in the ITT population is presented in Table S 5.

Table S 5 Analysis of time to recurrence of a mood event, per MADRS or YMRS criteria only (ITT population)

	Quetiapine vs Placebo	Lithium vs Placebo	Quetiapine vs Lithium
	$N_{Quetiapine}$ =404/ $N_{Placebo}$=404	$N_{Lithium}$ =364/ $N_{Placebo}$=404	$N_{Quetiapine}$ =404/ $N_{Lithium}$=364
Mood event			
Hazard ratio	0.29	0.48	0.64
95% CI	0.22, 0.38	0.37, 0.62	0.47, 0.87
p-value	<0.0001	<0.0001	0.0050

Table corresponds to Table 11.2.1- 13

Quetiapine was superior to placebo when used as monotherapy in increasing time to recurrence of a mood event, as well as a manic event and a depressed event as defined by rating scale criteria only. The estimated HR for time to recurrence of a mood event (quetiapine vs placebo) was 0.29 with a 95% CI = 0.22 to 0.38 (p<0.0001), corresponding to a risk reduction of 71%).

Table S 6 Summary of efficacy results between mood events, LS means and treatment comparisons (ITT population)

Outcome variable	LS mean (SE)			Quetiapine vs placebo		
	Quetiapine (N = 404)	Placebo (N =404)	Lithium (N =364)	Difference in LS means (SE)	95% CI	P-value
SDS total score, mean change[a]	-0.53 (0.26)	0.62 (0.27)	-0.06 (0.28)	-1.16 (0.36)	-1.85, -0.46	0.0011

Table S 6 Summary of efficacy results between mood events, LS means and treatment comparisons (ITT population)

Outcome variable	LS mean (SE)			Quetiapine vs placebo		
	Quetiapine (N = 404)	Placebo (N =404)	Lithium (N =364)	Difference in LS means (SE)	95% CI	P-value
Additional measures[b]						
YMRS total score	3.5 (0.1)	4.2 (0.2)	3.7 (0.2)	-0.8 (0.2)	-1.2, -0.3	0.002
MADRS total score	3.4 (0.2)	4.8 (0.2)	4.3 (0.2)	-1.4 (0.3)	-1.9, -0.9	<0.001
CGI-BP Severity of Illness	1.6 (0.03)	1.7 (0.04)	1.6 (0.04)	-0.19 (0.05)	-0.29, -0.1	<0.0001
CGI-BP Global Improvement	3.4 (0.05)	3.7 (0.08)	3.6 (0.07)	-0.28 (0.09)	-0.45, -0.10	0.0025
PANSS-P score	7.8 (0.1)	8.0 (0.1)	7.9 (0.1)	-0.2 (0.1)	-0.4, 0.0	0.103
MOS-Cog	29.9 (0.2)	28.8 (0.3)	30.3 (0.3)	1.1 (0.4)	0.3, 1.8	0.007
WPAI						
Work time missed (absenteeism)	3.6 (1.2)	4.9 (1.6)	2.7 (1.9)	-1.3 (1.9)	-5.0, 2.5	0.516
Impairment while working (presenteeism)	14.0 (1.6)	20.3 (2.1)	13.4 (2.1)	-6.3 (2.6)	-11.4, -1.3	0.014
Overall work impairment	8.0 (1.6)	8.1 (2.1)	4.1 (2.2)	-0.1 (2.6)	-5.3, 5.0	0.961
Activity impairment	13.6 (1.7)	21.2 (2.1)	12.8 (2.3)	-7.6 (2.6)	-12.7, -2.4	0.004
TMT						
TMT Part A	64.1 (1.9)	61.6 (2.7)	60.3 (2.5)	2.5 (3.2)	-3.7, 8.7	0.429
TMT Part B	126.3 (2.7)	134.7 (3.8)	134.6 (3.5)	-8.4 (4.5)	-17.1, 0.3	0.060

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

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

ITT Intent-to-Treat. PLA Placebo. QTP Quetiapine. LI Lithium. N Number of patients in treatment group. SD Standard deviation. SDS Sheehan Disability Scale. YMRS Young Mania Rating Scale. MADRS Montgomery-Asberg Depression Rating Scale. CGI-BP Clinical Global Impression – Bipolar. PANSS-S Positive and Negative Syndrome Scale-Positive Subscale. TMT Trail Making Test. MOS-Cog Medical Outcomes Study Cognitive Scale. WPAI Work Productivity and Activity Impairment Questionnaire.

Table derived from: Table 11.2.4- 1, Table 11.2.5- 1, Table 11.2.6- 1, Table 11.2.6- 13, Table 11.2.7- 1, Table 11.2.8- 1, Table 11.2.9- 1, Table 11.2.10- 1 and Table 11.2.11- 2

Quetiapine significantly improved the patients' level of functioning during recurrence prevention treatment (ie, between mood events), compared with placebo, as demonstrated in the analysis of the SDS total score (p=0.0011) in the ITT population.

Quetiapine was more effective during recurrence prevention treatment (ie, between mood events), compared with placebo, in suppressing manic and depressed symptoms, as assessed

by YMRS, MADRS; in suppressing overall bipolar symptoms, mania symptoms, and depressed symptoms as assessed by CGI-BP, in improving cognitive function as assessed by MOS-Cog and in improving work presenteeism as assessed by the WPAI subscale "Impairment while working" and in improving the patients' ability to perform regular daily activities, as assessed by the WPAI subscale "Activity impairment".

There was no significant difference between quetiapine and placebo during recurrence prevention treatment in suppressing psychotic symptoms assessed by the PANSS-P scale. The results were consistent with the low score observed at baseline in all treatment groups, indicating that very few psychotic symptoms were present. Also, there was no significant difference between quetiapine and placebo during recurrence prevention treatment in completing the Trail Making Test assessed by TMT Part A and B, in improving work productivity loss, as assessed by the WPAI subscale "Overall work impairment", and in reducing work absenteeism, as assessed by the WPAI subscale "Work time missed" subscale.

Safety results

Quetiapine was generally safe and well tolerated in the recurrence prevention treatment of bipolar I disorder across the dose range 300 mg/day to 800 mg/day. For 404 patients who were randomized to quetiapine, the mean daily dose of quetiapine at randomization was 549.5 mg. The mean median dose during randomized treatment phase was 546 mg/day. The mean median serum concentration in lithium patients was 0.63 mEq/L in the ITT population and 0.77 mEq/L in patients in the PP population.

The number (%) of patients who had at least 1 adverse event in any category is summarized in Table S 7 and in Table S 8.

Table S 7 Patients in various categories of adverse events (Randomized safety population)

	Quetiapine N=404 n (%)	Placebo N=404 n (%)	Lithium N=418 n (%)
Any adverse event	203 (50.2)	228 (56.4)	250 (59.8)
Drug-related adverse event[a]	99 (24.5)	102 (25.2)	143 (34.2)

[a] As judged by the investigator.
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. Patients with events in more than 1 category are counted once in each of those categories.
Table corresponds to Table 11.3.2.1- 1

Table S 8 Patients in various categories of adverse events ongoing at randomization or reported during RTP (Randomized safety population)

	Quetiapine N=404 n (%)	Placebo N=404 n (%)	Lithium N=418 n (%)
Serious adverse event	5 (1.2)	11 (2.7)	10 (2.4)
Serious adverse event leading to death	0	0	0
Serious adverse event not leading to death	5 (1.2)	11 (2.7)	10 (2.4)
Adverse events leading to discontinuation	14 (3.5)	13 (3.2)	20 (4.8)

[a] As judged by the investigator.
N Number of patients in treatment group. n Number of patients. RTP Randomized Treatment Phase
Note: Events ongoing at randomization or reported during randomized treatment phase. Patients with multiple events in the same category are counted only once. Patients with events in more than 1 category are counted once in each of those categories.
Note: Table includes AEs starting during OL phase where the patients were treated with quetiapine.
Note: Two patients (E0102021 and E1730007) in the Lithium group had an SAE starting during OL while treated with QTP.
Table corresponds to Table 11.3.2.1- 2

There were 3 deaths during the study, all of which occurred during the open-label treatment. One patient died from cardio-respiratory arrest, 1 from cardiomyopathy and 1 had a gun-shot wound. None of the deaths were considered by the investigator to be related to study drug.

The incidences of SAEs and DAEs were low. There were 5 patients (1.2%) in the quetiapine treatment group who had an SAE reported during the randomized treatment period or an SAE ongoing at randomization, 11 patients (2.7%) in the placebo treatment group and 10 patients (2.4%) in the lithium treatment group. The number of patients with AEs leading to discontinuation, reported during the randomized treatment period was 14 (3.5%) in the quetiapine treatment group, 13 (3.2%) in the placebo treatment group and 20 (4.8%) in the lithium treatment group.

The incidence of common AEs (occurring at an incidence of ≥5% in any treatment group) is summarized in Table S 9.

Table S 9 Common adverse events (≥5%) by preferred term and treatment group (Randomized safety population)

MedDRA preferred term [a]	Quetiapine (N=404) n(%)	Placebo (N=404) n(%)	Lithium (N=418) n(%)
Headache	36 (8.9)	32 (7.9)	48 (11.5)
Somnolence	27 (6.7)	17 (4.2)	11 (2.6)
Insomnia	26 (6.4)	69 (17.1)	52 (12.4)
Nausea	18 (4.5)	33 (8.2)	53 (12.7)
Tremor	12 (3.0)	8 (2.0)	31 (7.4)
Diarrhoea	11 (2.7)	21 (5.2)	26 (6.2)

Table S 9 Common adverse events (≥5%) by preferred term and treatment group (Randomized safety population)

MedDRA preferred term [a]	Quetiapine (N=404) n(%)	Placebo (N=404) n(%)	Lithium (N=418) n(%)
Vomiting	8 (2.0)	12 (3.0)	47 (11.2)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
N Number of patients in treatment group. n Number of patients. MedDRA Medical Dictionary of Regulatory Activities v10.
Note: Common adverse event: occurring at an incidence of ≥5% in any randomized treatment group.
Events reported during randomized treatment phase sorted by decreasing frequency in the quetiapine treatment group.
Table corresponds to Table 11.3.2.2- 2

During the randomized treatment phase, the most commonly reported AEs by preferred term in the quetiapine treatment group were "headache" (8.9% of patients in the quetiapine treatment group, 7.9% in the placebo treatment group and 11.5% in the lithium treatment group), "somnolence" (6.7% of patients in the quetiapine treatment group, 4.2% in the placebo treatment group and 2.6% in the lithium treatment group), and "insomnia" (6.4% of patients in the quetiapine treatment group, 17.1% in the placebo treatment group and 12.4% in the lithium treatment group). The most commonly reported AEs in the lithium treatment group were nausea, insomnia, headache, and vomiting. The most commonly reported AEs were predominantly of mild or moderate intensity.

Changes in mean values from baseline in glucose regulation variables were similar across treatment groups. In the subset of blood samples collected >8 h since last meal, the mean increase in glucose was 1.3 mg/dL, 1.7 mg/dL, and 3.2 mg/dL in the quetiapine, placebo, and lithium treatment groups, respectively. Treatment emergent clinically important blood glucose values ≥126 mg/dL in the subset of blood samples collected >8 h after last meal, were more common in the quetiapine treatment group (30 patients [9.3%]) compared with the placebo treatment group (13 patients [4.2%]) and the lithium treatment group (17 patients [5.4%]). The corresponding incidence densities (observations per 100 patient-years) were 16.4 in quetiapine-treated patients, compared with 11.4 in placebo- and lithium-treated patients. From enrollment to end of open-label treatment, there was an increase in glucose of 3.7 mg/dL (>8 h). Mean changes in other glucose regulation variables during open-label treatment were small. 5.3% (>8 h), had a treatment emergent glucose value >126 mg/mL at any time during open-label treatment.

The proportion of patients with AEs potentially related to diabetes mellitus was low. During randomized treatment, there were 6 patients (1.5%) with AEs potentially associated with diabetes reported in the quetiapine treatment group, compared with 1 patient with AEs (0.2%) in the placebo treatment group and 6 patients (1.4%) in the lithium treatment group. Of these, 3 patients in the quetiapine treatment group and 1 patient in the lithium treatment group had an AE coded to the MedDRA preferred term of "diabetes mellitus" or "diabetes mellitus non-insulin dependent" reported.

The proportion of patients with AEs potentially associated with suicide was low and similar in the quetiapine treatment group (3 patients, 0.7%) compared with the placebo treatment group (8 patients, 2.0%) and the lithium treatment group (3 patients, 0.7%).

The incidence of AEs potentially associated with EPS in the quetiapine treatment group (4.0%) was similar to placebo (4.5%), while it was 9.1% in the lithium treatment group. There were 4 patients with adverse events "tardive dyskinesia" reported in the study. All 4 patients had events reported to have an onset during the first week of open-label treatment, and 1 patient was treated with quetiapine 1 week prior to enrollment. Two of the patients had their "tardive dyskinesia" reported to be resolved during open-label treatment. Two of the patients were treated with trihexyphenidyl already at enrollment, 1 of which was reported to be treatment for tardive dyskinesia. The course of the observations in all 4 patients together suggests that quetiapine was unlikely to be a contributing factor in these "tardive dyskinesia" AEs. There was no apparent difference in changes in SAS, BARS, or AIMS scores across treatment groups. Most patients within each treatment group had no worsening in scores.

Incidence of treatment emergent somnolence and sedation was generally low. There were 31 patients (7.7%) with AEs potentially associated with somnolence in the quetiapine treatment group compared with 25 patients (6.2%) in the placebo and 18 patients (4.3%) in the lithium treatment group. Adverse events potentially associated with somnolence were more common during the open-label treatment phase compared with the randomized treatment phase, with 933 patients with adverse events (38.4%).

In the randomized treatment phase, the incidence of neutrophil concentrations below 1.5×10^9 cells/L was similar between the quetiapine and placebo treatment groups (6 patients in each treatment group). 3 of these patients in the quetiapine treatment group had their neutrophil counts below 1.0×10^9 cells/L, but not below 0.5×10^9 cells/L. There were 2 patients in the lithium treatment group with neutrophil concentrations below 1.5×10^9 cells/L. During open-label treatment, 2 patients had a neutrophil count of $<0.5 \times 10^9$ cells/L, with no AEs associated with infection, and both normalized during the study.

All treatment groups decreased in total cholesterol, LDL and triglycerides during randomized treatment. Decreases in lipid laboratory data were smaller in the quetiapine treatment group compared with the placebo and lithium treatment groups, except for HDL, however, HDL levels changed very little in all treatment groups. Patients in the quetiapine treatment group showed a higher proportion of clinically important lipid concentrations at any time during the randomized treatment period compared with patients in the placebo or the lithium treatment groups. Quetiapine-treated patients showed a higher incidence of clinically important elevated triglyceride concentration (22.7%) than placebo patients (8.7%) or lithium patients (9.3%).

Patients in the quetiapine treatment group showed a small increase in body weight and BMI during randomized treatment (0.63 kg), while patients in the placebo and lithium treatment groups lost weight after discontinuing open-label quetiapine treatment (-1.51 kg and –0.92 kg, respectively). From enrollment to end of randomized treatment, the mean change in weight data in patients treated with quetiapine was a weight gain of 2.9 kg.

There were no major differences between the quetiapine and placebo treatment groups for vital signs measurements. During randomized treatment, more patients in the lithium treatment group had >15 bpm decreases in pulse rate (18.2% in the lithium treatment group vs 13.5% in both the quetiapine and placebo treatment groups), while more patients in the quetiapine and placebo treatment groups had >15 bpm increases in pulse rate (8.9% and 10.3%, respectively) than in the lithium treatment group (5.3%).

There were no major differences between the quetiapine and placebo treatment groups for ECG. During randomized treatment, heart rate decreased and QTc Fridericia interval increased more in the lithium treatment group (with a mean of -9.81 bpm and 7.05 ms, respectively), compared with the quetiapine (with a mean of –2.30 bpm and 1.49 ms, respectively) and placebo treatment groups (with a mean of -4.91 bpm and 0.92 ms, respectively).