Notice of correction 1/22/14: *In Figure 2, the number of patients randomized to quetiapine who discontinued due to mood event has been corrected to n = 87.*

Continuation of Quetiapine Versus Switching to Placebo or Lithium for Maintenance Treatment of Bipolar I Disorder (Trial 144: A Randomized Controlled Study)

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ABSTRACT

Objective: Quetiapine, combined with lithium or divalproex, demonstrates efficacy in the maintenance treatment of bipolar I disorder. This study investigated the efficacy and safety of quetiapine monotherapy as maintenance treatment in bipolar I disorder compared with switching to placebo or lithium.

Method: Patients aged ≥ 18 years with *DSM-IV*-diagnosed bipolar I disorder and a current or recent manic, depressive, or mixed episode received open-label quetiapine (300–800 mg/d) for 4–24 weeks. Patients achieving stabilization were randomized to continue quetiapine or to switch to placebo or lithium (0.6–1.2 mEq/L) for up to 104 weeks in a double-blind trial. Outcome measures included times to recurrence of any mood event (primary outcome measure), manic event, or depressive event. Safety assessments included adverse events and laboratory values. The study was terminated early after planned interim analysis provided positive results. The study was conducted between March 2005 and July 2007.

Results: Of 2,438 patients starting open-label quetiapine, 1,226 (50.3%) were randomized to double-blind treatment, including 1,172 (95.6%) in the intent-to-treat population. Time to recurrence of any mood event was significantly longer for quetiapine versus placebo (hazard ratio [HR] = 0.29; 95% CI, 0.23–0.38; $P < .0001$) and for lithium versus placebo (HR = 0.46; 95% CI, 0.36–0.59; $P < .0001$). Quetiapine and lithium significantly increased time to recurrence of both manic events (quetiapine: HR = 0.29; 95% CI, 0.21–0.40; $P < .0001$; lithium: HR = 0.37; 95% CI, 0.27–0.53; $P < .0001$) and depressive events (quetiapine: HR = 0.30; 95% CI, 0.20–0.44; $P < .0001$; lithium: HR = 0.59; 95% CI, 0.42–0.84; $P < .004$) compared with placebo. Overall rates of adverse events were generally similar between treatment groups, and safety findings for quetiapine were consistent with its known profile.

Conclusions: In patients stabilized during acute quetiapine treatment, continuation of quetiapine significantly increased time to recurrence of any mood, manic, or depressive event compared with switching to placebo. Switching to lithium was also more effective than placebo for the prevention of manic and depressive events.

Trial Registration: clinicaltrials.gov Identifier: NCT00314184

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Bipolar I disorder is a chronic illness characterized by recurrent manic and depressive episodes. Atypical antipsychotics such as quetiapine are effective in the acute treatment of manic episodes.[1–3] In addition, quetiapine has been shown to be effective as monotherapy in the acute treatment of depressive episodes of bipolar I and bipolar II disorder,[3–8] while olanzapine in combination with fluoxetine (and, to a lesser extent, as monotherapy) has also demonstrated efficacy in bipolar I depression.[9]

Studies have additionally examined the effectiveness of atypical antipsychotics in the long-term maintenance treatment of bipolar disorder, either as monotherapy or combined with medications such as lithium and divalproex. Olanzapine and aripiprazole were studied primarily in patients who had responded to these drugs in the acute treatment of a manic or mixed episode, and these studies demonstrated a stronger effect overall in the prevention of manic episodes than in depressive episodes.[10–16]

Quetiapine is an atypical antipsychotic approved in the United States, the European Union, and other countries as monotherapy or in combination with lithium or divalproex in the acute treatment of manic episodes and as monotherapy in the acute treatment of depressive episodes of bipolar I or bipolar II disorder. Quetiapine is the only drug approved (United States, European Union, and other countries) as monotherapy for the acute treatment of both poles of bipolar disorder.[5–8,17–23] Quetiapine has also gained approval for the maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex, based on 2 placebo-controlled, randomized trials.[24,25]

The objectives of the current randomized trial were to investigate the efficacy and safety of quetiapine monotherapy as maintenance treatment in bipolar I disorder, in comparison with switching to placebo, in patients who had stabilized from an acute episode during open-label quetiapine treatment. Switching to lithium monotherapy was included as a reference intervention, and comparisons of the efficacy of quetiapine versus lithium were included as supportive analyses.

METHOD

Study Design

This international study (Study D1447C00144, in short, Trial 144) included a prerandomization phase, which consisted of open-label quetiapine treatment for up to 24 weeks in patients with a current or recent manic, depressive, or mixed episode of bipolar I disorder (Figure 1). Patients who achieved stabilization by at least week 20 and who maintained stability for at least 4 subsequent weeks—defined by a Young Mania Rating Scale (YMRS)[26] total score ≤ 12 and a Montgomery-Asberg Depression Rating Scale (MADRS)[27] total score ≤ 12—subsequently entered the double-blind, randomized

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Clinical Points

- In patients who respond to quetiapine, maintenance treatment with quetiapine (300–800 mg/d) significantly increases the time to recurrence of a mood event compared with placebo.
- Maintenance treatment with quetiapine increases the time to recurrence of both manic and depressive events and is effective regardless of the index mood event.
- Maintenance treatment with lithium is shown, for the first time, to increase the time to recurrence of a depressive as well as a manic event.

phase, which was planned for up to 104 weeks. During this phase, patients either continued quetiapine or were gradually switched to placebo or lithium.

The study was conducted between March 2005 and July 2007 at 128 centers in 15 countries in Asia, Europe, Central and South America, and the United States (clinicaltrials.gov Identifier: NCT00314184). The study design adhered to the current amendment of the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice guidelines and was approved by the ethical review boards of participating centers. Written informed consent was obtained from all patients after complete description of the study.

Patient Population

Key inclusion and exclusion criteria for patients entering the prerandomization and randomized phases are shown in Table 1. Patients were recruited from psychiatry units, community practices, and institutional review board–approved advertisements but were investigated only as outpatients during the study.

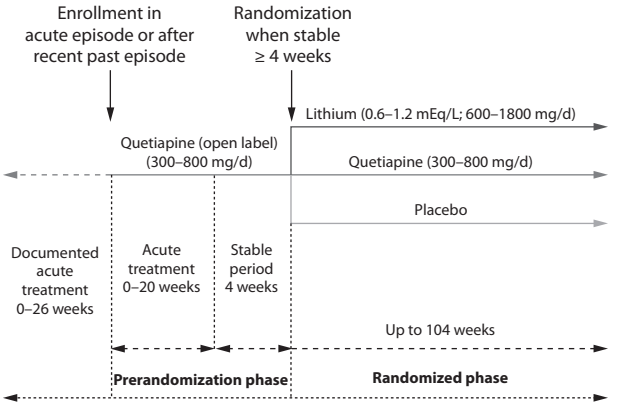
Study Medication

During the prerandomization phase, patients either initiated or continued open-label treatment with quetiapine (300–800 mg/d). Patients initiated on quetiapine received 100 mg on day 1, rising in 100-mg increments to 400 mg on day 4 and 600 mg on day 5. From day 6, the quetiapine dose was titrated by investigators between 300 and 800 mg/d, depending on efficacy and tolerance. Quetiapine was administered twice daily in divided doses.

Patients who fulfilled stability criteria were eligible for randomization to receive quetiapine, lithium, or placebo twice daily. Patients were randomized in balanced blocks with equal probability of receiving quetiapine, lithium, or placebo. Treatments given were determined by a randomization schedule prepared by the Biostatistical Group, AstraZeneca Research and Development, Södertälje, Sweden. Assignment of patients was through the Fisher Automated Clinical Trials Services centralized randomization and drug allocation system (Fisher Clinical Services, Allentown, Pennsylvania).

Using a double-dummy technique, quetiapine tablets and lithium capsules were identical in appearance and taste

Figure 1. Study Flow



to respective placebo medications. Quetiapine tablets used during the prerandomization phase were systematically replaced with tablets of the blinded investigational product according to a schedule designed by the investigator. Replacement started on day 1 and was completed by 2 weeks following randomization. During the randomized phase, the quetiapine dose was adjusted within the range of 300 to 800 mg/d, depending on efficacy and tolerance. The lithium dose was started at 600 mg/d and increased to 900 mg/d at day 4. After 2 weeks and subsequently at every visit, blood samples were taken for determination of trough serum lithium concentrations, and lithium doses were adjusted to obtain concentrations between 0.6 mEq/L and 1.2 mEq/L. To ensure blinding of lithium treatment, a programmed automatic system sent a reply for each blood sample and suggested a medication dosage for lithium or dummy recommendations for placebo.

Patients were allowed to continue medications for nonpsychiatric illnesses unless these medications were associated with known significant interactions with study medications. Low doses of zolpidem tartrate (maximum 10 mg/d), zaleplon (maximum 20 mg/d), zopiclone (maximum 7.5 mg/d), and chloral hydrate (maximum 1 g/d) for insomnia; lorazepam (maximum 2 mg/d) for anxiety; and anticholinergic medications for extrapyramidal symptoms (EPS) were permitted throughout the study. No other psychoactive medications were allowed in the 4 weeks prior to randomization or during the randomized phase.

Efficacy Measures

The primary outcome measure was the time to recurrence of any mood event (manic, depressed, or mixed). *Recurrence* was defined as at least 1 of the following: initiation of an antipsychotic, antidepressant, anxiolytic (other than lorazepam), or other medication to treat a mood event; hospitalization for a mood event; YMRS score ≥ 20 or MADRS score ≥ 20 at 2 consecutive assessments or final assessment if the patient discontinued[26,27]; or discontinuation from the study if, according to the investigator, discontinuation was due to a mood event.

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Table 1. Key Inclusion and Exclusion Criteria for the Prerandomization and Randomized Phases

Study Phase			
Prerandomization Phase		Randomized Phase	
Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years Male or female Bipolar I disorder (*DSM-IV*) ≥ 1 manic, mixed, or depressive episode in 2 years prior to index episode At enrollment, a current manic, mixed, or depressive episode (*DSM-IV*) or a past manic, mixed, or depressive episode treated with quetiapine (documented by medical records)	*DSM-IV* diagnosis of anxiety disorder treated with medication in the past year Known intolerance or lack of response to quetiapine or lithium Substance/alcohol dependence/abuse at enrollment (except caffeine or nicotine dependence) Use of cytochrome P450 3A4 inducers in 14 days prior to enrollment Unstable/inadequately treated medical illness Thyroid stimulating hormone > 10% above upper limit of normal Unstable diabetes mellitus (including enrollment HbA_{1c} > 8.5%, admission to hospital for diabetes or diabetes-related illness in past 12 weeks, change in oral hypoglycemic or insulin dose in past 4 weeks) Females of childbearing potential not using reliable method of contraception, or who were pregnant or lactating	Stabilization (YMRS score ≤ 12 and MADRS score ≤ 12) during last 4 weeks Treatment with quetiapine (300–800 mg/d) during last 4 weeks	Hospitalization due to mood episode or suicide or homicide attempt during prerandomization phase Electroconvulsive therapy during prerandomization phase Suicide or homicide attempt during prerandomization phase

Secondary outcome measures included the time to recurrence of a manic or a depressive event, based on the relevant mood event criteria described above. The time to all-cause discontinuation, which was defined as premature discontinuation due to a mood event or any other reason, was included as a measure of patient acceptance.

To evaluate interepisodic mood symptoms, the severity of manic and depressive symptoms was assessed using YMRS, MADRS, and Clinical Global Impressions-Bipolar (CGI-BP) Severity of Illness and Global Improvement rating scales.[28] Psychotic symptom severity was measured using the Positive and Negative Syndrome Scale—Positive symptom subscale (PANSS-P).[29] Patient-reported outcomes included the Sheehan Disability Scale (SDS) to assess functioning,[30] the Medical Outcomes Study Cognitive Scale (MOS-Cog) to assess cognitive symptoms,[31] and the Work Productivity and Activity Impairment Questionnaire (WPAI) to measure work productivity.[32] Times needed to complete parts A and B of the investigator-rated Trail Making Test (TMT) were also analyzed to assess cognitive symptoms.[33]

Assessments during the randomized phase were performed at weeks 0, 1, 2, 4, 6, 8, and every 4 weeks thereafter to week 104 (YMRS, MADRS, CGI-BP); at weeks 0, 4, 8, 12, 28, 40, 52, 68, 84, and 104 (PANSS-P); at weeks 0, 4, and every 4 weeks thereafter to week 104 (SDS); and at weeks 0, 4, 8, 12, 20, 28, 40, 52, 68, 84, and 104 or, if possible, whenever early termination occurred (MOS-Cog, WPAI, and TMT).

Safety Measures

The incidence and severity of adverse events and withdrawals due to adverse events were recorded at each assessment. Adverse events were reported using Medical Dictionary for Regulatory Activities (MedDRA) terminology (http://www.meddramsso.com).

Additional safety measures included laboratory assessments (fasting glucose, insulin, glycosylated hemoglobin [HbA_{1c}], and lipid levels), vital signs, weight, and body mass index (BMI), electrocardiogram (ECG) parameters, and physical examination. Movement disorders were assessed by the Simpson-Angus Scale (SAS),[34] Barnes Akathisia Rating Scale (BARS),[35] and Abnormal Involuntary Movement Scale (AIMS)[36] and by adverse events potentially associated with EPS (including akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, and dyskinesia). Suicidality was assessed independently by standardized methodology using Columbia-type analyses.[37]

Statistical Analyses

Time to recurrence of any mood event was analyzed by Cox proportional hazards modeling, with geographical region included as covariate. Hazard ratios (HRs) for time to recurrence of a mood event, with corresponding 95% CIs, were determined for quetiapine versus placebo, lithium versus placebo, and quetiapine versus lithium. The HR offers an estimate of the relative likelihood of a mood event and provides an assessment of treatment efficacy by comparing time to an event. The time to event was censored when a patient completed or discontinued the study without experiencing a manic, depressed, or mixed event. To reduce any adverse impact of potential discontinuation effects of open-label quetiapine on analyses and conclusions, a post hoc analysis was performed in which data were censored to exclude events within the first 4 weeks of randomized treatment.

The same Cox proportional hazards modeling was utilized to assess times to manic or depressive events (patients with mixed symptoms were allocated by investigators to groups according to predominance of manic or depressive

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symptoms). Times to any mood, manic, and depressive events and time to all-cause discontinuation were additionally explored by Kaplan-Meier estimates and curves.

Young Mania Rating Scale, MADRS, CGI-BP, PANSS-P, MOS-Cog, TMT, and WPAI scores were analyzed in the intent-to-treat (ITT) population using mixed-model repeated measures analysis of all assessments between randomization and up to but excluding the first mood event. Treatment, visit, and treatment-and-visit interaction were included in the model as fixed effects, with geographical region and baseline scores as covariates and subjects nested within treatment as random effects. The SDS total score was summarized for each patient using mean change from baseline across all assessments between randomization and up to but excluding the first mood event. Mean changes in SDS score were analyzed using analysis of covariance, with baseline SDS score and region as covariates and treatment as fixed effect.

For efficacy measures of time to any mood, manic, or depressive event, as well as change in SDS total score, a robust stepwise semisequential procedure was employed throughout the confirmatory part of the study to ensure a multiple level of significance of .05.

Descriptive statistics were used to report adverse events and summarize changes from baseline in laboratory test results, vital signs, ECG parameters, and SAS, BARS, and AIMS scores. For glucose and lipid parameters, 2 evaluations were conducted, 1 including all samples in the safety population regardless of fasting status (*presumed fasting*) and 1 in the sample subgroup for which the last meal was reported by patients >8 hours before sampling (*documented fasting*). In addition, incidence densities for glucose levels were calculated as ([total number of patients with glucose values ≥7.0 mmol/L emerging during randomized treatment/total patient-years of exposure] ×100), where the time until first value ≥7.0 mmol/L (or until the last dose, for patients without values ≥7.0 mmol/L) was calculated for each patient.

Primary efficacy analyses were conducted on the interim ITT population, which included all patients randomized to quetiapine or placebo for whom data were collected up to the interim date. To assess the robustness of conclusions from the primary analyses, secondary analyses were also performed on the total ITT population and on the per-protocol population—the subset of ITT patients without major protocol violations or deviations. Safety analyses were performed on the open-label safety population, including all patients who received treatment during the prerandomization phase and on the randomized safety population, including all patients who received treatment during the randomized phase.

Interim Analysis

Original plans called for the study to be terminated after 600 recurrences of mood events. Based on emerging evidence from 2 long-term studies,[24,25] which suggested that conclusive findings could be reached with a lower number of mood events, an interim analysis was added as an amendment to the study protocol. Interim analysis was conducted on patients randomized to quetiapine and placebo (but not lithium) by an external independent group of 3 statisticians following recurrence of approximately 150 manic and 150 depressive events. 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 to ensure an overall significance level of .05.[38,39]

RESULTS

Patients

A total of 2,438 patients were enrolled in the prerandomization phase (n = 1,174, manic; n = 710, depressed; and n = 554, mixed index episode), including 2,428 patients in the open-label safety population. Of the 2,438 patients enrolled, 1,226 (50.3%) were randomized and included in the randomized safety population, with 1,172 of these patients (95.6%) in the total ITT population (n = 404, quetiapine; n = 364, lithium; and n = 404, placebo). Reasons for discontinuation of open-label treatment, including discontinuation due to early study termination in 237 patients, are shown in Figure 2. Fifty-four patients were excluded from the ITT population because of inadequate serum lithium concentration monitoring (Figure 2). Another 206 patients in the ITT group were excluded from the per-protocol population, resulting in a per-protocol population of 966 patients (n = 382, quetiapine; n = 208, lithium; and n = 376, placebo). Most excluded patients were receiving lithium (n = 156) and primarily had median serum lithium concentrations outside the predefined therapeutic range of 0.6 to 1.2 mEq/L. The interim analysis was performed on the interim ITT population of 730 patients (n = 366, quetiapine and n = 364, placebo).

Demographic baseline disease characteristics did not differ between patients in the quetiapine, lithium, and placebo groups in the ITT population (Table 2). Treatment compliance based on pill counts was high and broadly equivalent in all groups. Use of lorazepam, sleep medication, and anticholinergic drugs was similar across treatment groups.

The mean (SD) of the patients' individual median daily quetiapine dose was 497 (195) mg in the prerandomization phase; for patients with manic, depressed, and mixed index episodes, the mean (SD) median dose was 532 (189) mg, 462 (189) mg, and 467 (201) mg, respectively. During the randomized phase, the mean (SD) median quetiapine dose was 546 (173) mg, with a median treatment duration of 158 days; for patients who presented with manic, depressed, and mixed index episodes, the mean (SD) median dose was 550 (176) mg, 527 (176) mg, and 562 (158) mg, respectively. For lithium, the mean (SD) median serum concentration was 0.63 (0.45) mEq/L in the ITT population (n = 346) and 0.77 (0.13) mEq/L in the per-protocol population (n = 208), with a median treatment duration of 83 days (ITT population). In the placebo group, the median exposure duration was 74 days. Total exposure to quetiapine in the prerandomization phase was 509 patient-years. In the randomized phase (ITT population), total exposures were 211 patient-years for

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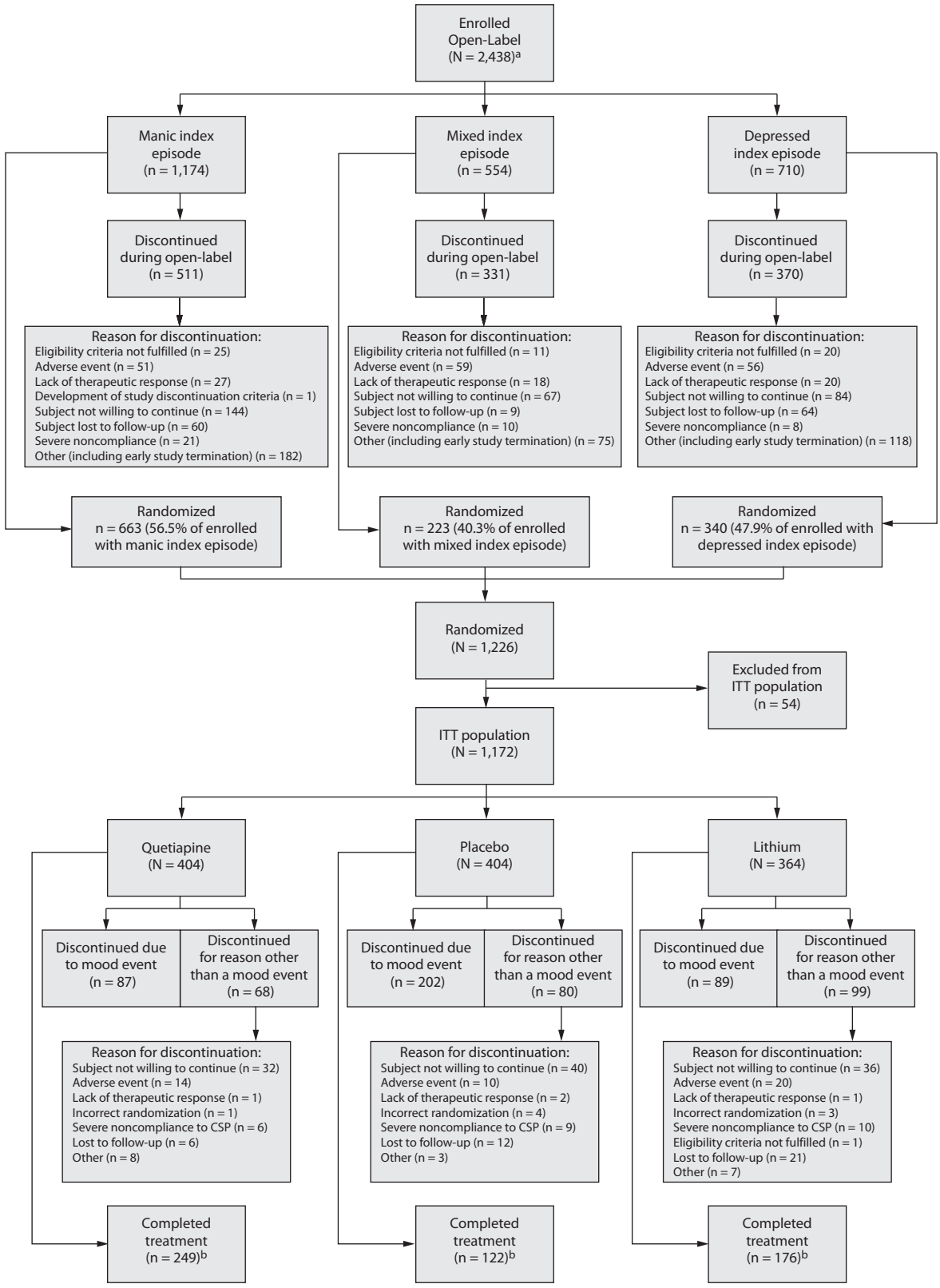
Figure 2. Disposition of Bipolar I Patients in the Prerandomization (all patients enrolled) and Randomized (ITT) Treatment Phases



[a]Of the 2,438 patients enrolled in the open-label study, 10 did not receive open-label treatment, hence the open-label safety population was 2,428 patients.
[b]*Completed treatment* was defined as completing maximum 104 weeks of randomized treatment or remaining on randomized treatment until the study was terminated per protocol.
Abbreviation: CSP = clinical study protocol.

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Table 2. Demographic and Current Disease Characteristics at Enrollment (all patients enrolled) and at Randomization (intent-to-treat population)

Demographic and Current Disease Characteristics	Prerandomization Phase Open-Label Quetiapine (N = 2,438)	Randomized Phase (intent to treat)			
		Quetiapine (n = 404)	Placebo (n = 404)[a]	Lithium (n = 364)	Total (N = 1,172)[a]
Sex, n (%)					
Male	1,131 (46.4)	182 (45.0)	210 (52.0)	155 (42.6)	547 (46.7)
Female	1,307 (53.6)	222 (55.0)	194 (48.0)	209 (57.4)	625 (53.3)
Age, mean (SD), y	38.4 (12.3)	39.9 (12.3)	40.0 (12.9)	38.4 (12.5)	39.5 (12.6)
Weight, mean (SD), kg	73.8 (19.5)	72.2 (18.9)	71.7 (17.7)	70.7 (19.7)	71.6 (18.7)
Race, n (%)					
White	1,597 (65.5)	259 (64.1)	260 (64.4)	221 (60.7)	740 (63.1)
Black	158 (6.5)	17 (4.2)	20 (5.0)	22 (6.0)	59 (5.0)
Asian	331 (13.6)	61 (15.1)	58 (14.4)	56 (15.4)	175 (14.9)
Other	352 (14.4)	67 (16.6)	66 (16.3)	65 (17.9)	198 (16.9)
DSM-IV bipolar I disorder, most recent episode, n (%)					
Mania	1,174 (48.2)	212 (52.5)	223 (55.2)	193 (53.0)	628 (53.6)
Depression	710 (29.1)	114 (28.2)	115 (28.5)	99 (27.2)	328 (28.0)
Mixed	554 (22.7)	78 (19.3)	66 (16.3)	72 (19.8)	216 (18.4)
With rapid-cycling course, n (%)					
Unknown	2 (0.1)	0 (0)	0 (0)	1 (0.3)	1 (0.1)
No	1,966 (80.6)	343 (84.9)	357 (88.4)	308 (84.6)	1,008 (86.0)
Yes	470 (19.3)	61 (15.1)	47 (11.6)	55 (15.1)	163 (13.9)
Rating scale total score, mean (SD)					
YMRS					
Overall	15.8 (11.1)	3.9 (3.7)	3.7 (3.6)	3.7 (3.5)	3.8 (3.6)
Index episode:					
Mania[b]	20.9 (8.8)	4.3 (3.9)	4.2 (3.8)	4.3 (3.6)	4.3 (3.8)
Depression[c]	6.3 (5.7)	2.7 (2.8)	2.3 (2.7)	2.5 (3.1)	2.5 (2.9)
Mixed[d]	17.3 (7.8)	4.5 (3.7)	4.4 (3.4)	3.8 (3.2)	4.25 (3.4)
MADRS					
Overall	15.1 (11.1)	3.55 (3.5)	3.4 (3.4)	3.3 (3.5)	3.4 (3.5)
Index episode:					
Mania[b]	6.8 (5.8)	2.4 (2.7)	2.4 (2.7)	2.2 (2.8)	2.3 (2.8)
Depression[c]	24.4 (8.3)	5.3 (3.8)	4.8 (3.9)	4.7 (3.6)	4.9 (3.8)
Mixed[d]	20.9 (9.6)	4.2 (3.7)	4.3 (3.6)	4.5 (3.8)	4.3 (3.7)

[a]Percentages may not add to 100 due to rounding.
[b]In prerandomization phase, n = 1,174; in randomized phase, n = 212 for quetiapine, n = 222 or 223 for placebo, and n = 193 for lithium.
[c]In prerandomization phase, n = 710; in randomized phase, n = 113 or 114 for quetiapine, n = 115 for placebo, and n = 99 for lithium.
[d]In prerandomization phase, n = 554; in randomized phase, n = 78 for quetiapine, n = 66 for placebo, and n = 72 for lithium.
Abbreviations: *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; MADRS = Montgomery-Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale.

Table 3. Hazard Ratios (HRs) for Time to Recurrence of Any Mood Event (primary outcome measure), Manic Event, or Depressive Event (intent-to-treat population)[a]

Study Population	Recurrent Event								
	Any Mood Event			Any Manic Event			Any Depressive Event		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Quetiapine versus placebo	0.29	0.23–0.38	< .0001	0.29	0.21–0.40	< .0001	0.30	0.20–0.44	< .0001
Lithium versus placebo	0.46	0.36–0.59	< .0001	0.37	0.27–0.53	< .0001	0.59	0.42–0.84	< .004
Quetiapine versus lithium	0.66	0.49–0.88	.005	0.78	0.53–1.16	.226	0.54	0.35–0.84	.006

[a]*Recurrence* was defined as the initiation of an antipsychotic, antidepressant, anxiolytic (other than lorazepam), or other medication to treat a mood event; hospitalization for a mood event; YMRS or MADRS total score ≥ 20 at 2 consecutive assessments or at the final assessment if the patient discontinued; or discontinuation from the study by the patient if, according to the investigator, discontinuation was due to a mood event.

quetiapine, 130 patient-years for lithium, and 131 patient-years for placebo.

Main Efficacy Measures

Interim analysis. The time to recurrence of any mood event in the interim ITT population (n = 730) was significantly longer in patients who continued quetiapine compared with patients who switched to placebo. The HR for the time to recurrence of any mood event for quetiapine versus placebo was 0.26 (95% CI, 0.19–0.35; $P < .0001$), corresponding to a risk reduction of 74% in favor of quetiapine. Based on positive results from the interim analysis, the study was terminated according to predefined criteria.

Primary outcome measure. Analysis of the total ITT population (n = 1,172) supported interim analysis by showing a significantly longer time to recurrence of any mood

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Figure 3. Time to Recurrence of Any Mood Event (primary outcome measure, Kaplan-Meier curves, ITT population)

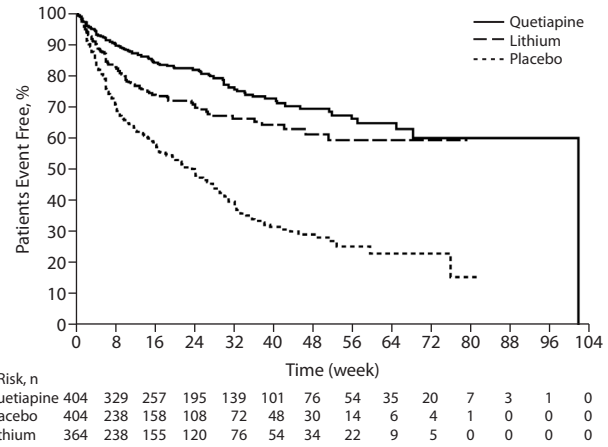


Figure 4. Time to All-Cause Discontinuation (Kaplan-Meier curves, ITT population)

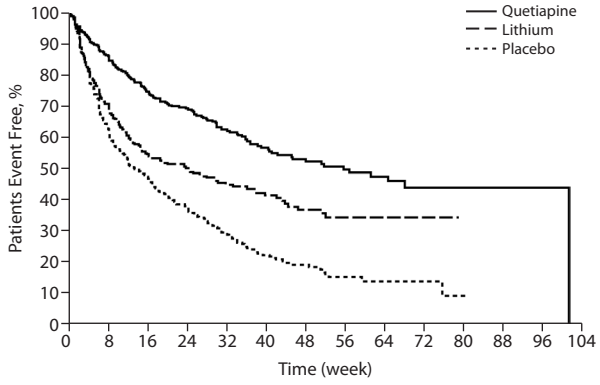


Figure 5. Time to Recurrence of a Manic Event (Kaplan-Meier curves, ITT population)

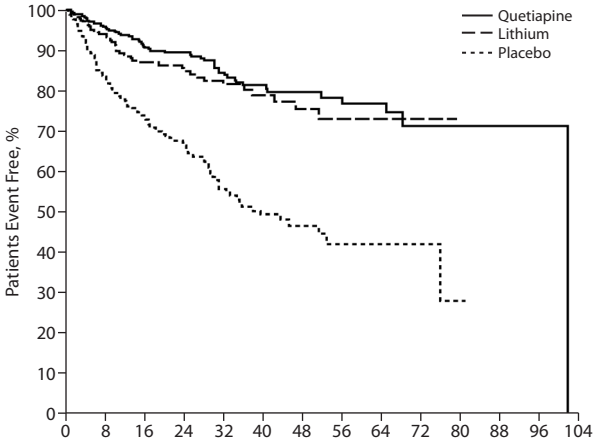
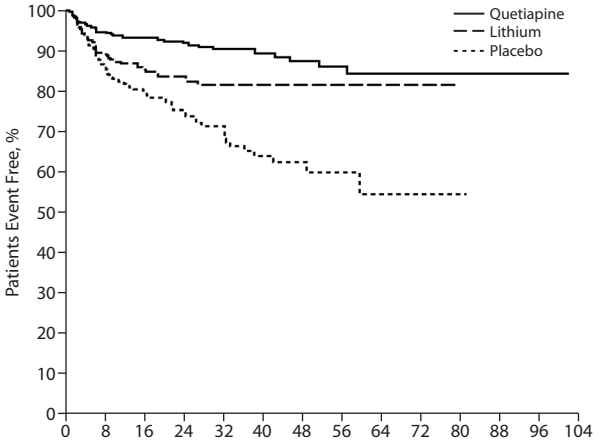


Figure 6. Time to Recurrence of a Depressive Event (Kaplan-Meier curves, ITT population)



event in patients who continued quetiapine compared with switching to placebo. The HR for the time to recurrence of any mood event for quetiapine versus placebo was 0.29 (95% CI, 0.23–0.38) (Figure 3). Continuation of quetiapine was also associated with a significantly longer time to recurrence of any mood event than switching to lithium. HRs for time to recurrence of any mood event for quetiapine versus placebo, lithium versus placebo, and quetiapine versus lithium are presented in Table 3.

When data were censored to exclude events in the first 4 weeks after randomization, the HR for the time to recurrence of any mood event was 0.27 ($P < .0001$) for quetiapine versus placebo, 0.41 ($P < .0001$) for lithium versus placebo, and 0.70 ($P = .041$) for quetiapine versus lithium in the ITT population.

Confirmatory analyses on the per-protocol population supported outcomes from the ITT population in demonstrating a significantly longer time to recurrence of any mood event for quetiapine versus placebo (HR = 0.28; 95% CI, 0.21–0.36; $P < .0001$) and for lithium versus placebo (HR = 0.34; 95% CI, 0.25–0.47; $P < .0001$), but without a significant difference between quetiapine and lithium (HR = 0.79; 95% CI, 0.55–1.13; $P = .194$).

Secondary outcome measures. Time to all-cause discontinuation was significantly longer in both the quetiapine and lithium groups compared with placebo and was significantly longer in the quetiapine than in the lithium group ($P < .0001$, all group comparisons; Figure 4).

In the ITT population, quetiapine and lithium were significantly more effective than placebo in increasing the time to manic and depressive events (Table 3, Figure 5, and Figure 6). Quetiapine was significantly more effective than lithium regarding time to recurrence of a depressive but not a manic event (Table 3).

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Table 4. Recurrence Rates and Hazard Ratios (HRs) for Time to Recurrence of Any Mood Event, Manic Event, or Depressive Event, Stratified According to Index Episode (intent-to-treat population)

Index Episode in Study Population	Recurrent Event		
	Any Mood Event	Any Manic Event	Any Depressive Event
Mania			
Quetiapine versus placebo	HR = 0.31 (95% CI, 0.22–0.44)	HR = 0.33 (95% CI, 0.22–0.48)	HR = 0.26 (95% CI, 0.13–0.54)
Quetiapine	23.6%	18.4%	5.2%
Placebo	48.4%	36.8%	11.7%
Lithium versus placebo	HR = 0.46 (95% CI, 0.33–0.65)	HR = 0.41 (95% CI, 0.27–0.61)	HR = 0.65 (95% CI, 0.35–1.19)
Lithium	26.4%	17.6%	8.8%
Placebo	48.4%	36.8%	11.7%
Depression			
Quetiapine versus placebo	HR = 0.29 (95% CI, 0.18–0.46)	HR = 0.26 (95% CI, 0.12–0.53)	HR = 0.32 (95% CI, 0.18–0.58)
Quetiapine	23.7%	9.6%	14.0%
Placebo	54.8%	22.6%	32.2%
Lithium versus placebo	HR = 0.47 (95% CI, 0.30–0.74)	HR = 0.30 (95% CI, 0.13–0.69)	HR = 0.58 (95% CI, 0.34–1.01)
Lithium	27.3%	7.1%	20.2%
Placebo	54.8%	22.6%	32.2%
Mixed			
Quetiapine versus placebo	HR = 0.26 (95% CI, 0.14–0.48)	HR = 0.18 (95% CI, 0.06–0.53)	HR = 0.32 (95% CI, 0.14–0.70)
Quetiapine	17.9%	6.4%	11.5%
Placebo	56.1%	22.7%	33.3%
Lithium versus placebo	HR = 0.48 (95% CI, 0.27–0.86)	HR = 0.34 (95% CI, 0.12–0.95)	HR = 0.57 (95% CI, 0.28–1.17)
Lithium	23.6%	6.9%	16.7%
Placebo	56.1%	22.7%	33.3%

Table 5. Hazard Ratios (HRs) for Time to Recurrence of Any Mood Event, Stratified According to Rapid-Cycling Status (intent-to-treat population)[a,b]

	Rapid Cycling			
	Yes		No	
Study Population	HR	95% CI	HR	95% CI
Quetiapine versus placebo	0.36	0.19–0.70	0.28	0.22–0.37
Lithium versus placebo	0.60	0.32–1.12	0.44	0.34–0.57
Quetiapine versus lithium	0.56	0.27–1.17	0.68	0.50–0.94

[a]Rapid-cycing: at least 4 mood episodes within the 12 months prior to enrollment.
[b]Number of patients with event/number of patients at risk: *Yes* group: quetiapine = 15/61; placebo = 25/47; lithium = 16/55; *No* group: quetiapine = 76/343; placebo = 183/357; lithium = 78/308.

When data were stratified by index episode (ITT population), quetiapine and lithium demonstrated advantages over placebo, regardless of whether patients entered the study with manic, depressive, or mixed index episodes (Table 4). In patients with and without rapid-cycling status (ie, at least 4 mood episodes within the 12 months prior to enrollment), quetiapine demonstrated advantages over placebo in increasing the time to recurrence of any mood event, with HRs of 0.36 and 0.28, respectively (Table 5).

Quetiapine, compared with placebo, was associated with significant improvements in interepisode scores on YMRS ($P = .002$), MADRS ($P < .001$), CGI-BP Severity of Illness ($P < .0001$), and CGI-BP Global Improvement scales ($P = .0025$), with a trend toward improvement on the PANSS-P ($P = .103$; Table 6). Quetiapine was additionally associated with significant improvements in interepisodic scores on the SDS ($P = .0011$), MOS-Cog ($P = .007$), and 2 of 4 measures on the WPAI (presenteeism [ie, impairment while working ($P = .014$)] and activity impairment [$P = .004$]), with placebo-like effects on the TMT (see Table 6). In interepisode scale scores, lithium differed significantly from placebo on the MOS-Cog ($P < .001$)and for 2 measures on the WPAI (presenteeism [$P = .018$] and activity impairment [$P = .006$]).

Safety and tolerability measures. During open-label treatment with quetiapine, 1,699 of 2,428 patients (70.0%) reported at least 1 adverse event, including 1275 patients (52.5%) with events judged to be drug-related. During this phase, 170 patients (7.0%) experienced adverse events leading to discontinuation, most commonly sedation (n = 40, 1.6%) and somnolence (n = 26, 1.1%). Serious adverse events leading to death were reported in 3 patients (0.1%), including 1 case each of cardiorespiratory arrest, cardiomyopathy, and gunshot wound (suicide/accidental gunshot); none of these deaths was considered related to quetiapine. Serious nonfatal adverse events were reported by 52 patients (2.1%).

During the randomized phase encompassing 1,226 patients in the safety population, 203 patients (50.2%) receiving quetiapine, 250 (59.8%) receiving lithium, and 228 (56.4%) receiving placebo reported an adverse event which was judged to be drug-related in 99 (24.5%), 143 (34.2%), and 102 (25.2%) patients, respectively. Adverse events led to discontinuation in 14 (3.5%), 20 (4.8%), and 13 (3.2%) patients in these respective groups. No single adverse event led to discontinuation in any group with an incidence > 1%. Serious adverse events were reported by 5 patients (1.2%) in the quetiapine, 10 (2.4%) in the lithium, and 11 (2.7%) in the placebo group. There were no deaths during the randomized phase.

Adverse events potentially associated with EPS were reported by 212 patients (8.7%) during the prerandomization phase. During randomized treatment, adverse events potentially associated with EPS were reported by 16 (4.0%), 38 (9.1%), and 18 (4.5%) patients receiving quetiapine,

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Table 6. Estimated Group Differences in Interepisode Score Changes for Secondary Efficacy Variables in All Patients (intent-to-treat population)[a]

	Quetiapine (n = 404) vs Placebo (n = 404)				Lithium (n = 364) vs Placebo (n = 404)			
Outcome Measure[b,c]	Difference	SE	95% CI	*P* Value	Difference	SE	95% CI	*P* Value
YMRS	−0.8	0.2	−1.2 to −0.3	.002	−0.5	0.3	−1.1 to 0.0	.053
MADRS	−1.4	0.3	−1.9 to −0.9	<.001	−0.6	0.3	−1.2 to 0.0	.066
CGI-BP-S	−0.19	0.05	−0.29 to −0.10	<.0001	−0.10	0.06	−0.21 to 0.00	.0551
CGI-BP-GI	−0.28	0.09	−0.45 to −0.10	.0025	−0.12	0.10	−0.32 to 0.08	.235
PANSS-P	−0.2	0.1	−0.4 to 0.0	.103	0.0	0.1	−0.3 to 0.2	.769
SDS	−1.16	0.36	−1.85 to −0.46	.0011	−0.68	0.37	−1.41 to 0.04	.0652
MOS-Cog	1.1	0.4	0.3 to 1.8	.007	1.5	0.4	0.6 to 2.4	<.001
WPAI								
Absenteeism[d]	−1.3	1.9	−5.0 to 2.5	.516	−2.2	2.5	−7.1 to 2.6	.368
Presenteeism[e]	−6.3	2.6	−11.4 to −1.3	.014	−7.0	2.9	−12.7 to −1.2	.018
Overall work impairment	−0.1	2.6	−5.3 to 5.0	.961	−4.0	3.0	−10.0 to 1.9	.184
Activity impairment	−7.6	2.6	−12.7 to −2.4	.004	−8.4	3.1	−14.4 to −2.4	.006
TMT								
Part A	2.5	3.2	−3.7 to 8.7	.429	−1.4	3.5	−8.2 to 5.5	.701
Part B	−8.4	4.5	−17.1 to 0.3	.060	−0.1	5.0	−9.8 to 9.6	.982

[a]Interepisode: period of time between consecutive mood events.
[b]All outcomes measures were analyzed using mixed model repeated measures, apart from SDS, which was analyzed using analysis of covariance.
[c]Negative score changes denote improvement, with the exception of the MOS-Cog scale.
[d]Work time missed.
[e]Impairment while working.
Abbreviations: CGI-BP-GI = Clinical Global Impressions-Bipolar Global Improvement, CGI-BP-S = Clinical Global Impressions-Bipolar Severity of Illness, MADRS = Montgomery-Asberg Depression Rating Scale, MOS-Cog = Medical Outcomes Study Cognitive Scale, PANSS-P = Positive and Negative Syndrome Scale Positive subscale, SDS = Sheehan Disability Scale, TMT = Trail Making Test, WPAI = Work Productivity and Activity Impairment Questionnaire, YMRS = Young Mania Rating Scale.

Table 7. Incidence and Incidence Density of Adverse Events (≥ 5% in any group) During the Prerandomization and Randomized Phases (open-label and randomized safety populations)

Prerandomization Phase		Randomized Phase (n = 1,626)						
			Quetiapine (n = 404)		Placebo (n = 404)		Lithium (n = 418)	
Adverse Event	Open-Label Quetiapine (N = 2,428) Incidence, n (%)	Adverse Event	Incidence, n (%)	Incidence Density[a]	Incidence, n (%)	Incidence Density[a]	Incidence, n (%)	Incidence Density[a]
Somnolence	621 (25.6)	Headache	36 (8.9)	18.4	32 (7.9)	27.3	48 (11.5)	32.2
Dry mouth	337 (13.9)	Somnolence	27 (6.7)	13.6	17 (4.2)	13.5	11 (2.6)	6.6
Sedation	311 (12.8)	Insomnia	26 (6.4)	13.0	69 (17.1)	61.3	52 (12.4)	34.6
Dizziness	224 (9.2)	Nausea	18 (4.5)	8.8	33 (8.2)	26.8	53 (12.7)	34.5
Headache	200 (8.2)	Tremor	12 (3.0)	5.8	8 (2.0)	6.2	31 (7.4)	19.5
Constipation	168 (6.9)	Diarrhea	11 (2.7)	5.3	21 (5.2)	16.8	26 (6.2)	16.5
Weight increase	127 (5.2)	Vomiting	8 (2.0)	3.9	12 (3.0)	9.4	47 (11.2)	29.9

[a]Incidence density was calculated as (total number of patients with event/total patient-years of exposure) × 100.

lithium, and placebo, respectively. There were no apparent differences between treatment groups for changes in mean SAS, BARS, or AIMS score during randomized treatment. Most patients in each treatment group had no worsening in EPS rating scale score during the randomized phase. Occurrences of the other most commonly reported adverse events during the prerandomization and randomized phases are shown in Table 7, together with incidence densities that adjust for different durations of treatment in the 3 groups.

A suicide attempt was an exclusion criterion for entry to the randomized phase (see Table 1). Columbia-type analyses during the randomized phase indicated that the overall incidence of *suicidal behavior/ideation* was low and similar in the quetiapine (n = 3, 0.74%), lithium (n = 3, 0.72%), and placebo (n = 8, 1.98%) groups. Relative risks of suicidal behavior/ideation were 0.38 (95% CI, 0.10–1.40) for quetiapine versus placebo, 0.36 (95% CI, 0.10–1.36) for lithium versus placebo, and 1.03 (95% CI, 0.21–5.10) for quetiapine versus lithium.

Mean changes in body weight, BMI, blood glucose, HbA_{1c}, insulin, and lipid parameters during the prerandomization and randomized phases are shown in Table 8. Clinically important elevations in blood glucose (ie, ≥ 7.0 mmol/L) at any time after randomization in subgroups with documented fasting glucose concentrations were recorded in 30 patients (8.5%) in the quetiapine, 17 (4.4%) in the lithium, and 13 (3.5%) in the placebo group. Incidence densities for documented fasting glucose concentrations ≥ 7.0 mmol/L were 16.4, 11.4, and 11.4 per 100 patient-years, respectively, in these groups. The incidence of adverse events potentially related to diabetes (including thirst, polyuria, diabetes mellitus, an increase in blood glucose, an increase in blood insulin, diabetes mellitus type 1 and type 2, diabetic complication, an increase in HbA_{1c}, hyperinsulinemia, or polydipsia) was 1.5% in the quetiapine, 1.4% in the lithium, and 0.2% in the placebo group during randomized treatment.

Changes in thyroid laboratory data during the randomized phase were generally small in all groups. Mean

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Table 8. Mean Changes in Weight and Selected Laboratory Assessments During the Prerandomization and Randomized Treatment Phases (open-label and randomized safety populations)

	Prerandomization Phase Open-Label Quetiapine (N = 2,428)	Randomized Phase (n = 1,626)		
		Quetiapine (n = 404)	Placebo (n = 404)	Lithium (n = 418)
Body weight change				
Weight change, mean (SD), kg	1.72 (4.06)	0.63 (4.70)	−1.51 (4.05)	−0.92 (3.67)
Weight increase ≥ 7%, %[a]	16.8	10.6	2.6	5.4
BMI change, mean (SD), kg/m^2	0.62 (1.49)	0.24 (1.73)	−0.55 (1.53)	−0.33 (1.35)
Laboratory change, mean (SD)[b]				
Glucose, mmol/L	0.21 (1.02)	0.06 (1.21)	0.13 (1.10)	0.18 (0.88)
HbA_{1c}, %	0.05 (0.41)	0.12 (0.42)	0.06 (0.41)	−0.07 (0.40)
Insulin, pmol/L	24.53 (122.15)	9.69 (127.12)	8.59 (129.89)	0.29 (134.37)
TC, mmol/L	0.18 (0.94)	−0.18 (0.85)	−0.37 (0.81)	−0.43 (0.76)
LDL-C, mmol/L	0.13 (0.76)	−0.08 (0.74)	−0.22 (0.71)	−0.32 (0.66)
HDL-C, mmol/L	−0.03 (0.28)	−0.04 (0.30)	0.00 (0.28)	−0.01 (0.27)
Triglycerides, (mmol/L)	0.17 (1.35)	−0.14 (1.27)	−0.36 (1.37)	−0.26 (1.1)
Shift in laboratory parameters, n/n (%)[c]				
Glucose < 7.0 to ≥ 7.0 mmol/L	NA	30/355 (8.5)	13/370 (3.5)	17/390 (4.4)
TC < 6.21 to ≥ 6.21 mmol/L	NA	27/314 (8.6)	17/316 (5.4)	11/335 (3.3)
LDL-C < 4.2 to ≥ 4.2 mmol/L	NA	28/344 (8.1)	14/332 (4.2)	13/353 (3.7)
HDL-C > 1.04 to ≤ 1.04 mmol/L	NA	58/257 (22.6)	45/261 (17.2)	40/269 (14.9)
Triglycerides < 2.26 to ≥ 2.26 mmol/L	NA	52/266 (19.5)	22/287 (7.7)	22/294 (7.5)

[a]At end of treatment period.
[b]Mean changes are from enrollment to end of prerandomization treatment or from randomization to end of randomized treatment in all samples (documented fasting).
[c]Proportion of patients with normal values at randomization and with clinically important changes in laboratory parameters at any time (documented fasting).
Abbreviations: BMI = body mass index, HbA_{1c} = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NA = not applicable, TC = total cholesterol.

thyroid-stimulating hormone (TSH) levels increased in the lithium group (2.02 μU/mL), compared with a decrease in the placebo group (0.39 μU/mL) and no change in the quetiapine group. More patients had clinically relevant elevated TSH values (> 5 μU/mL) during randomized treatment in the lithium group (n = 69/343, 20.1%) compared with the placebo (n = 10/338, 3.0%) and quetiapine groups (n = 11/350, 3.1%).

There were no major differences between treatment groups for changes in vital signs, ECG parameters, or physical examination findings during randomized treatment.

DISCUSSION

This is the first large, randomized, placebo-controlled study to evaluate the efficacy and safety of quetiapine monotherapy in the maintenance treatment of bipolar I disorder. Using a trial design frequently used to assess efficacy for other drugs in the maintenance treatment of bipolar disorder, continuation of quetiapine at doses between 300 mg/d and 800 mg/d was associated with a significantly longer time to recurrence of any mood event when compared with switching to placebo in patients who had stabilized on quetiapine. In addition, quetiapine was associated with significantly longer times to both manic and depressive events, regardless of whether the patient's index episode was manic, depressive, or mixed, suggesting that quetiapine possesses equivalent efficacy against both poles of the illness. Following dose titration based on efficacy and tolerance, the mean median quetiapine dose was 546 mg/d for all patients during the randomization phase. Both the mean median quetiapine dose and the range of quetiapine doses were broadly similar during the randomization phase in patients who presented with manic, depressed, or mixed index episodes.

These findings add to existing data from 2 large-scale studies[24,25] with a similar design that demonstrated the efficacy of quetiapine as adjunct to lithium or divalproex in the maintenance therapy of patients with bipolar I disorder. The findings regarding patients with an index depressive episode can also be compared with the outcomes of the continuation phases (up to 52 weeks) of 2 previous studies of the efficacy and safety of quetiapine monotherapy in patients with bipolar I or bipolar II depression.[7,8] Combined data from the continuation phases of these 2 studies indicate that, in patients previously treated with quetiapine, continued quetiapine treatment significantly increased the time to recurrence of any mood event or depressive event compared with placebo, while there was no statistically significant difference regarding time to recurrence of a manic/hypomanic event.[40] As such, quetiapine is the first and so far the only atypical antipsychotic shown to be effective as maintenance treatment in the prevention of both manic and depressive recurrences of bipolar I disorder. Moreover, this effect of quetiapine was observed as monotherapy and as an add-on to lithium or divalproex.

This trial also demonstrated the efficacy of lithium monotherapy as maintenance treatment relative to placebo. Lithium prevented both manic and depressive events, which contrasts with the results of a meta-analysis by Geddes et al.[41] Their analysis of long-term studies with lithium, which excluded trials that randomly assigned patients who had been stable on long-term lithium regimens to continue or suddenly discontinue the drug, reported significant efficacy for lithium in the prevention of manic but not depressive episodes.

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The current trial also allows comparisons of quetiapine versus lithium. Continuation of quetiapine was associated with significantly longer times to recurrence of any mood event than switching to lithium. However, this observation should be interpreted with caution, because of the enriched design's resulting in a selection bias in favor of quetiapine, as all patients had both responded to and tolerated quetiapine during the prerandomization phase. For a fair comparison of quetiapine and lithium, other designs are warranted, such as starting with combined quetiapine and lithium during the prerandomization phase and then randomization to quetiapine monotherapy, lithium monotherapy, switch to placebo, and, as a potential fourth arm, continuation of combined quetiapine and lithium. An alternative option would be randomization of patients to quetiapine or lithium (and, potentially, to placebo or combination therapy) during the index episode. Another point of note is that the mean median serum lithium concentration in the ITT population (0.63 mEq/L) was at the lower limit of the target range of 0.6–1.2 mEq/L. This indicates that lithium was possibly not optimally dosed in this study and/or that medication adherence adversely impacted lithium levels.[42–44]

Quetiapine was generally well tolerated across the dose range 300 to 800 mg/d during randomized treatment. Rates of quetiapine-associated emergent adverse events as well as adverse events leading to discontinuation were lower in the randomized phase than the prerandomization phase, during which all patients received quetiapine. This suggests that patients who experienced quetiapine-associated adverse events were more likely to discontinue during the prerandomization phase and were less likely to enter the randomized phase.

There was a mean increase in body weight of 1.72 kg during the prerandomization phase, while, during the longer randomized phase, there were mean weight changes of +0.63 kg in the quetiapine, –0.92 kg in the lithium, and –1.51 kg in the placebo group. Mean blood glucose concentrations (documented fasting) increased by 0.21 mmol/L during the prerandomization phase, followed during the randomization phase by a mean increase of 0.06 mmol/L in patients receiving quetiapine, compared with increases of 0.18 mmol/L and 0.13 mmol/L in patients receiving lithium and placebo, respectively. The incidence density of a single-emergent fasting blood glucose value ≥ 7.0 mmol/L in patients with documented fasting was higher in the quetiapine than lithium and placebo groups. However, the samples tested could not be confirmed as fasting because, despite an 8-hour interval following the last meal, patients could have ingested calories from other sources.

This study was not designed to identify the emergence of diabetes mellitus based on fasting blood glucose assessments, which requires confirmation of fasting values ≥ 7.0 mmol/L within a few days of initial testing.[45] Blood samples in the current study were taken 12 weeks apart, with no requirement for repeating abnormal assessments. Given the absence of definitive diagnostic testing within the design of this study, reliable and accurate determination of the incidence and risk of diabetes mellitus in patients enrolled in the study is not possible.

As for other atypical antipsychotics, it is important that clinicians consider the appropriate assessment of metabolic parameters during quetiapine therapy. Patients with an established diagnosis of diabetes mellitus should be monitored regularly for worsening of glucose control, while patients with risk factors for diabetes mellitus should undergo fasting blood glucose measurement before starting therapy, with periodic monitoring during treatment. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing. Most patients will benefit from encouragement to exercise regularly, follow a healthy diet, and maintain an optimal weight. Close clinical monitoring of the weight and BMI of patients periodically throughout the treatment period is essential. Physicians are also advised that blood lipid levels may be affected by atypical antipsychotics.

In conclusion, this study demonstrates for the first time that quetiapine, as well as lithium, is effective as monotherapy in the prevention of manic as well as depressive recurrences in the maintenance treatment of bipolar I disorder in patients who had stabilized during open-label treatment with quetiapine. Together with the previous findings for quetiapine in combination with lithium or divalproex,[24,25] the results of this study increase therapeutic opportunities for bipolar patients requiring long-term treatment.

Drug names: aripiprazole (Abilify), fluoxetine (Prozac and others), lithium (Lithobid and others), lorazepam (Ativan and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), quetiapine (Seroquel), zaleplon (Sonata and others), zolpidem (Ambien, Edluar, and others).

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Author contributions: For this article, Dr Weisler contributed to the acquisition, analysis, and interpretation of data, the drafting and critical revision of the manuscript, and the supervision of manuscript development. Dr Nolen served as advisor for the analysis and interpretation of the results, especially regarding the lithium arm, and contributed to the drafting and critical revision of the manuscript. Ms Hellqvist contributed to the analysis and interpretation of data and the critical revision of the manuscript. Dr Paulsson contributed to the conception and design of the study, the acquisition, analysis, and interpretation of data, and the drafting and critical revision of the manuscript. Dr Neijber contributed to the acquisition, analysis, and interpretation of data and the drafting and critical revision of the manuscript.

Please see the eAppendix at PSYCHIATRIST.COM ***for the list of Trial 144 study investigators.***

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Centers for Disease Control and Prevention, the NIMH, Abbott, AstraZeneca, Biovail, Bristol-Myers Squibb, Cephalon, Corcept, Eli Lilly, Forest, GlaxoSmithKline, Johnson & Johnson, Medscape Advisory Board, Organon, Otsuka America Pharma, Pfizer, Pharmacia, Sanofi, Sanofi-Synthelabo, Shire, Solvay, Sunovion, Takeda, Transcept Pharma, TransTech, Validus, and Wyeth; has been on Speaker's Bureaus of Abbott, AstraZeneca, Biovail, Bristol-Myers Squibb, Burroughs Wellcome, Cephalon, Ciba Geigy, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson, Novartis, Organon, Pfizer, Sanofi, Sanofi-Synthelabo, Shire, Solvay, Sunovion, Validus, and Wyeth; and has held or holds stock in Bristol-Myers Squibb, Cortex, Merck, and Pfizer. **Dr Nolen** has received research grants from the Netherlands Organization for Health Research and Development, the European Union, the Stanley Medical Research Institute, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Wyeth; has received honoraria/speaker's fees from AstraZeneca, Eli Lilly, Pfizer, Servier, and Wyeth; and has served in advisory boards for AstraZeneca, Cyberonics, Pfizer, and Servier. **Ms Hellqvist** and **Dr Paulsson** are employees, and **Dr Neijber** is a former employee, of AstraZeneca R&D.
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