Research Article

EFFICACY AND TOLERABILITY OF EXTENDED RELEASE QUETIAPINE FUMARATE MONOTHERAPY AS MAINTENANCE TREATMENT OF MAJOR DEPRESSIVE DISORDER: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Background: *Primary objective: evaluate the efficacy (time to recurrence of depressive symptoms) of once daily extended release quetiapine fumarate (quetiapine XR) as maintenance monotherapy treatment to prevent relapse for major depressive disorder (MDD).* **Methods:** *Time-to-event (maximum 52 weeks), double-blind, multicenter, randomized withdrawal, placebo-controlled study of quetiapine XR (50–300 mg/day) comprising four treatment phases: enrollment (up to 28 days), open-label run-in (4–8 weeks), open-label stabilization (12–18 weeks), and randomization (up to 52 weeks). Seven hundred and seventy-six patients stabilized on quetiapine XR were eligible for randomization (Montgomery–Åsberg Depression Rating Scale [MADRS] score $\leq$12 and Clinical Global Impression-Severity of Illness [CGI-S] score $\leq$3); 391 received quetiapine XR and 385 received placebo (same dose as last open-label visit). Primary endpoint: time to recurrence of depressive event from randomization. Secondary outcomes included changes from randomization in MADRS total, CGI-S, Pittsburgh Sleep Quality Index (PSQI) global, and Hamilton Anxiety Rating Scale (HAM-A) total scores. Adverse events were recorded throughout.* **Results:** *Risk of recurrence of depressive event was significantly ($P<.001$) reduced by 66% (HR = .34; 95% CI: .25, .46) in patients*

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randomized to continue with quetiapine XR versus patients randomized to switch to placebo. During the randomized phase, quetiapine XR maintained improvements in secondary outcomes (P<.001 for all): MADRS (0.15 versus 2.03), CGI-S (−0.03 versus 0.23); PSQI global (0.06 versus 1.35), and HAM-A total score (0.20 versus 1.58), respectively. The most common AEs (>10% any group) during the randomized period were headache and insomnia. **Conclusions:** ***Quetiapine XR maintenance therapy significantly reduced the risk of a depressive event in patients with MDD stabilized on quetiapine XR, with a safety and tolerability profile consistent with the known profile of quetiapine. Depression and Anxiety 27:964–976, 2010.***

Key words: *atypical antipsychotics; depression; efficacy; major depressive disorder; monotherapy; Phase III study; quetiapine; tolerability*

INTRODUCTION

Up to 80% of patients with major depressive disorder (MDD) experience recurrent depression during their lifetime[1] and approximately 30% relapse within 1 year of receiving antidepressant treatment in a primary-care setting.[2]

Several agents can be used in the treatment of MDD (including selective serotonin reuptake inhibitors [SSRIs], serotonin-noradrenaline/norepinephrine reuptake inhibitors [SNRIs], tricyclic antidepressants, and monoamine oxidase inhibitors [MAOIs]). However, it can take 2–4 weeks of treatment before patients begin to respond.[3] Moreover, around 50% of patients do not achieve a response and 60–70% do not achieve full remission of symptoms.[4,5] Residual symptoms of MDD are associated with relapse, which increases the risk of suicide, functional impairment, and utilization of health-care resources.[6] Additionally, the tolerability profiles of antidepressants, which may impact on patients' adherence to treatment, should also be considered.[7] As patients with MDD may require long-term therapy, there is a need for additional treatment options that maintain their antidepressant effect over time.

Two randomized, placebo-controlled trials showed quetiapine monotherapy to be effective for the acute treatment of patients with bipolar I or II depression,[8–10] whereas the long-term efficacy of quetiapine monotherapy in patients with bipolar depression has been confirmed in two maintenance studies.[11,12] In patients with MDD, once daily extended release quetiapine fumarate (quetiapine XR) has demonstrated acute efficacy as monotherapy[13–15] and adjunct therapy.[16,17]

The mode of action of quetiapine has not been fully understood. Although questions remain, the recent characterization of the major active human metabolite, norquetiapine (N-desalkylquetiapine) has provided potential new mechanistic explanations for the antidepressant effects seen in clinical trials.[18] Both quetiapine and norquetiapine are antagonists at serotonin 5-HT_{2A} and dopamine D_2 receptors, exhibiting moderate-to-high affinity for these receptor subtypes. Norquetiapine is also a potent inhibitor of the norepinephrine transporter (NET).[18,19] Evidence for the clinical relevance of these findings has been supported by positron emission tomography imaging of NET occupancy in quetiapine-treated subjects.[20] Other atypical antipsychotics have not demonstrated NET inhibition at clinically relevant doses; however, it is a property shared by a number of traditional antidepressant therapies, such as SNRIs, and is believed to contribute to the antidepressant effect of quetiapine.[21]

This study assessed the efficacy and tolerability of quetiapine XR monotherapy as maintenance treatment for patients with MDD stabilized with quetiapine XR.

MATERIALS AND METHODS

STUDY DESIGN AND TREATMENT

This double-blind, randomized withdrawal, parallel group, multicenter, placebo-controlled study (Amethyst; D1448C00005) comprised four treatment phases: enrollment (up to 28 days), open-label run-in (4–8 weeks), open-label stabilization (12–18 weeks), and randomization (up to 52 weeks). Patients continued in the randomized phase for up to 52 weeks, or until they met the criteria for a depressive event. Pre-defined rules specified that the study be stopped after (a) 101 depressive events had occurred after randomization and (b) ≥88 depressive events occurred ≥30 days after randomization. Centers were notified when the pre-specified number of events was approaching so that they could prepare for study termination.

During the open-label run-in phase, patients received quetiapine XR 50 mg/day on Days 1 and 2 and increasing to 150 mg/day on Days 3 and 4. The dose could be increased to 300 mg/day on Day 5, based on the investigator's clinical judgment. Patients started the open-label stabilization phase on the same dose of quetiapine XR as they exited the open-label run-in phase. Patients meeting randomization criteria (stable for ≥12 weeks) were randomized to continue with quetiapine XR or switched to placebo at the same dose as the last visit of the open-label stabilization phase. During the stabilization and randomization phases, investigators were permitted to adjust the dosage to 50, 150, or 300 mg/day, as clinically indicated. Quetiapine XR was administered once daily in the evening.

This study was approved by the institutional review boards for each study site and performed in accordance with the Declaration of

Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Written informed consent was obtained from all patients before participation.

PATIENTS

Male or female outpatients (18–65 years), with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth edition, Text Revision (DSM-IV TR) diagnosis of single episode or recurrent MDD, were eligible for inclusion. Patients were required to have a 17-item Hamilton Depression Rating Scale (HAM-D)[22] total score ≥ 20 and HAM-D Item 1 (depressed mood) score ≥ 2 at enrollment. For inclusion in the open-label stabilization and randomized phases, patients were required to have a Montgomery–Åsberg Depression Rating Scale (MADRS)[23] total score ≤ 12 and a Clinical Global Impression-Severity of Illness (CGI-S)[24] score ≤ 3 (mild illness). Additionally, for inclusion in the randomized phase, patients were required to have received quetiapine XR for ≥ 12 weeks during the open-label stabilization phase.

Exclusion criteria were: diagnosis of a DSM-IV TR Axis I disorder other than MDD within 6 months before enrollment or any DSM-IV TR Axis II disorder, which would significantly impact on their current psychiatric status; current MDD episode duration >12 months or <4 weeks from enrollment; history of inadequate response to 6 weeks' treatment with ≥ 2 classes of antidepressants during the current depressive episode; current serious suicidal or homicidal risk; HAM-D Item 3 score ≥ 3; suicide attempt within 6 months of enrollment; substance dependence or abuse <6 months before enrollment; any clinically significant medical illness; and any clinically significant deviation from reference range in clinical laboratory test results. Before the open-label run-in phase, patients could not have received: any antipsychotic, mood stabilizer, anticonvulsant (except carbamazepine), or antidepressant medications within 7 days; MAOIs, anxiolytics, or hypnotics within 14 days; or fluoxetine within 28 days. Psychotherapy was permitted during the study period if it had been ongoing for ≥ 3 months before enrollment.

Patients were discontinued from the study during the open-label stabilization phase if they: were hospitalized for depressive symptoms; attempted suicide; were at risk of a suicide attempt, had a MADRS score ≥ 15 at two consecutive visits; had a CGI-S score ≥ 5 (severely ill); or initiated prohibited pharmacological treatment for depressive symptoms. The same criteria applied to the randomized phase (except MADRS score ≥ 18). These criteria ensured stabilized patients entered the randomized phase.

EFFICACY EVALUATIONS

Primary analysis and definition of a depressive event. The primary efficacy variable was time from randomization to recurrence of a depressive event (relapse). A depressive event was defined as ≥ 1 of the following: (a) initiation of pharmacological treatment by the investigator to treat depression or self-medication with prohibited medications for ≥ 1 week, (b) hospitalization for depressive symptoms, (c) MADRS score ≥ 18 at 2 consecutive assessments 1 week apart, or at the final assessment if patient discontinued, (d) CGI-S score ≥ 5, and (e) suicide attempt or discontinuation from the study due to imminent risk of suicide. Investigators identified depressed events throughout the study and before database lock, the depressed event criteria were reviewed in the blinded data to determine if any patients meeting these criteria had been missed.

Secondary efficacy variables. The secondary efficacy variables evaluated the efficacy of quetiapine XR versus placebo in maintaining improvement of symptoms and were change from randomization to study end in MADRS total score, CGI-S score, HAM-A total,[25] and psychic and somatic cluster scores, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q: SF) percentage maximum total score,[26] Q-LES-Q Item 15 (satisfaction with medication) and Item 16 (overall life satisfaction) scores, Pittsburgh Sleep Quality Index (PSQI) global score,[27] and Sheehan Disability Scale (SDS) Global Functional Impairment score.[28]

To ensure consistency throughout the study, each rater administering the MADRS, HAM-A, HAM-D, and CGI scales received training in conducting these assessments and only qualified raters were permitted to conduct assessments. In addition, certification was required for MADRS and HAM-D scale administration. Only qualified physician raters administered the CGI. To reduce scoring variability, it was recommended that the same rater conducted all assessments for a given patient for a specific scale throughout the course of the study.

SAFETY AND TOLERABILITY

Safety and tolerability analyses considered changes from enrollment and changes from randomization, providing data from the open-label (run-in and stabilization) and randomized (maintenance) phases. Adverse events (AEs), serious AEs (SAEs), and withdrawals due to AEs were recorded during these phases.

Treatment discontinuation symptoms (TDSS) in randomized patients were measured for 14 days following the last dose of open-label treatment using an 18-item TDSS scale. This scale was a modification of the 17-item scale developed by Michelson et al.[29] based on the 43-item Discontinuation Emergent Signs and Symptoms scale,[30] with the inclusion of the additional TDSS of vomiting, nausea, and insomnia, as these are known to be potential AEs associated with quetiapine XR.

The incidence of suicidality was assessed during the open-label and randomized phases using MADRS Item 10 score (suicidal thoughts).

Tolerability was assessed through physical and laboratory measurements (enrollment, end of open-label treatment, randomization, and end of randomization) and electrocardiogram (ECG) recordings (enrollment, randomization, and Weeks 28 and 52 [or final visit] of the randomized phase). Measurements of vital signs (blood pressure and pulse rate) were performed at every visit. Changes in body weight were recorded at enrollment, 12, and 24 weeks after initiation of treatment at randomization; and at Weeks 12, 24, 36, 48, and 52 (or final visit) of the randomized phase.

Extrapyramidal symptoms (EPS) were assessed by the Simpson–Angus Scale (SAS),[31] Barnes Akathisia Rating Scale (BARS),[32] and Abnormal Involuntary Movement Scale (AIMS).[33] All investigators performing BARS and SAS ratings received instructions on how to use these scales and it was recommend that the same rater conduct all assessments for a given patient.

STATISTICAL ANALYSIS

A Cox proportional hazards model, which took into account the time in study for each patient, was used to analyze the primary efficacy variable during the randomized phase and to estimate a hazard ratio (HR) and associated 95% confidence interval (CI) comparing the risk of a depressive event with quetiapine XR versus placebo.

For all secondary variables, the mean of all assessments between randomization and up to, but excluding, the visit where a depressive event was recorded and an analysis of covariance model (with score at randomization, treatment, and center as fixed effect) were used. If no depressive event was recorded for a patient, all visits after randomization with available score data were used.

All statistical analyses were two-sided with a significance level of 5%. Descriptive statistics were provided for all variables.

Data analyses were performed on the open-label safety population (all patients who entered the open-label phase and received study drug), the randomized safety population (all patients who received randomized study treatment during the randomized phase, classified by actual treatment taken), and the intention-to-treat (ITT) population (randomized patients who received study drug, classified by the treatment they were intended to receive).

RESULTS

PATIENTS

One thousand eight hundred and seventy-six patients were enrolled at 237 centers in Europe (Bulgaria, Finland, France, Germany, Romania, Russia, the Slovak Republic, and the United Kingdom), Canada, South Africa, and the United States between December 22, 2005 and August 1, 2007. One thousand eight hundred and fifty-four patients received quetiapine XR during the open-label phase. Seven hundred and eighty-seven patients completed the open-label stabilization phase, 776 patients were randomized to receive quetiapine XR ($n = 391$) or placebo ($n = 385$), and 15 patients ($n = 10$ quetiapine XR; $n = 5$ placebo) completed 52 weeks of treatment (Fig. 1). The study design and pre-defined number of events meant that 45.1% of randomized patients were discontinued when the study was terminated by the sponsor. The study was stopped when both the pre-defined number of depressive events had been reached (≥ 101) and when ≥ 88 depressive events had occurred ≥ 30 days after randomization. At study termination, 187 patients had experienced a depressive event (including 98 patients who experienced a depressive event after 30 days of randomized treatment).

The open-label safety population comprised 1,854 patients, open-label only population of 1,078 patients, randomized safety population of 776 patients (quetiapine XR $n = 391$; placebo $n = 385$), and ITT population of 771 patients (quetiapine XR $n = 387$; placebo $n = 384$). Five patients were excluded from the ITT population because the associated site was not compliant with good clinical practice.

Baseline demographic and clinical characteristics were similar across treatment groups (Table 1).

TREATMENT

The mean (SD) daily dose of quetiapine XR during the open-label phase (total amount of study drug taken during the phase divided by the number of days on treatment) was 160.2 mg/day (81.4). At the end of the open-label phase, those patients who went on to receive randomized treatment with quetiapine XR were receiving doses of 50 mg/day (23.3%), 150 mg/day (43.5%), and 300 mg/day (33.2%) quetiapine XR. At randomization (last open-label dose) the mean [SD] dose of quetiapine XR was similar for the quetiapine XR (176.6 mg/day [95.5]) and placebo (177.9 mg/day [90.8]) groups. In total, 89% ($n = 348$) of quetiapine XR patients received the same dose at study end, as at the end of the open-label phase, 5.1% ($n = 20$) received a higher dose and 5.9% ($n = 23$) a lower dose. The mean [SD] daily doses during the randomized period (quetiapine XR 177.1 mg/day [95.6], placebo 182.1 mg/day [91.5]) did not differ considerably from the mean doses at randomization.

The total exposure to study drug over the study was 298 and 257 days/patient for patients randomized to quetiapine XR and placebo, respectively. During the randomized phase, the mean duration of exposure was higher for quetiapine XR (167.0 days) versus placebo (126.3 days), reflecting the higher rate of recurrence of depressive events in the placebo group.

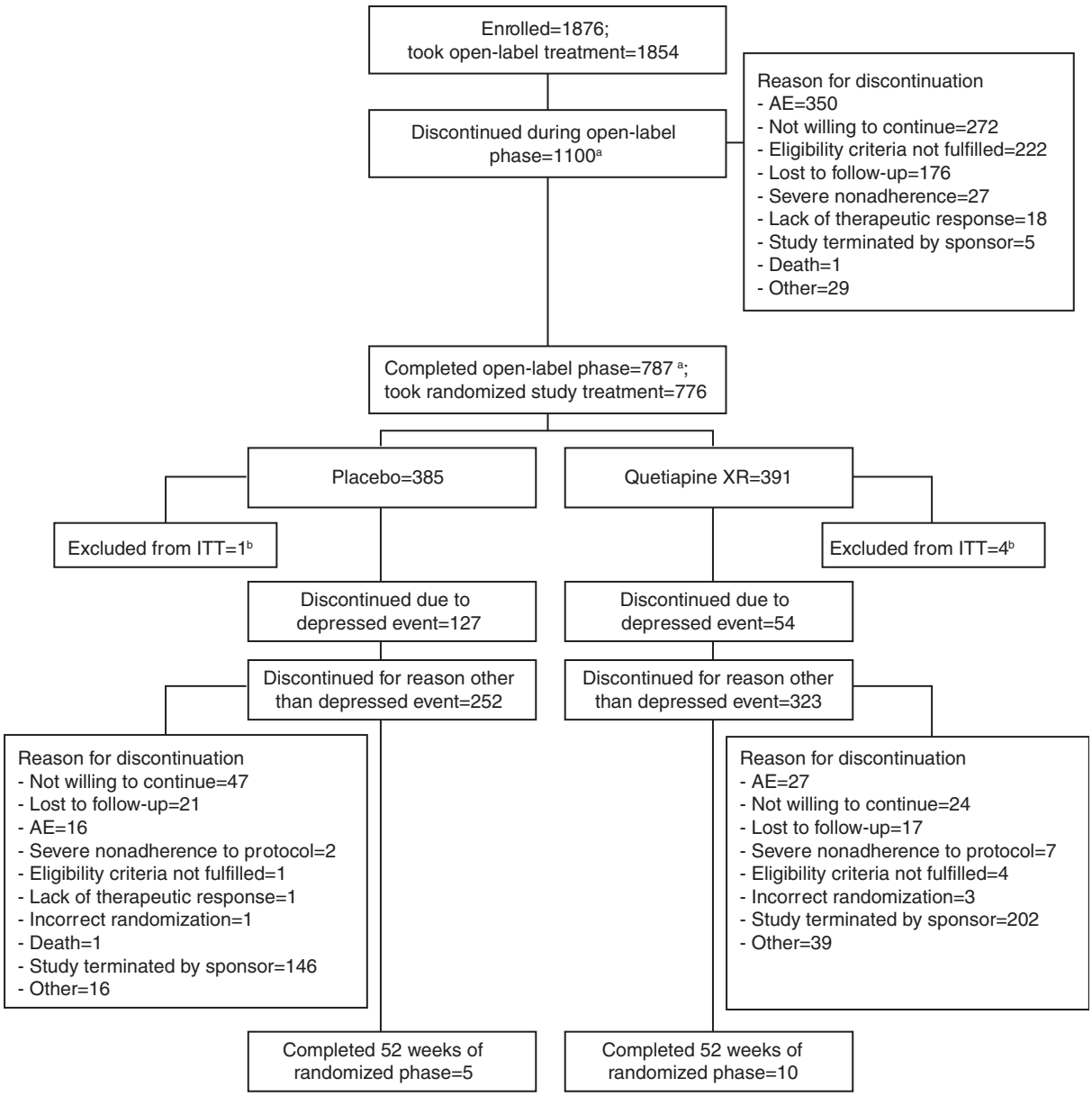
EFFICACY

The risk of a depressive event with quetiapine XR was significantly reduced compared with placebo, as assessed by increased time to an event (HR = .34; 95% CI = .25, .46; $P<.001$). In total, 55 (14.2%) quetiapine XR- and 132 (34.4%); placebo-treated patients experienced a depressive event (Fig. 2). When analyzed by last open-label dose, quetiapine XR at doses of 50 mg (HR = .46; 95% CI = .23, .91; $P<.05$), 150 mg (HR = .36; 95% CI = .22, .57; $P<.001$), and 300 mg (HR = .26; 95% CI = .15, .45; $P<.001$) significantly increased time to a depressive event.

The distribution of the six different criteria for a depressive event was similar between treatment groups, with the most frequent criterion met being MADRS score ≥ 18 (51/88, quetiapine XR; 120/203, placebo) (Table 2). In the randomized safety population, the median number of days to MADRS score ≥ 18 was 63 days for quetiapine XR and 29 days for placebo.

Quetiapine XR significantly increased the time to a depressive event when events occurring within the first 30 days of randomized treatment were removed to exclude the effect of patients transitioning to placebo. The estimated HR was .49 (95% CI = .32, .73; $P<.001$) and the number of depressive events was 39 (11.0%) and 59 (20.7%) in the quetiapine XR and placebo groups, respectively.

During the randomized phase, quetiapine XR significantly increased time to any discontinuation versus placebo (HR .58 [95% CI = .48, .71; $P<.001$]). The number of discontinuations for any reason, excluding study cessation by the sponsor, was 175 (45.2%) and 233 (60.7%) with quetiapine XR and placebo, respectively. The number of discontinuations due to termination by the sponsor was 202 (52.2%) and 146 (38.0%) with quetiapine XR and placebo, respectively. Of the 55 depressive events analyzed from the quetiapine XR group, investigators discontinued one patient from the study due to reasons other than a depressive event (study termination), although the patient fulfilled the criteria for a depressive event (MADRS total score ≥ 18). Of the 132 depressive events analyzed from the placebo group, investigators discontinued five patients who met the criteria for a depressive event for reasons



[a]This number includes 11 patients who were assigned a randomization number, but did not receive randomized study treatment

[b]5 patients were excluded from the ITT population because the site was not compliant with good clinical practice

AE, adverse event; ITT, intent-to-treat

Figure 1. Patient disposition.

other than a depressive event (AE [$n = 2$]; lost to follow-up [$n = 1$]; lack of therapeutic response [$n = 1$] and sponsor decision [$n = 1$]).

The mean changes from randomization to study end (or discontinuation for patients experiencing a depressive event) for each of the secondary efficacy variables are presented in Table 3. Quetiapine XR was significantly more effective versus placebo in maintaining improvement in MADRS total, CGI-S, HAM-A total, HAM-A psychic and somatic cluster, PSQI global, and SDS scores. No difference between quetiapine XR and placebo ($P = .303$) was established with regard to Q-LES-Q: SF % maximum total score; however, significant improvement was maintained with quetiapine XR versus placebo in Q-LES-Q Items 15 and 16.

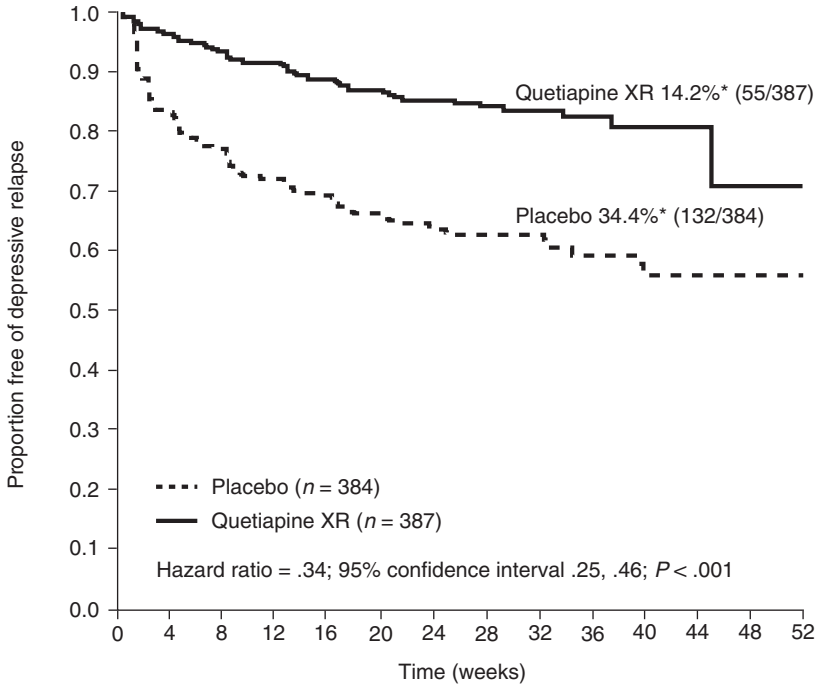
TOLERABILITY

Open-label phase. The overall incidence of AEs, SAEs, reasons for discontinuation, most commonly

TABLE 1. Baseline demographics and clinical characteristics (open-label and ITT populations)

	Open-label total population	ITT population	
Demographic	Quetiapine XR (n = 1,854)	Placebo[a] (n = 384)	Quetiapine XR[b] (n = 387)
Gender, n (%)			
Male	672 (36.2)	130 (33.9)	132 (34.1)
Female	1,182 (63.8)	254 (66.1)	255 (65.9)
Age (years), mean (*SD*)	43.1 (12.1)	43.8 (11.5)	45.4 (11.2)
Weight (kg), mean (*SD*)	83.6 (22.2)	83.4 (23.4)	82.5 (21.2)
Years since first depressive episode, mean (*SD*)	13.7 (11.4)	12.6 (10.9)	14.8 (12.1)
Total number of depression-related hospitalizations, mean (*SD*)	0.5 (1.7)	0.5 (1.6)	0.6 (2.1)
Clinical characteristic, mean (*SD*)	Open-label baseline	Randomization baseline	
HAM-D	24.0 (3.1)	–	–
MADRS	28.8 (5.9)	5.3 (3.7)	5.8 (3.6)
CGI-S	4.5 (0.7)	1.8 (0.8)	1.9 (0.8)

[a]Patients who received quetiapine XR during the open-label phase and went on to receive placebo in the randomized phase.
[b]Patients who received quetiapine XR in both the open-label and randomized phases. ITT, intent-to-treat; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression-Severity of Illness.



Number of patients remaining

Quetiapine XR	387	357	331	307	270	226	173	140	116	88	88	46	7	7
Placebo	384	296	256	230	203	170	126	126	83	47	45	28	28	28

*Percentage of patients with a depressive event

46 quetiapine XR patients reached Week 44, and 7 continued beyond Week 48. 11 quetiapine XR patients were still receiving treatment when the last relapse occurred at approximately Week 45
ITT, intent-to-treat

Figure 2. Time from randomization to occurrence of a depressive event (ITT population).

reported AEs (≥5%), and AEs potentially related to somnolence, EPS, and sexual dysfunction during the open-label period are shown in Table 4.

During the open-label phase, the proportion of patients with MADRS Item 10 score ≥4 was 4.1 versus 2.6% at open-label baseline. The proportion of open-label

TABLE 2. Patients fulfilling a depressed event criterion[a] (ITT population)

	Placebo ($n = 384$)	Quetiapine XR ($n = 387$)
MADRS score ≥18 at two consecutive assessments 1 week apart or at the final assessment if patient discontinued treatment	120 (31.3)	51 (13.2)
CGI-S score ≥5	44 (11.5)	23 (5.9)
Initiation of pharmacological treatment by investigator to treat depressive symptoms	35 (9.1)	12 (3.1)
Initiation of pharmacological treatment by patient to treat depressive symptoms	3 (0.8)	2 (0.5)
Hospitalization for depressive symptoms	1 (0.3)	0
Suicide attempt or discontinuation due to imminent risk of suicide	0	0

[a]Patients may have met more than one criterion and may, therefore, be counted twice. ITT, intent-to-treat; MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression-Severity of Illness.

TABLE 3. Change from randomization to study end or discontinuation for all secondary efficacy analyses (ITT population)

	Estimated change from randomization		
Efficacy outcome variable LSM (SE)	Placebo ($n = 384$)	Quetiapine ($n = 387$)	*P*-value versus placebo
MADRS total score	2.03 (0.21)	0.15 (0.20)	<.001
CGI-S score	0.23 (0.04)	−0.03 (0.03)	<.001
HAM-A total score	1.58 (0.18)	0.20 (0.17)	<.001
HAM-A psychic score	1.23 (0.12)	0.16 (0.11)	<.001
HAM-A somatic score	0.33 (0.09)	0.06 (0.09)	<.05
Q-LES-Q: SF % maximum total score	−0.36 (0.65)	0.52 (0.59)	.303
Q-LES-Q Item 15 score	−0.24 (0.04)	−0.13 (0.04)	<.05
Q-LES-Q Item 16 score	−0.12 (0.04)	0.02 (0.03)	<.01
PSQI global score	1.35 (0.17)	0.06 (0.15)	<.001
SDS Global Functioning Impairment score	0.44 (0.28)	−0.45 (0.25)	<.05

ITT, intent-to-treat; LSM, least squares means; MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression-Severity of Illness; HAM-A, Hamilton Anxiety Rating Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SDS, Sheehan Disability Scale.

patients having an AE potentially related to suicidality was 1.2%.

There were no clinically relevant mean changes from baseline in ECG, hematology, or clinical chemistry parameters during the open-label phase. The proportion of patients who experienced a clinically important shift (≥126 mg/dl) in fasting glucose at the end of open-label treatment was 2.5% (based on 1,096 patients who started the open-label phase with a nonclinically significant glucose level) (Table 5). Potentially clinically important increases and decreases in supine pulse (33.5 and 15.8%, respectively) and systolic blood pressure (18.4 and 19.2%, respectively) were recorded (Table 5). Table 5 shows mean changes from baseline to the end of the open-label phase for weight, clinical laboratory, and EPS assessments, and clinically important shifts in glucose and lipid levels.

Randomized period. The incidence of AEs, SAEs, and discontinuations due to AEs were similar in both treatment groups (Table 4). No SAEs were considered related to treatment. The most commonly reported AEs (≥5% in any group), and AEs potentially associated with somnolence, EPS, and sexual dysfunction are shown in Table 4.

During the first 2 weeks of the randomized phase, mean TDSS scores were slightly higher for placebo (2.9) versus quetiapine XR (1.8). The most pronounced differences between placebo and quetiapine XR were seen for the symptoms of insomnia, sweating, chills, nausea, and diarrhea.

During the randomized phase, the number of patients with MADRS Item 10 score ≥4 was comparable between the quetiapine XR and placebo groups (0.3 and 0.5%, respectively), and similar to that at randomized baseline (0% for both).

There were no clinically relevant mean changes from baseline in vital signs, ECG, hematology, or clinical chemistry parameters. The proportion of patients who experienced a clinically important shift (≥126 mg/dl) in fasting glucose at the end of treatment was 2.8 and 3.3% in the quetiapine XR and placebo groups, respectively (Table 5). Table 5 shows mean changes from baseline to study end for weight, clinical laboratory, and EPS assessments, and clinically important shifts in glucose and lipid levels.

DISCUSSION

This is the first randomized, placebo-controlled study to evaluate the efficacy and tolerability of once-daily quetiapine XR, as monotherapy for the maintenance treatment of patients with MDD. During the 52-week randomized treatment phase, quetiapine XR monotherapy (50–300 mg/day) significantly reduced the risk of a depressive event in patients with MDD compared with placebo; the majority of depressive events occurred in the placebo group during the first 30 days after randomization. The recurrence rate for quetiapine XR (11%) in this study was similar to that in a 52-week study with sertraline (13%).[34] A comparable recurrence rate was also seen in a shorter (8-week open-label phase followed by a 24-week randomized phase) study with citalopram (13.8%).[35]

As well as a reduced risk of recurrence, the level of improvement in depressive and anxiety symptoms in the open-label (stabilization) phase was maintained during the randomized (maintenance) period with

TABLE 4. Treatment-emergent AEs, most common AEs (≥5%), AEs leading to discontinuation (≥0.5%) occurring in any group, and AEs of special interest during the open-label (subset of open-label safety population and total open-label safety population) and randomized (randomized safety population) phases

	Open-label phase	Randomized phase		
n (%)	Open-label phase quetiapine XR[a] (*n* = 391)	Open-label total population (*n* = 1,854)	Placebo (*n* = 385)	Quetiapine XR (*n* = 391)
Any AE	337 (86.2)	1,584 (85.4)	233 (60.5)	246 (62.9)
Serious AE	2 (0.5)	39 (2.1)	8 (2.1)	8 (2.0)
Serious AE leading to death	0	3 (0.2)[b]	1 (0.3)[c]	0
Drug-related AE	301 (77.0)	1,420 (76.6)	109 (28.3)	129 (33.0)
AE leading to discontinuation	8 (2.0)	368 (19.8)	20 (5.2)	25 (6.4)[d]
Most common AEs, *n* (%)				
Somnolence	122 (31.2)	592 (31.9)	0	15 (3.8)
Dry mouth	124 (31.7)	486 (26.2)	6 (1.6)	14 (3.6)
Sedation	68 (17.4)	348 (18.8)	1 (0.3)	10 (2.6)
Fatigue	42 (10.7)	239 (12.9)	10 (2.6)	17 (4.3)
Dizziness	45 (11.5)	229 (12.4)	17 (4.4)	26 (6.6)
Headache	36 (9.2)	178 (9.6)	44 (11.4)	27 (6.9)
Weight increased	40 (10.2)	140 (7.6)	6 (1.6)	38 (9.7)
Increased appetite	28 (7.2)	92 (5.0)	0	0
Constipation	32 (8.2)	130 (7.0)	1 (0.3)	8 (2.0)
Irritability	17 (4.3)	124 (6.7)	12 (3.1)	3 (0.8)
Nausea	25 (6.4)	106 (5.7)	38 (9.9)	14 (3.6)
Nasopharyngitis	17 (4.3)	62 (3.3)	25 (6.5)	28 (7.2)
Insomnia	11 (2.8)	58 (3.1)	57 (14.8)	22 (5.6)
Diarrhea	15 (3.8)	53 (2.9)	26 (6.8)	21 (5.4)
Incidence of AEs potentially related to[e], *n* (%)				
Somnolence (total)	194 (49.6)	970 (52.3)[f]	2 (0.5)[g]	26 (6.6)
Somnolence	122 (31.2)	592 (31.9)	0	15 (3.8)
Sedation	68 (17.4)	348 (18.8)	1 (0.3)	10 (2.6)
Lethargy	11 (2.8)	52 (2.8)	1 (0.3)	2 (0.5)
Sluggishness	3 (0.8)	7 (0.4)	0	0
EPS (total)	32 (8.2)	124 (6.7)	7 (1.8)[h]	11 (2.8)
Restlessness	13 (3.3)	39 (2.1)	4 (1.0)	2 (0.5)
Extrapyramidal disorder	5 (1.3)	28 (1.5)	2 (0.5)	3 (0.8)
Tremor	8 (2.0)	27 (1.5)	1 (0.3)	3 (0.8)
Akathisia	6 (1.5)	23 (1.2)	0	1 (0.3)
Dyskinesia	0	3 (0.2)	0	0
Hypokinesia	0	3 (0.2)	0	0
Drooling	0	1 (0.1)	0	1 (0.3)
Muscle rigidity	1 (0.3)	1 (0.1)	0	0
Muscle contractions involuntary	0	0	0	1 (0.3)
Sexual dysfunction (total)	8 (2.0)	23 (1.2)	2 (0.5)	6 (1.5)
AEs leading to discontinuation, *n* (%)				
Total	8 (2.0)	368 (19.8)	20 (5.2)	25 (6.4)
Somnolence	3 (0.8)	84 (4.5)	0	1 (0.3)
Sedation	0	57 (3.1)	0	1 (0.3)
Fatigue	0	38 (2.0)	0	0
Weight increased	1 (0.3)	14 (0.8)	0	0
Depression	0	14 (0.8)	3 (0.8)	2 (0.5)
Irritability	0	12 (0.6)	0	1 (0.3)
Dizziness	0	10 (0.5)	0	0
Suicidal ideation	0	9 (0.5)	1 (0.3)	0
Blood thyroid-stimulating hormone increased	0	1 (0.1)	0	3 (0.8)
Insomnia	0	4 (0.2)	3 (0.8)	3 (0.8)
Hypothyroidism	1 (0.3)	1 (0.1)	1 (0.3)	2 (0.5)

Ordered by decreasing incidence in the open-label phase.
[a]Results from the open-label phase for those patients who received quetiapine XR during the open-label and randomized treatment phases.
[b]Deaths (reported due to death [cause not documented], metastatic neoplasm, and myocardial infarction) were not considered related to study treatment.
[c]Death due to worsening of hypertensive cardiovascular disease.
[d]Two patients (0.5%) discontinued the study due to an AE potentially associated with somnolence.
[e]Patients with multiple events falling under the same preferred term are counted only once during each phase (open-label or randomized phase).
[f]Most of these events were reported during the first week of open-label treatment and generally decreased over 16 weeks of treatment.
[g]These events were reported during the first 4 weeks of randomized treatment.
[h]All these events occurred within the first 14 days of randomized treatment.
Most AEs potentially associated with somnolence, EPS, and sexual dysfunction were mild or moderate in intensity during both phases. AE, adverse event; EPS, extrapyramidal symptoms.

TABLE 5. Clinical laboratory parameters, body weight and EPS assessments at open-label and randomization baselines and at the endpoint in each phase, and mean changes from baseline to the end of each phase (open-label safety population)

	Open-label phase	Randomized phase	
	Total ($n = 1854$)	Placebo ($n = 385$)	Quetiapine XR ($n = 391$)
Glucose (mg/dl)[a]			
Mean (SD) baseline	91.28 (14.18)	94.47 (19.64)	93.92 (18.55)
Mean (SD) at phase endpoint	94.28 (18.57)	96.70 (16.27)	98.75 (23.71)
Mean (SD) change	2.59 (16.44)	2.13 (17.28)	3.18 (22.00)
Insulin (uIU/ml)[a]			
Mean (SD) baseline	12.01 (11.74)	14.70 (18.31)	14.21 (14.69)
Mean (SD) at phase endpoint	14.54 (15.89)	14.99 (16.45)	15.04 (14.37)
Mean (SD) change	3.15 (14.34)	0.64 (15.04)	0.71 (13.43)
Total cholesterol (mg/dl)[a]			
Mean (SD) baseline	200.14 (42.44)	197.27 (41.36)	203.52 (41.80)
Mean (SD) at phase endpoint	200.18 (42.02)	196.33 (40.30)	199.52 (44.90)
Mean (SD) change	−2.07 (32.09)	−2.00 (28.60)	−5.22 (30.68)
LDL cholesterol (mg/dl)[a]			
Mean (SD) baseline	116.15 (35.45)	114.70 (35.72)	116.53 (37.78)
Mean (SD) at phase endpoint	115.70 (36.36)	114.26 (34.37)	114.62 (37.28)
Mean (SD) change	−1.94 (26.76)	−1.18 (25.58)	−3.43 (25.08)
HDL cholesterol (mg/dl)[a]			
Mean (SD) baseline	55.23 (15.44)	52.74 (15.67)	53.79 (16.15)
Mean (SD) at phase endpoint	52.86 (15.28)	53.48 (14.63)	52.61 (15.79)
Mean (SD) change	−2.72 (9.03)	1.00 (8.18)	−0.06 (8.57)
Triglycerides (mg/dl)[a]			
Mean (SD) baseline	148.15 (107.20)	155.72 (105.68)	171.45 (118.93)
Mean (SD) at phase endpoint	165.45 (118.48)	147.69 (98.57)	164.70 (106.64)
Mean (SD) change	16.91 (97.64)	−10.30 (86.17)	−10.67 (99.03)
Prolactin[b] (ng/ml)			
Mean (SD) baseline	8.80 (10.80)	8.19 (9.52)	7.83 (7.70)
Mean (SD) at phase endpoint	8.10 (9.06)	8.24 (10.72)	8.03 (5.13)
Mean (SD) change	−0.87 (13.90)	0.02 (6.90)	0.17 (7.97)
Weight (kg)			
Mean (SD) baseline	83.6 (22.2)	84.6 (23.0)	84.5 (21.5)
Mean (SD) at phase endpoint	84.7 (22.0)	83.3 (22.9)	84.3 (22.2)
Mean (SD) change	1.6 (4.7)	−0.9 (4.2)	−0.1 (4.9)
Clinically important shifts at the end of treatment, *n* (%)[c]			
Glucose	27 (2.5)	8 (3.3)	7 (2.8)
(≥126 mg/dl)[a]	$N = 1,096$	$N = 246$	$N = 251$
Total cholesterol	66 (6.8)	13 (5.8)	10 (4.7)
(≥240 mg/dl)[a]	$N = 969$	$N = 224$	$N = 212$
HDL cholesterol	105 (10.6)	10 (4.8)	19 (9.4)
(≤40 mg/dl)[a]	$N = 990$	$N = 207$	$N = 202$
LDL cholesterol	57 (5.6)	15 (6.5)	10 (4.4)
(≥160 mg/dl)[a]	$N = 1,024$	$N = 232$	$N = 225$
Triglycerides	143 (15.3)	16 (8.0)	25 (14.0)
(≥200 mg/dl)[a]	$N = 934$	$N = 201$	$N = 178$
Weight	137 (12.2)	10 (2.9)	20 (5.4)
(≥7% increase)	$N = 1,124$	$N = 351$	$N = 369$
Supine pulse	$N = 1796$	$N = 372$	$N = 387$
≥15 increase	602 (33.5)	71 (19.1)	109 (28.2)
≥15 decrease	283 (15.8)	68 (18.3)	53 (13.7)
Systolic blood pressure	$N = 1,796$	$N = 372$	$N = 387$
≥20 increase	331 (18.4)	63 (16.9)	79 (20.4)
≥20 decrease	344 (19.2)	59 (15.9)	66 (17.1)
Mean change (SD) from baseline in			
SAS	−0.2 (1.3)	0 (0.8)	0 (0.8)
BARS	−0.1 (0.5)	0 (0.3)	0 (0.3)
AIMS	−0.1 (1.1)	0 (0.4)	0 (0.4)

Baselines were open-label baseline and randomization.

[a]Fasting status confirmed. This status was determined based upon a documented report from the patient that the last meal was ≥8 hr before blood sample taken for baseline and post-baseline laboratory measurements. However, not all samples could be confirmed as fasted despite there being an 8 hr interval since the last meal, as patients could have had caloric intake.

[b]Normal prolactin range: 2–20 ng/ml (men); 2–29 ng/ml (women).

[c]Based on the number of patients who started the open-label phase with a nonclinically significant measurement. HDL, high-density lipoprotein; LDL, low-density lipoprotein; SAS, Simpson-Angus Scale; BARS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale.

quetiapine XR versus placebo. Improvements seen with quetiapine XR were maintained for all secondary endpoints, with the exception of Q-LES-Q: SF % maximum total score. These results are similar to those observed in other MDD maintenance treatment studies. In an olanzapine/fluoxetine combination study, improvements in MADRS and CGI-S scores were maintained,[36] whereas in a venlafaxine study, improvements in HAM-A and CGI-S scores were maintained.[37]

During the open-label stabilization phase, the most common reason for discontinuation was an AE, and the most common AEs leading to discontinuation (including somnolence, sedation, and fatigue) (Table 4) were consistent with those observed during short-term monotherapy studies.[13–15] The most common AEs during the open-label phase (including somnolence, dry mouth, sedation, and fatigue) were more frequently reported during the first week of treatment.

Higher incidences of headache, insomnia, diarrhea, and nausea were reported with placebo during the randomized (maintenance) period, and were mainly reported during the first week of treatment. Consequently, these AEs may be explained partly as discontinuation symptoms associated with patients switching from quetiapine XR to placebo; TDSS scores during the 2-week postrandomization phase were slightly higher with placebo versus quetiapine XR.

Small mean increases in glucose and insulin levels and mean decreases in total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were observed throughout the study. At the end of the randomized phase, 10 quetiapine XR- and 17 placebo-treated patients experienced clinically important elevated glucose levels. The most noticeable differences in clinical laboratory assessments across the two phases of this study were the mean change in triglyceride levels, where an increase in triglycerides was observed during the open-label period compared with a decrease during the randomized phase in the quetiapine XR group.

During the randomized phase, 5.4% of patients treated with quetiapine XR had a $\geq$7% increase in weight (Table 5). Although changes in weight have been reported in other long-term studies in patients with MDD, these are not directly comparable with this research as they are not maintenance studies.

In this study, a lower percentage of patients reported a $\geq$7% increase in weight than in a maintenance study of quetiapine XR 300 mg/day (9.0%) and 600 mg/day (11.3%) in patients with bipolar depression.[12] Weight gain $\geq$7% was observed in 12% of patients in the open-label (stabilization) phase with a mean increase of 1.6 kg (Table 5); however, no mean increase in weight occurred during the randomized (maintenance) phase, indicating that weight gain seems to occur early in treatment with quetiapine XR. As patients with psychiatric disorders may be at increased metabolic risk, physicians should consider the potential for effects, such as changes in weight, plasma glucose, and lipid levels, before initiating any maintenance treatment option in patients with MDD.

Among AEs of special interest, AEs potentially related to somnolence (somnolence, sedation, lethargy, sluggishness) were the most common, occurring in approximately 50% of patients during the open-label phase (Table 4). Most of these events were reported during the first week of open-label treatment and generally decreased over 16 weeks of treatment. During the randomized phase, more patients receiving quetiapine XR (6.6%) reported a higher incidence of AEs potentially related to somnolence than those receiving placebo (0.5%). Most AEs potentially related to somnolence were mild-to-moderate in intensity. Somnolence may be an important consideration in the early days of treatment with quetiapine XR.

EPS-related AEs, in particular akathisia, dystonia, and parkinsonism, are commonly reported in patients treated with SSRIs.[38] Although the long-term tolerability of quetiapine XR has not been established, quetiapine immediate release is characterized by a lower propensity to cause EPS than other antipsychotics,[39,40] and this suggests that quetiapine may have less potential than standard antipsychotic agents to induce tardive dyskinesia. However, findings from the Clinical Antipsychotic Trials of Intervention Effectiveness study suggest that there are no significant differences between atypical antipsychotics and their propensity to cause EPS in patients with schizophrenia.[41] In this present study, the incidence of EPS-related AEs with quetiapine XR during the randomized phase (2.8%), and in particular akathisia (0.3%), was low (Table 4) and, at treatment end, the majority of patients had experienced no change in SAS, BARS, and AIMS scores. Tardive dyskinesia was not reported as an AE in this study.

Quetiapine XR was generally well tolerated during maintenance treatment of MDD, with a tolerability profile consistent with that observed in patients who received acute treatment with quetiapine XR as monotherapy or adjunct therapy.[13,15–17] In order to optimize treatment outcomes, it is essential to balance efficacy with safety and tolerability and to consider the individual preferences and needs of the patient.

Strengths of this study include the large number of patients recruited and the robust statistical analysis methods used. As MDD is often a chronic condition requiring long-term therapy to prevent recurrence of symptoms, the study design is particularly relevant to clinical practice and maintenance treatment in patients previously stabilized on quetiapine XR.

Limitations of this study include the study design, which led to 45.1% of patients discontinuing from the trial due to study termination and, therefore, having a shortened observation period. In addition, common psychiatric comorbidity was excluded from the patient population. The lack of a comparator arm makes it difficult to draw conclusions regarding the efficacy and

tolerability of quetiapine XR in maintenance treatment of patients with MDD compared with specific antidepressants. It should also be noted that the analysis of secondary efficacy variables was conservative as depressive events were not included in these analyses.

In summary, quetiapine XR (50–300 mg/day) is effective at reducing the risk of recurrence of a depressive event in patients with MDD stabilized on quetiapine XR and has a tolerability profile consistent with the known profile of quetiapine.

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