Drug product:	Seroquel	**SYNOPSIS**	
Drug substance(s):	Quetiapine XR		
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A Multicenter, Double-blind, Randomized-withdrawal, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR™) as Monotherapy in the Maintenance Treatment of Patients with Major Depressive Disorder Following an Open-Label Stabilization Period (AMETHYST STUDY)

Study centers

A total of 1876 patients were enrolled and 787 patients were randomized at 237 sites in North America, Europe, and South Africa.

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	22 December 2005	Therapeutic confirmatory (III)
Last patient completed	1 August 2007	

Objectives

The primary objective of the study was to evaluate the efficacy of quetiapine extended release (XR) compared with placebo in increasing time from randomization to a depressed event in patients with major depressive disorder (MDD).

A depressed event was defined as fulfilling at least 1 of the following: (a) Initiation of pharmacological treatment by the Investigator, other than the allowed hypnotics, to treat

depressive symptoms, (b) Initiation of pharmacological treatment by the patient for at least 1 week, other than the allowed hypnotics, to treat depressive symptoms, (c) Hospitalization for depressive symptoms, (d) Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥18 at 2 consecutive assessments 1 week apart or at the final assessment if the patient discontinued, (e) Clinical Global Impression-Severity of Illness (CGI-S) score ≥5, or (f) Suicide attempt or discontinuation from study due to imminent risk of suicide.

The secondary objectives of this study were the following:

1. To evaluate the effect of quetiapine XR compared with placebo on health-related quality of life in patients with MDD during long-term treatment.

2. To evaluate the efficacy of quetiapine XR compared with placebo in maintaining improvement of depressive symptoms in patients with MDD during long-term treatment.

3. To evaluate the effect of quetiapine XR compared with placebo on anxiety symptoms in patients with MDD during long-term treatment.

4. To evaluate the effect of quetiapine XR compared with placebo on quality of sleep in patients with MDD during long-term treatment.

5. To evaluate the effect of quetiapine XR compared with placebo on suicidal ideation in patients with MDD during long-term treatment.

6. To evaluate the effect of quetiapine XR compared with placebo on functional disability in patients with MDD during long-term treatment.

7. To evaluate if quetiapine XR compared with placebo is safe and well tolerated in patients with MDD during long-term treatment.

Study design

This was a multicenter, randomized-withdrawal, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy (time to depressed event) and safety of quetiapine XR for up to 52 weeks of maintenance treatment in adult patients with MDD. The study comprised 4 periods: an enrollment period of up to 28 days; an open-label run-in period of 4 to 8 weeks, an open-label stabilization treatment period of at least 12 weeks (which could have been extended 6 additional weeks to meet eligibility criteria for randomization), and a randomized treatment period of up to 52 weeks.

Target population and sample size

Male or female patients 18 to 65 years old, with a documented clinical diagnosis of MDD together with an acute depressed episode confirmed by Mini-International Neuropsychiatric Interview and meeting the Diagnostic and Statistical Manual of Mental Disorders (4th Edition, Text Revision of either:

- Criteria 296.2x MDD, Single Episode

  or

- Criteria 296.3x MDD, Recurrent

The patient must have had a current episode of depression that was at least 4 weeks and less than 12 months in duration prior to enrollment. The patients must also have had a Hamilton Rating Scale for Depression (HAM-D) total score of ≥20 and a HAM-D item 1 score of ≥2 at enrollment to have been eligible for the study.

For inclusion in the open-label stabilization and randomized treatment phases, the patient had to have a MADRS score ≤12 and a CGI-S score ≤3.

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

At the beginning of the open-label run-in treatment period the total daily dose of quetiapine XR was increased from 50 mg/day (Day 1 and 2) to 150 mg/day (Day 3 and 4). Thereafter, and throughout the subsequent open-label stabilization treatment period, Investigators were permitted to adjust the dose to 50, 150, or 300 mg/day based on their clinical judgment. Starting at Visit 10 (day of randomization), open-label quetiapine XR tablets were replaced with tablets of blinded quetiapine XR or placebo tablets at the same dose as was administered at the end of the open-label treatment period. During the randomized treatment phase as well, Investigators were permitted to adjust the dose to 50, 150, or 300 mg/day based on their clinical judgment.

Duration of treatment

This study consisted of an open-label run-in treatment period of 4 to 8 weeks and an open-label stabilization treatment period of at least 12 weeks (patients were permitted to return to the clinic for up to 3 more visits [ie, for up to 6 more weeks] to meet eligibility criteria for randomization), followed by a randomized treatment period of up to 52 weeks.

Criteria for evaluation (main variables)

The outcome variables are presented in Table S1.

Table S1 Outcome variables

Primary efficacy outcome variable

Time from randomization to occurrence of a depressed event

Secondary efficacy variables supporting the primary objective

Occurrence of a depressed event, average change from randomization for the following: MADRS total score, CGI-S score.

Other secondary efficacy variables

Average change from randomization for the following: HAM-A total score, HAM-A psychic anxiety factors score, HAM-A somatic anxiety factors score, MADRS Item 10 score, Q-LES-Q percentage of the maximum total score (Items 1 to 14), Q-LES-Q Item 15 score, Q-LES-Q Item 16 score, PSQI global score, SDS total score (Items 1 to 3), SDS number of unproductive days, SDS number of under-productive days.

Safety variables

Laboratory values, physical examination, vital signs, weight, BMI, waist circumference, ECG, SAS, BARS, AIMS, AEs (including EPS-related), TDSS, MADRS Item 10 score ≥4 or an AE related to suicidality.

AE Adverse event. AIMS Abnormal Involuntary Movement Scale. BARS Barnes Akathisia Rating Scale. BMI Body mass index. CGI-S Clinical Global Impression–Severity of Illness. ECG Electrocardiogram. EPS Extrapyramidal symptoms. HAM-A Hamilton Rating Scale for Anxiety. MADRS Montgomery-Åsberg Depression Rating Scale. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. SAS Simpson-Angus Scale. SDS Sheehan Disability Scale. TDSS Treatment Discontinuation Signs and Symptoms.

Statistical methods

The main analysis of the time to depressed event was a Cox proportional hazards model to estimate the hazards ratio of time to depressed event between quetiapine XR and placebo, with 95% confidence intervals. The hypothesis that the hazard ratio was equal to 1 was tested and a p-value less than 5% was considered statistically significant. The analysis was stratified by region (United States of America [US]/non-US). If a patient discontinued from or completed the study without meeting the criteria for a depressed event, the time of censoring was the date of the patient's final visit.

For all secondary variables, the mean of all assessments between randomization and up to, but excluding, the visit where a depressed event was recorded was analyzed using Analysis of covariance with the score at randomization as a covariate and treatment and region as fixed effect. If no depressed event was recorded for a patient, all visits after randomization with available score data were used.

All statistical tests were 2-sided with a significance level of 5%. Where appropriate, 95% confidence intervals were presented. Descriptive statistics were provided for all variables.

In addition, the proportion of patients experiencing a depressed event in each treatment group over the course of treatment was presented.

For the open-label treatment period and the randomized treatment period, descriptive statistics are presented to summarize scores at all visits and changes from randomization (or enrollment if appropriate) to all visits in the period (observed cases and final assessment).

Descriptive statistics of incidence rates were used to evaluate adverse events (AEs) (including serious AEs [SAEs], AEs leading to withdrawal, and deaths) and reasons for early withdrawal from study. Other safety analyses were summarized by means of descriptive statistics (mean, median, standard deviation [SD], minimum and maximum value) and frequency tables.

Total patient years of exposure and incidence densities were calculated for common AEs. Incidence densities adjust for the time exposed to drug and were expressed as events per patient-year. Incidence rates were tabulated and presented for AEs occurring at a rate of ≥2% in any of the treatment groups, SAE, AEs leading to discontinuation, and special interest AEs using the following intervals. Open-label phase intervals were ≤1 week, >1 to ≤2 weeks, >2 to ≤4 weeks, >4 to ≤8 weeks, >8 to ≤12 weeks, >12 to ≤16 weeks, and >16 to ≤18 weeks. Randomized treatment phase intervals ≤1 week, >1 to ≤2 weeks, >2 to ≤4 weeks, >4 to ≤14 weeks, >14 to ≤24 weeks, >24 to ≤34 weeks, >34 to ≤44 weeks, and >44 weeks.

Analysis sets included the open-label safety population (all patients who entered the open-label treatment period and received study treatment); the randomized safety population (all patients who entered the randomized treatment period and received randomized study treatment, according to actual treatment taken); the intention to treat (ITT) population (all randomized patients who received study treatment, classified according to their randomized treatment); and the per protocol (PP) population (all patients from the ITT population who had no protocol violations or deviations that might affect efficacy).

Patient population

Analysis sets and patient baseline characteristics for the randomized treatment groups within the ITT population are presented in Table S2.

Table S2 Analysis sets and patient baseline characteristics

		PLA	QTP XR
Analysis sets			
N open-label safety		NA	1854
N randomized safety		385	391
N ITT		384	387
N PP		290	303
Demographic characteristics (ITT analysis set)			
Sex: n (%)	Male	130 (33.9)	132 (34.1)
	Female	254 (66.1)	255 (65.9)
Age: years	Mean (SD)	43.8 (11.5)	45.4 (11.2)
	Min to max	19 to 65	19 to 65
Race: n (%)	Caucasian	339 (88.3)	336 (86.9)
	Black	37 (9.7)	33 (8.5)
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Region: n (%)	US	250 (65.1)	252 (65.1)
	Non-US	134 (34.9)	135 (34.9)
Region code: n (%)	North America	273 (71.1)	271 (70.0)
	South Africa	2 (0.5)	4 (1.0)
	Europe	109 (28.4)	112 (28.9)
Baseline disease characteristics (ITT analysis set)			
DSM-IV TR diagnosis: n (%)			
296.2x MDD, single episode		64 (16.7)	51 (13.2)
296.3x MDD, recurrent		320 (83.3)	336 (86.8)
MADRS	Mean (SD)	27.7 (5.8)	28.59 (5.9)
HAM-D	Mean (SD)	24.0 (3.1)	24.1 (3.2)
CGI-S	Mean (SD)	4.4 (0.7)	4.49 (0.8)

CGI-S Clinical Global Impression-Severity of Illness. DSM-IV TR Diagnostic and Statistical Manual of Mental Disorders (4th Edition) Text Revision. HAM-D Hamilton Rating Scale for Depression. ITT Intention to treat. MADRS Montgomery-Åsberg Depression Rating Scale. MDD Major depressive disorder. N Number of patients in treatment group. n Number of patients. NA Not applicable. PLA Placebo. PP Per protocol. QTP XR Quetiapine extended release. SD Standard deviation. US United States of America.

A total of 1854 patients received quetiapine XR during the open-label phase of the study; 776 patients received randomized study treatment. The most common reasons for discontinuation during the open-label phase were AE (19%) and not willing to continue (15%). Discontinuations due to a depressed event during randomized treatment were less common in the quetiapine XR group (14%) than in the placebo group (33%). Other than depressed events and termination of the study by the sponsor, the most frequent reason for discontinuation was AE in the quetiapine XR group (7%) and not willing to continue in the placebo group (12%). During randomized treatment, exposure to study drug was greater in the quetiapine XR group than in the placebo group (167 days vs 126 days). A total of 787 patients completed the open-label phase and received up to 16 weeks of open-label quetiapine XR. A total of 776 patients were randomized to and received either quetiapine XR or placebo. Of the 391 patients who were randomized to receive quetiapine XR, 173 patients received at least 24 weeks of randomized treatment with quetiapine XR, 88 received at least 36 weeks of randomized treatment with quetiapine XR, and 46 received at least 44 weeks of randomized treatment with quetiapine XR.

Overall, the randomized quetiapine XR and placebo groups were well matched for demographic and baseline disease characteristics: the majority of patients were female (66% for both groups), most were Caucasian (87% and 88%, respectively), and the mean ages were 45 and 44 years, respectively. Demographics and baseline characteristics were similar for the open-label safety population and the open-label only population.

Compliance and use of concomitant medication was generally comparable during the open-label and randomized phases and similar for the 2 randomized treatment groups.

Efficacy

The main efficacy results are summarized in Table S3.

Table S3 Efficacy results, randomized treatment period (ITT population)

Outcome variable		PLA	QTP XR	Hazard ratio / estimated difference (95% CI)	p-value
Primary analysis	N	384	387		
Time to depression relapse	Number of relapses (%)	132 (34.4%)	55 (14.2%)	0.34 / (0.25, 0.46)[a]	<0.001[b]
Secondary analyses					
MADRS total score[c]	LS mean[b] (SE)	2.03 (0.21)	0.15 (0.20)	Diff: 1.88 (0.28) / (1.61, 2.44)	<0.001
CGI-S score[c]	LS mean[b] (SE)	0.23 (0.04)	-0.03 (0.03)	Diff: 0.26 (0.05) / 0.16, 0.35)	<0.001
HAM-A total score[c]	LS mean[b] (SE)	1.58 (0.18)	0.20 (0.17)	Diff: 1.37 (0.25) / (0.89, 1.86)	<0.001
HAM-A psychic anxiety factors score[c]	LS mean[b] (SE)	1.23 (0.12)	0.16 (0.11)	Diff: 1.07 (0.16) / (0.76, 1.38)	<0.001
HAM-A somatic anxiety factors score[c]	LS mean[b] (SE)	0.33 (0.09)	0.06 (0.09)	Diff: 0.27 (0.13) / (0.03, 0.52)	0.031
SDS total score[c]	LS mean[b] (SE)	0.44 (0.28)	-0.45 (0.25)	Diff: 0.89 (0.37) / (0.16, 1.61)	0.016
Q-LES-Q percentage of the maximum total score[c]	LS mean[b] (SE)	-0.36 (0.65)	0.52 (0.59)	Diff: -0.88 (0.86) / (-2.57, 0.80)	0.303
Q-LES-Q Item 15	LS mean[b] (SE)	-0.24 (0.04)	-0.13 (0.04)	Diff: -0.12 (0.06) / (-0.23, -0.01)	0.039
Q-LES-Q Item 16	LS mean[b] (SE)	-0.12 (0.04)	0.02 (0.03)	Diff: -0.14 (0.05) / (-0.23, -0.04)	0.004
PSQI global score[c]	LS mean[b] (SE)	1.35 (0.17)	0.06 (0.15)	Diff: 1.30 (0.22) / (0.87, 1.73)	<0.001

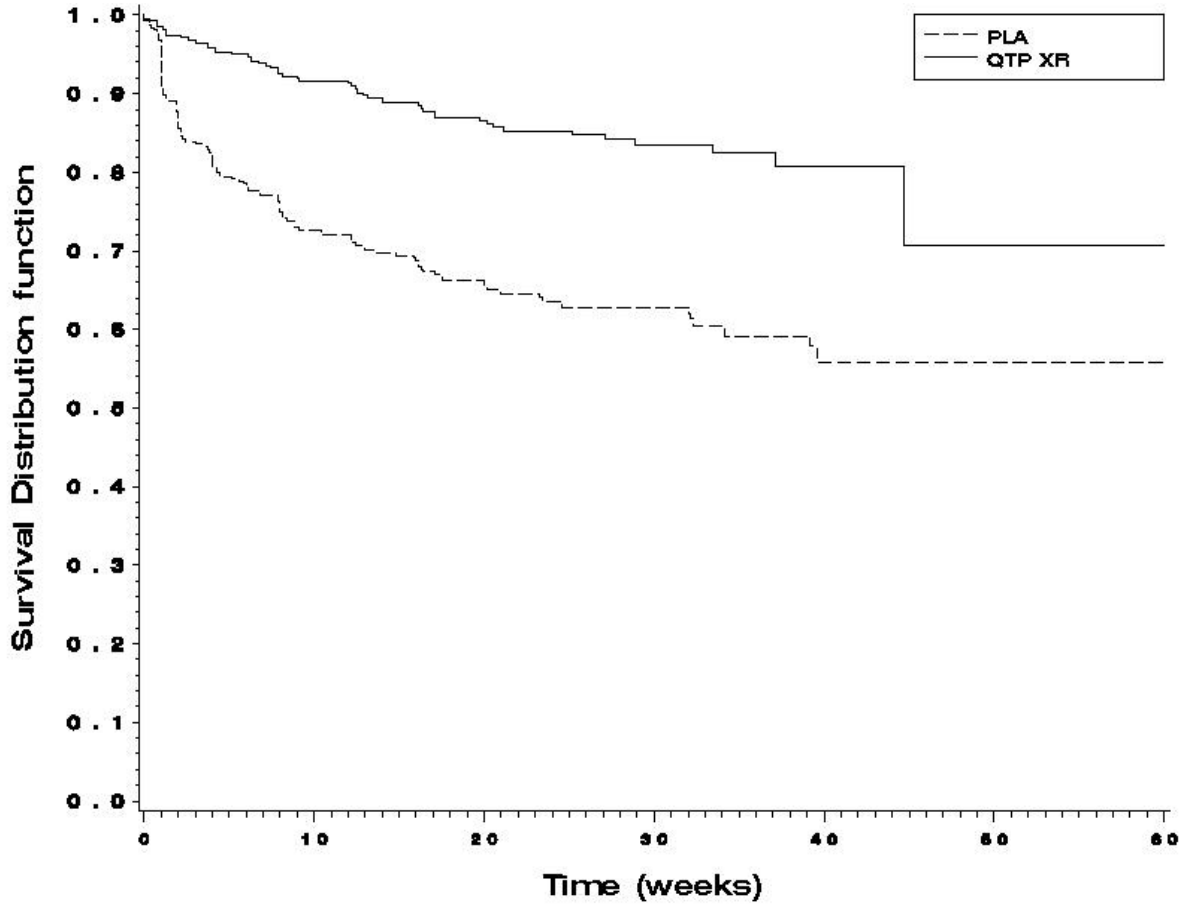
[a] Hazard ratio estimated by Cox proportional hazards model.
[b] Estimate of LS mean change during randomized period from an ANCOVA of the average of all post-baseline measurements from randomization up to, but not including, the relapse; the score at randomization was a covariate, and treatment and region were fixed effects.
[c] Change from randomization

ANCOVA Analysis of covariance. CGI-S Clinical Global Impression-Severity of Illness. CI Confidence interval. HAM-A Hamilton Rating Scale for Anxiety. ITT Intention to treat. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. PLA Placebo. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. QTP XR Quetiapine extended release. N Number of patients in treatment group. SDS Sheehan Disability Scale. SE Standard error.

Quetiapine XR at flexible doses of 50 mg, 150 mg, or 300 mg significantly increases the time to a depressed event compared with placebo when used as monotherapy in the maintenance treatment of patients with MDD. Results using the PP population and results from secondary analyses generally supported this conclusion. Quetiapine XR was superior to placebo in

maintaining the level of improvement of both depressive and anxiety symptoms, as measured by MADRS total score, CGI-S score, and Hamilton Rating Scale for Anxiety scores, respectively. Quetiapine XR was also superior to placebo in maintaining the level of functioning in the analysis of Sheehan Disability Scale total score and maintaining the quality of sleep in the analysis of Pittsburgh Sleep Quality Index global score. The superiority of quetiapine XR to placebo with regard to maintaining health-related quality of life enjoyment and satisfaction as assessed by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) scale was not established; however, quetiapine XR was superior to placebo with regard to maintaining satisfaction with medication and overall satisfaction with life, as measured by individual Items 15 and 16, respectively, of the Q-LES-Q. Finally, the superiority of quetiapine XR to placebo in reducing suicidal ideation in patients was not established. Kaplan Meier curves for time to a depressed event are presented in Figure S1.

Figure S1 Time to a depressed event, Kaplan Meier curves (ITT population)



ITT Intention to treat. PLA Placebo. QTP XR Quetiapine extended release.
Figure corresponds to Figure 11.2.1.1.

The depressed event rate was lower in the quetiapine XR-treated group compared with that in the placebo-treated group during the entire randomized phase. The Kaplan Meier curves showed consistency with the Cox-proportional hazard analysis of time to a depressed event.

Safety results

Exposure to study drug was considerably greater in the quetiapine XR group than in the placebo group. Total randomized exposure was 33% greater in the quetiapine XR group (167 days in the quetiapine XR group compared with 126 days in the placebo group).

Adverse events

The number (%) of patients who had at least 1 treatment-emergent AE in any category during open-label and randomized phases is summarized in Table S4.

Table S4 Patients who had a treatment-emergent adverse event in any category (open-label safety, subset of open-label safety, and randomized safety populations)

Analysis set	**Total open-label safety**	**Subset of open-label safety[a]**	**Randomized safety**	
Phase	**Open-label**	**Open-label**	**Randomized**	
	QTP XR N=1854	**QTP XR N=391**	**PLA N=385**	**QTP XR N=391**
Category of adverse event	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any adverse event	1584 (85.4)	337 (86.2)	233 (60.5)	246 (62.9)
Serious adverse event	39 (2.1)	2 (0.5)	8 (2.1)	8 (2.0)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related adverse event[b]	1420 (76.6)	301 (77.0)	109 (28.3)	129 (33.0)
Adverse events leading to discontinuation[c]	368 (19.8)	8 (2.0)	20 (5.2)	25 (6.4)

[a] Results from open-label phase for those patients who received quetiapine XR during the open-label and randomized phases.
[b] As judged by the Investigator.
[c] Interpretation of percentages of patients in the quetiapine XR group who discontinued due to an adverse event should be considered in light of the longer exposure to study drug in that treatment group compared with the placebo group.
Note: Patients with multiple events in the same category are counted only once during each phase (open-label or randomized).
Note: Percentages are calculated as n/N*100.
N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP XR Quetiapine extended release.

During the open-label phase of the study, the incidence of any AE was 85.4% and most were considered drug-related by the Investigator (76.6%). The proportion of patients having AEs leading to discontinuation was 19.8%. The incidence of SAEs, including deaths, was low

(2.1%). A total of [redacted] reported during the open-label phase; none was considered to be related to study treatment.

For patients participating in the open-label phase who were later randomized to quetiapine XR, the incidence of any AE was 86.2% and the incidence of drug-related AEs was 77.0%. The incidence of SAEs and the incidence of AEs leading to discontinuation were low overall (0.5% and 2.0%, respectively).

During the randomized phase of the study, the overall incidence of any AE was comparable between the quetiapine XR and placebo groups (62.9% and 60.5%, respectively). Drug-related AEs were reported slightly more frequently for the quetiapine XR group compared with the placebo group (33.0% and 28.3%, respectively). The incidence of AEs leading to discontinuation was comparable for the quetiapine XR and placebo groups (6.4% and 5.2%, respectively), even though exposure to study drug was considerably higher in the quetiapine XR group. [redacted] The incidence of non-fatal SAEs was low (≤2%) and comparable for the 2 treatment groups.

The incidence of common treatment-emergent AEs during randomized treatment (occurring at an incidence of ≥2% in any treatment group) is shown by preferred term in Table S5.

Table S5 Common (≥2%) treatment-emergent adverse events by preferred term (open-label safety, subset of open-label safety, and randomized safety populations)

Analysis set	**Total open-label safety**	**Subset of open-label safety[a]**	**Randomized safety**	
Phase	**Open-label**	**Open-label**	**Randomized**	
	QTP XR	**QTP XR**	**PLA**	**QTP XR**
	N=1854	**N=391**	**N=385**	**N=391**
MedDRA preferred term[b]	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Weight increased	140 (7.6)	40 (10.2)	6 (1.6)	38 (9.7)
Nasopharyngitis	62 (3.3)	17 (4.3)	25 (6.5)	28 (7.2)
Headache	178 (9.6)	36 (9.2)	44 (11.4)	27 (6.9)
Dizziness	229 (12.4)	45 (11.5)	17 (4.4)	26 (6.6)
Insomnia	58 (3.1)	11 (2.8)	57 (14.8)	22 (5.6)
Diarrhea	53 (2.9)	15 (3.8)	26 (6.8)	21 (5.4)
Arthralgia	49 (2.6)	12 (3.1)	9 (2.3)	19 (4.9)
Fatigue	239 (12.9)	42 (10.7)	10 (2.6)	17 (4.3)
Back pain	44 (2.4)	16 (4.1)	10 (2.6)	15 (3.8)
Somnolence	592 (31.9)	122 (31.2)	0	15 (3.8)

Table S5 Common (≥2%) treatment-emergent adverse events by preferred term (open-label safety, subset of open-label safety, and randomized safety populations)

Analysis set	Total open-label safety	Subset of open-label safety[a]	Randomized safety	
Phase	Open-label	Open-label	Randomized	
	QTP XR	QTP XR	PLA	QTP XR
	N=1854	N=391	N=385	N=391
MedDRA preferred term[b]	n (%)	n (%)	n (%)	n (%)
Upper respiratory tract infection	47 (2.5)	14 (3.6)	16 (4.2)	15 (3.8)
Dry mouth	486 (26.2)	124 (31.7)	6 (1.6)	14 (3.6)
Nausea	106 (5.7)	25 (6.4)	38 (9.9)	14 (3.6)
Sinusitis	25 (1.3)	6 (1.5)	9 (2.3)	12 (3.1)
Sedation	348 (18.8)	68 (17.4)	1 (0.3)	10 (2.6)
Blood pressure increased	0	0	2 (0.5)	9 (2.3)
Myalgia	49 (2.6)	6 (1.5)	5 (1.3)	9 (2.3)
Urinary tract infection	0	0	4 (1.0)	9 (2.3)
Constipation	130 (7.0)	32 (8.2)	1 (0.3)	8 (2.0)
Musculoskeletal pain	0	0	5 (1.3)	8 (2.0)
Vomiting	39 (2.1)	8 (2.0)	9 (2.3)	8 (2.0)
Pain in extremity	36 (1.9)	8 (2.0)	8 (2.1)	6 (1.5)
Anxiety	35 (1.9)	8 (2.0)	10 (2.6)	5 (1.3)
Irritability	124 (6.7)	17 (4.3)	12 (3.1)	3 (0.8)
Increased appetite	92 (5.0)	28 (7.2)	0	0
Dyspepsia	59 (3.2)	14 (3.6)	0	0
Lethargy	52 (2.8)	11 (2.8)	0	0
Restlessness	39 (2.1)	13 (3.3)	0	0
Edema peripheral	37 (2.0)	10 (2.6)	0	0
Disturbance in attention	38 (2.0)	5 (1.3)	0	0
Vision blurred	37 (2.0)	4 (1.0)	0	0

[a] Results from open-label phase for those patients who received quetiapine XR during the open-label and randomized phases.

[b] Patients with multiple events in the same category are counted only once for that preferred term during each phase (open-label or randomized).

Note: Common adverse event is defined as an event occurring at an incidence of ≥2% in any treatment group.

Note: Events sorted by decreasing frequency in the QTP XR treatment group.

Note: Percentages are calculated as n/N*100.

MedDRA Medical Dictionary for Regulatory Activities. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP XR Quetiapine extended release.

During the open-label phase, the most common AEs included somnolence (31.9%), dry mouth (26.2%), and sedation (18.8%), all of which are consistent with the known pharmacological profile of quetiapine. Most AEs were of mild or moderate intensity for both groups of patients. The incidence of AEs of special interest during the open-label phase were as follows: AEs potentially related to extrapyramidal symptoms (EPS), 6.7%; AEs potentially related to QT prolongation, 0; AEs potentially related to neutropenia or agranulocytosis, 0.4%; AEs potentially related to diabetes mellitus (DM), 1.0%; AEs potentially related to syncope, 0.5%; AEs potentially related to nausea and vomiting, 6.9%; AEs potentially related to sexual dysfunction, 1.2%; AEs potentially related to somnolence, 52.3%; and AEs potentially related to suicidality, 1.2%.

In the subset of patients participating in the open-label phase who were later randomized to quetiapine XR, the most common AEs included somnolence (31.9%), dry mouth (26.2%), sedation (18.8%), fatigue (12.9%), and dizziness (12.4%). Most common AEs for these patients were of mild or moderate intensity. The incidence of AEs of special interest for these patients was as follows: AEs potentially related to EPS, 8.2%; AEs potentially related to QT prolongation, 0; AEs potentially related to neutropenia or agranulocytosis, 0.3%; AEs potentially related to DM, 1.3%; AEs potentially related to syncope, 0.8%; AEs potentially related to nausea and vomiting, 7.4%; AEs potentially related to sexual dysfunction, 2.0%; AEs potentially related to somnolence, 49.6%; and AEs potentially related to suicidality, 0.3%.

During the randomized phase, the most common AE preferred terms reported were weight increased (9.7%, quetiapine XR group and 1.6%, placebo group); nasopharyngitis (7.2%, quetiapine XR group and 6.5%, placebo group); headache (6.9%, quetiapine XR group and 11.4%, placebo group); and dizziness (6.6%, quetiapine XR group and 4.4%, placebo group). Both insomnia and diarrhea were reported less frequently for the quetiapine XR group (5.6% and 5.4%, respectively) compared with the placebo group (14.8% and 6.8%, respectively). Most AEs were mild to moderate in intensity. With regard to AEs of interest, AEs potentially related to EPS, DM, sexual dysfunction, or suicidality occurred at similar incidences for the quetiapine XR and placebo groups. No AEs potentially related to QT prolongation were reported during the study, and no AEs potentially related to neutropenia or agranulocytosis were reported for the quetiapine XR group. AEs of nausea and vomiting were reported more frequently in the placebo group compared with the quetiapine XR group (10.9% vs 4.9%). Administration of quetiapine XR was associated with somnolence (6.6% in the quetiapine XR group compared with 0.5% in the placebo group). The incidence of syncope was low for both the quetiapine XR group (0.8%) and the placebo group (0).

Clinical laboratory results, vital signs, and other safety results

For the open-label safety population, no clinically significant changes in hematology, hepatic, renal, or electrolyte laboratory parameters were observed during the open-label phase. Mean increases were observed for the following parameters: thyroid stimulating hormone (TSH) (0.42 [4.22] µIU/mL), insulin (4.82 [18.44] µIU/mL), Homeostatic Model Assessment of Insulin Resistance ($HOMA_R$) (1.51 [6.13]), and triglycerides (16.91 [97.64] mg/dL). A

mean decrease in prolactin was also observed (-0.87 [13.90] ng/dL). In general, notable mean changes were associated with variability in the data as indicated by large SDs, comparable median changes, or both. When glucose regulation data were compared for patients in different diabetic risk categories, mean increases in glucose and $HOMA_R$ were largest for patients with diabetes compared with patients at risk of developing diabetes and patients with no known diabetic risk. Mean increases in insulin were largest for patients at risk of developing diabetes, and mean decreases in Quantitative Insulin Sensitivity Check Index (QUICKI) were highest for patients with no known diabetic risk. In general, glucose regulation data were variable as indicated by large SDs and the small number of patients with diabetes.

No clinically significant mean changes in supine, standing, or orthostatic vital signs were observed during the open-label phase. The incidence of potentially clinically important values for supine vital signs was <5% for any value or change during the open-label phase, except as follows: increase and decrease in supine pulse (27.8% and 10.9%, respectively); increase and decrease in systolic blood pressure (13.9% and 12.1%, respectively). For electrocardiograms (ECGs), a mean increase (3.5 [10.7] beats per minute [bpm]) was observed for heart rate for the open-label safety population during the open-label phase, and 13.5% of patients had an increase ≥15 bpm. Mean increases in weight (1.6 [4.7] kg) and waist circumference (1.8 [11.2] cm) were observed, and 12.2% of patients had a ≥7% increase in weight. Weight gain was more frequent in patients having lower body mass indices. Mean increases in weight and waist circumference from open-label baseline to end of randomized treatment for the quetiapine XR group were 1.9 (5.4) kg and 2.2 (12.1) cm, respectively. In the group of patients who received quetiapine XR during both phases, 76 (20.5%) patients had a ≥7% increase in weight from open-label baseline to end of randomized treatment. During the open-label phase, 8.9% of patients developed 3 or more metabolic risk factors.

In the subset of patients who were randomized to quetiapine XR, no clinically significant changes in hematology, hepatic, renal, or electrolyte laboratory parameters were observed during the open-label phase. Mean increases were observed for the following parameters: TSH (0.48 [1.41] µIU/mL), insulin (4.12 [19.22] µIU/mL), $HOMA_R$ (1.54 [7.48]), and triglycerides (18.83 [102.70] mg/dL). A mean decrease in prolactin was also observed (-1.06 [11.15] ng/dL). In general, notable mean changes were associated with variability in the data as indicated by large SDs, comparable median changes, or both.

Over the entire study, mean changes from open-label baseline to end of randomized treatment in glucose regulation parameters for the quetiapine XR group were as follows: glucose, 6.75 (21.36) mg/dL; insulin, 4.23 (20.06) µIU/mL; and $HOMA_R$, 1.49 (6.47). Over the entire study, mean changes in lipid parameters under assumed fasting conditions from open-label baseline to end of randomized treatment for the quetiapine XR group were as follows: cholesterol, -7.31 (35.80) mg/dL; high-density lipoproteins (HDLs), -3.90 (9.54) mg/dL; low-density lipoproteins (LDLs), -5.80 (30.85) mg/dL; and triglycerides, 10.02 (79.79) mg/dL. When glucose regulation data were compared for patients in different diabetic risk categories, mean increases in glucose, $HOMA_R$, and insulin were largest for patients with diabetes compared with patients at risk of developing diabetes and patients with no known

diabetic risk. Mean decreases QUICKI were highest for patients at risk of developing diabetes. Mean changes in glycosylated hemoglobin were similar for the 3 diabetic risk subgroups. In general, glucose regulation data were also variable as indicated by large SDs and the small number of patients with diabetes.

In the subset of patients participating in the open-label phase who were later randomized to quetiapine XR, no clinically significant mean changes in supine, standing, or orthostatic vital signs were observed during the open-label phase. The incidence of clinically important supine vital signs was <5% for any value or change, except as follows: increase or decrease in supine pulse (43.2% and 21.2%, respectively); increase or decrease in supine systolic blood pressure (24.3% and 29.9%, respectively); supine diastolic blood pressure (14.6%); orthostatic change in pulse (24.8%); and orthostatic change in systolic blood pressure (16.6%). For ECGs, a mean increase in heart rate (3.8 [11.2] bpm) was observed during the open-label phase. The incidence of a ≥15 bpm increase in heart rate was 24.5% and the incidence of a ≥15 bpm decrease in heart rate was 6.7%. The incidence of a ≥60 bpm increase in QT interval corrected using Fridericia's formula (QTcF) was 4.1%. Mean increases in weight (2.1 [4.7] kg) and waist circumference (1.6 [10.9] cm) were observed during the open-label phase. Mean increases in weight and waist circumference from open-label baseline to end of randomized treatment for the quetiapine XR group were 1.9 (5.4) kg and 2.2 (12.1) cm, respectively. The incidence of ≥7% increases in weight was 14.3% and the incidence of ≥7% decreases in weight was 2.1%. In the group of patients who received quetiapine XR during both phases, 76 (20.5%) patients had a ≥7% increase in weight from open-label baseline to end of randomized treatment. The incidence of patients with development of 3 or more metabolic risk factors was 19.9% and 12.5% when triglycerides were excluded as a risk factor.

During the randomized phase, no major differences were observed in mean changes for most laboratory parameters between the quetiapine XR and placebo groups. Exceptions included insulin, $HOMA_R$, and TSH, for which smaller mean changes were observed for the quetiapine XR group (0.44 [20.84] µIU/mL, 0.06 [8.17], and -0.1.5 [1.64] µIU/mL, respectively) compared with the placebo group (1.78 [22.36] µIU/mL, 0.54 [7.33], and -0.48 [4.18] µIU/mL, respectively). Mean decreases in cholesterol and LDLs were greater for the quetiapine XR group (-5.09 [31.15] mg/dL and -3.17 [26.73] mg/dL, respectively) compared with the placebo group (-2.41 [28.05] mg/dL and -1.87 [25.92] mg/dL, respectively). Data for these parameters were variable, as indicated by large SDs, comparable median changes, or both. When glucose regulation data for patients in the different diabetic risk subgroups were compared, greater mean changes in glucose, insulin, and $HOMA_R$ were observed in patients with diabetes in the quetiapine XR group (-5.61 [42.97] mg/dL, 9.23 µIU/mL, and -4.19 [15.10], respectively) compared with the placebo group (0.39 [34.28] mg/dL, 0.11 [35.86] µIU/mL, and -0.01 [13.10], respectively). In both the quetiapine XR and placebo groups, larger mean changes in glucose and QUICKI were observed for patients with no known diabetic risk compared with patients with diabetes and patients at risk of developing diabetes.

During the randomized phase, increases ≥15 bpm in supine pulse and decreases ≥20 millimeters of mercury in orthostatic systolic blood pressure were observed more

frequently for the quetiapine XR group (28.2% and 11.6%, respectively) compared with the placebo group (19.1% and 6.2%, respectively). ECG findings included a higher incidence of ≥15 bpm increases in heart rate and QTcF values ≥450 ms for the quetiapine XR group (10.2% and 2.5%, respectively) compared with the placebo group (6.6% and 0.3%, respectively). For both heart rate and QTcF interval, however, mean decreases were observed during the randomized phase. In addition, most patients in the quetiapine XR group with prolonged QTcF intervals had an increased QTcF interval at baseline. Although patients in the quetiapine XR group did not show a mean increase in weight, more patients in the quetiapine XR group (5.4%) compared with the placebo group (2.9%) had increases ≥7% in weight. Also, a small increase in waist circumference (0.5 cm) was reported for the quetiapine XR group. The incidence of patients with a treatment emergent shift from <3 to ≥3 metabolic risk factors was higher in the quetiapine XR group (17.6%) compared with the placebo group (12.8%). During the randomized phase, no mean change in total Simpson-Angus Scale score, total Barnes Akathisia Rating Scale global assessment score, or total Abnormal Involuntary Movement Scale score was observed for either the quetiapine XR group or placebo group.

During the randomized phase, Treatment Discontinuation Signs and Symptoms scale scores were somewhat higher in the placebo group compared with the quetiapine XR group, indicating that quetiapine XR was associated with signs and symptoms of discontinuation or interruption of treatment.