Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate extended release		
Edition No.:	Final		
Study code:	D1448C00002		
Date:	5 December 2007		

A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled and Active-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (Seroquel®) as Monotherapy in the Treatment of Patients with Major Depressive Disorder (Diamond Study)

Study center(s)

This study was conducted at 38 centers in the United States.

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	21 April 2006	Therapeutic confirmatory (III)
Last patient completed	22 May 2007	

Objectives

The **primary** objective of the study was to evaluate the efficacy of quetiapine extended-release (XR) versus placebo in patients with major depressive disorder (MDD).

Secondary objectives

1. To evaluate if quetiapine XR improves the health-related quality of life of patients with MDD, compared to placebo;

2. To evaluate if quetiapine XR improves satisfaction with medication in patients with MDD, compared to placebo;

3. To evaluate the efficacy of quetiapine XR compared to duloxetine in the treatment of patients with MDD;

4. To evaluate if quetiapine XR reduces anxiety symptoms in patients with MDD, compared to placebo;

5. To evaluate if quetiapine XR improves sleep quality in patients with MDD, compared to placebo;

6. To evaluate if quetiapine XR is effective in reducing suicidal ideation in patients with MDD, compared to placebo;

7. To evaluate if quetiapine XR improves somatic symptoms in the treatment of subjects with MDD, compared to placebo;

8. To evaluate if quetiapine XR is as safe and well-tolerated as placebo in the treatment of patients with MDD;

9. To evaluate if quetiapine XR improves health status in the treatment of patients with MDD.

An additional objective was to establish a panel of DNA samples from patients who provided separate consent for genetic research in order to enable exploratory studies of genetic factors that may influence drug response. The genetic research was optional for individual patients and centers and is not accounted for in this study report.

Study design

This was an 8-week, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in the treatment of patients with MDD versus placebo and duloxetine 60 mg. This study consisted of an up to 28-day enrollment and washout period, a 6-week randomized treatment period, and a 2-week post-treatment period that included titrated dose decreases during the first post-treatment week for patients randomly assigned to the quetiapine XR 300-mg/day and duloxetine 60-mg dose groups.

Target population and sample size

Male and female patients, 18 to 65 years old inclusive, with documented clinical diagnosis using the Mini-International Neuropsychiatric Interview (MINI) and meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) of either 296.2x Major Depressive Disorder, Single Episode, or 296.3x Major Depressive Disorder, Recurrent.

The patients had to have a Hamilton Rating Scale for Depression (HAM-D) score ≥22 to be eligible for the study. The aim of this study was to randomize a patient population with approximately 40% of the patients having a HAM-D score of ≥28.

The sample size calculation in this study was done to ensure an 80% power in demonstrating superior efficacy of each of the 2 quetiapine XR doses over placebo with regard to the primary outcome variable, change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 6. The appropriate sample size was attained by assuming an anticipated difference of 3.5 units from placebo and a standard deviation of 9 for the change in MADRS total score from randomization to Week 6. Based on a 2-sided test at a 5% significance level (ie, α=0.05), it was planned to randomize a sample size of 140 per treatment group and 560 in total to ensure a power of 90% in each individual comparison and an overall power of at least 80%. Assuming based on earlier studies that 93% of all patients assigned to randomized treatment were expected to be evaluable patients (to be included in the modified intent-to-treat [MITT] group), a total of about 600 patients assigned to randomized treatment were required to obtain 140 evaluable patients per treatment group. A total of 612 patients were assigned to randomized treatment, of whom 610 received treatment and were in the safety analysis set and 587 were included in the MITT analysis set. The study was not powered for a comparison of quetiapine XR versus duloxetine.

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

Quetiapine XR 50-mg or 300-mg tablets were orally administered in doses of quetiapine XR 150 mg or quetiapine XR 300 mg once daily, in the evening.

Duloxetine 30-mg capsules (over-encapsulated) were administered in doses of 60 mg/day. Placebo tablets matching quetiapine XR 50-mg tablets, placebo tablets matching quetiapine XR 300-mg tablets, and placebo capsules matching duloxetine 30-mg capsules (over-encapsulated) were administered once daily in the evening.

Study treatment was given in tablets or capsules of the following doses (Lot #): quetiapine XR 50-mg tablets (9003K, LJ4706, MC4605), quetiapine XR 300-mg tablets (9049K, 9051K, LM4613), placebo 50-mg matching tablets (CE888X, CL879X, CP021X), placebo 300-mg matching tablets (CE891X, CL888X, 73042001FC01), duloxetine 30-mg capsules (76057001FA02, 76057001FA03), and placebo 30-mg matching capsules (75022001FA02).

Duration of treatment

An initial washout period of 7 to 28 days (depending on the medications involved) was followed by a double-blind treatment period for up to 6 weeks (42 days). During a 2-week post-treatment period, patients randomly assigned to the quetiapine XR 300-mg/day dose group and the duloxetine 60-mg dose groups took titrated decreased doses of their randomly assigned study medication from Day 43 (final treatment visit) to Post-treatment Day 6. During the 2-week down-titration period, patients assigned to randomized treatment with quetiapine XR 150 mg/day received placebo from Day 43 (Final visit) to Day 49 (Post-treatment Day 6). For all groups, study drugs were stopped after Day 49. All patients

randomly assigned to treatment who completed the treatment period and assessments were asked to call in to an Interactive Voice Response System (IVRS) to participate in an assessment of discontinuation symptoms assessed by the Treatment Discontinuation Signs and Symptoms (TDSS) scale and return to the study center for 2 Post-treatment visits.

Criteria for evaluation (main variables)

The outcome variables are presented in Table S1.

Table S1 Outcome variables

Primary efficacy outcome variable

Change from randomization to Week 6 in the MADRS total score.

Secondary efficacy variables supporting the primary objective

Change from randomization to each assessment in MADRS total score; MADRS response, defined as a ≥50% reduction from randomization in the MADRS total score at Week 1 and Week 6; MADRS remission, defined as total score ≤8 at Week 6; change from randomization to Week 6 in the HAM-D total score and the HAM-D Item 1 score; change from randomization to Week 6 in CGI-S score; the proportion of patients with CGI-I score of "much/very much improved" at Week 6.

Secondary variable of particular interest

Change from randomization to Week 6 in Q-LES-Q percent maximum total score.

Other secondary efficacy variables

Change from randomization to Week 6 in Q-LES-Q Item 16 and Item 15 scores, HAM-A total score, HAM-A psychic anxiety subscale score, HAM-A somatic anxiety subscale score, HAM-D anxiety items score, HAM-D sleep disturbance items score, PSQI global score, MADRS Item 10 score, and EQ-5D score on each of the 5 domains and the visual analogue scale.

Safety variables

Laboratory values, physical examination, vital signs, weight, BMI, waist circumference, ECG, SAS, BARS, CSFQ, AEs (including EPS-related), TDSS, MADRS Item 10 score ≥4 or an AE related to suicidality, and incidences of suicidality using a Columbia-like analysis.

AE Adverse event. BARS Barnes Akathisia Rating Scale. BMI. Body Mass Index. CGI-I Clinical Global Impression - Improvement. CGI-S Clinical Global Impression - Severity. CSFQ Changes in Sexual Functioning Questionnaire. ECG Electrocardiogram. EPS Extrapyramidal symptoms. EQ-5D EuroQoL Health Utility Index. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. MADRS Montgomery-Åsberg Depression Rating Scale. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. SAS Simpson-Angus Scale. TDSS Treatment discontinuation signs and symptoms.

Statistical methods

All hypotheses were tested with 2-sided tests. Where appropriate, model-based point estimates were presented together with 2-sided 95% confidence intervals. Missing data were handled using the last observation carried forward (LOCF) approach, as appropriate.

The primary efficacy outcome variable (change in Montgomery-Åsberg Depression Rating Scale [MADRS] from randomization to Week 6) was analyzed using an analysis of covariance (ANCOVA) model that included randomization MADRS total score as covariate, treatment as fixed effect, and center as random effect. The secondary efficacy outcome variable of

particular interest (change in Quality of Life Enjoyment Satisfaction Questionnaire [Q-LES-Q] percent maximum total score from randomization to Week 6) was analyzed the same way as the primary variable. A step-wise sequential testing procedure was used for multiple comparisons across these 2 groups of efficacy variables to ensure that the overall significance level of 0.05 was preserved. First, the change in MADRS total score from randomization to Week 6 was tested for each dose versus placebo. If both the quetiapine XR doses were statistically significantly better than placebo, then the change in Q-LES-Q percent maximum total score from randomization to Week 6 was tested for each dose versus placebo. To handle multiplicity within each step, the Simes-Hommel procedure was used (Hommel 1988). No correction of multiplicity was applied for any other variables, or for the placebo and quetiapine XR comparisons with duloxetine.

Changes from randomization to each assessment in MADRS total score as well as changes from randomization to Week 6 in HAM-D total scores, HAM-D Item 1 score, Clinical Global Impression - Severity (CGI-S) score, Hamilton Rating Scale for Anxiety (HAM-A) total score, HAM-A psychic anxiety subscale score, HAM-A somatic anxiety subscale score, and Pittsburgh Sleep Quality Index (PSQI) global score were analyzed similarly to the primary objective. MADRS response at Week 1 and Week 6 and remission rates at Week 6, as well as the dichotomized Clinical Global Impression - Improvement (CGI-I) score ("much/very much improved" scores as one category vs all other scores as the second category) at Week 6 were analyzed utilizing logistic regression models. Changes from randomization to Week 6 in MADRS Item 10 (suicidal thoughts) score, HAM-D anxiety items (Items 10 and 11) score, HAM-D sleep disturbance items (Items 4-6) score, Q-LES-Q overall quality of life (Item 16) score, Q-LES-Q satisfaction with medication (Item 15) score, EuroQoL Health Utility Index (EQ-5D), as well as all safety assessments were presented by descriptive statistics.

The efficacy analyses were based on the MITT analysis set (Full Analysis Set), and the safety analyses were done on the data from patients in the safety analysis set.

Patient population

Analysis sets and patient baseline characteristics are presented in Table S2.

Table S2 Analysis sets and patient baseline characteristics

	PLA	QTP150	QTP300	DUL	Total
Analysis sets					
N (randomized)	157	152	152	151	612
N safety[b]	157	152	152	149	610
N MITT[c]	152	147	147	141	587
N PP	136	129	132	126	523
N TDSS	108	85	103	80	376
Completed 6-week randomized treatment period	124	100	113	105	442

Table S2 Analysis sets and patient baseline characteristics

		PLA	QTP150	QTP300	DUL	Total
Completed study[d]		100	73	92	71	336
Demographic characteristics (MITT analysis set)						
Sex: n (%)	Male	54 (35.5)	54 (36.7)	72 (49.0)	53 (37.6)	233 (39.7)
	Female	98 (64.5)	93 (63.3)	75 (51.0)	88 (62.4)	354 (60.3)
Age: years	Mean (SD)	42.3 (11.5)	40.9 (12.3)	41.6 (12.0)	40.2 (12.5)	41.3 (12.1)
	Min to max	19 to 63	18 to 64	19 to 65	19 to 65	18 to 65
Race: n (%)	Caucasian	105 (69.1)	111 (75.5)	110 (74.8)	107 (75.9)	433 (73.9)
	Black	39 (25.7)	30 (20.4)	31 (21.1)	25 (17.7)	125 (21.3)
	Oriental	2 (1.3)	1 (0.7)	1 (0.7)	1 (0.7)	5 (0.9)
	Other	6 (3.9)	5 (3.4)	5 (3.4)	8 (5.7)	24 (4.1)
Baseline disease characteristics (MITT analysis set)						
DSM-IV Diagnosis: n (%)						
296.2x MDD, Single Episode		22 (14.5)	17 (11.6)	18 (12.2)	16 (11.3)	73 (12.4)
296.3x MDD, Recurrent		130 (85.5)	130 (88.4)	129 (87.8)	125 (88.7)	514 (87.6)
MADRS total score	Mean (SD)	30.3 (5.0)	29.8 (5.3)	30.1 (5.2)	30.4 (4.5)	NC
HAM-D total score	Mean (SD)	25.2 (2.7)	25.2 (2.9)	25.4 (3.2)	25.2 (2.6)	NC
HAM-D Item 1	Mean (SD)	3.0 (0.4)	3.1 (0.5)	3.0 (0.5)	3.0 (0.4)	NC
HAM-A total score	Mean (SD)	18.3 (5.6)	18.4 (5.7)	18.4 (5.2)	19.3 (5.2)	NC
CGI-S score	Mean (SD)	4.4 (0.6)	4.4 (0.6)	4.4 (0.5)	4.4 (0.6)	NC
Q-LES-Q percent maximum total score	Mean (SD)	41.4 (13.8)	43.4 (14.7)	42.1 (13.7)	41.1 (13.1)	NC

[a] Patient E1009500 was screened for this study but mistakenly assigned to randomized treatment in another study. This patient was counted as screened for this study and was not counted as randomized in this study, but was not counted as a screen failure.
[b] Number of patients who received at least 1 dose of investigational product.
[c] Number of patients who took at least 1 dose of investigational product and had a randomization MADRS assessment and at least 1 valid MADRS assessment after randomization.
[d] Completed the randomization period and the 2-week follow-up period (TDSS).

CGI-S Clinical Global Impression Severity scale. DUL Duloxetine. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. MADRS Montgomery-Åsberg Depression Rating Scale. MDD Major depressive disorder. MITT Modified intention-to-treat. N Number of patients. NC Not calculated. PLA Placebo. PP Per-protocol. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR. SD Standard deviation. TDSS Treatment discontinuation signs and symptoms.

Efficacy results

The key efficacy results of the study are presented in Table S3.

Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)

Outcome variable	PLA N=152	QTP150 N=147	QTP300 N=147	DUL N=141
MADRS LS mean change from randomization	-11.18	-14.81[a]	-15.29[a]	-14.64[a]
Proportion with MADRS response (decrease in MADRS total score ≥50%)	36.2%	54.4%[b]	55.1%[a]	49.6%[c]
Proportion with MADRS remission (total score ≤8)	20.4%	26.5%	32.0%[c]	31.9%[c]
HAM-D LS mean change from randomization	-10.26	-13.12[a]	-14.02[a]	-12.37[c]
HAM-D Item 1 LS mean change from randomization	-1.07	-1.49[a]	-1.56[a]	-1.53[a]
CGI-S LS mean change from randomization	-1.06	-1.43[b]	-1.60[a]	-1.53[a]
Proportion improved on CGI-I	39.5%	54.1%[c]	59.2%[a]	56.7%[b]
Q-LES-Q % maximum total score LS mean change from randomization	11.26	13.68	13.59	16.69[b]
HAM-A total score LS mean change from randomization	-5.55	-7.76[b]	-7.38[b]	-7.83[a]

[a] p≤0.001 comparison with placebo.
[b] p<0.01 comparison with placebo.
[c] p<0.05 comparison with placebo.

CGI-S Clinical Global Impression Severity scale. CGI-I Clinical Global Impression Improvement scale. DUL Duloxetine. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

Note: For the analyses of MADRS and Q-LES-Q percent maximum total score change from randomization for the quetiapine XR groups, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy. P-values for the comparison between duloxetine and placebo and between duloxetine and quetiapine XR were not adjusted.

In patients with MDD, quetiapine XR at a dose of 150 mg/day or 300 mg/day was superior to placebo in reducing the level of depressive symptoms as demonstrated by the statistically significant change from randomization to Week 6 in the MADRS total score. Both quetiapine XR groups showed a greater improvement by Week 1 of treatment (p=0.002 and p=0.004 for 150 mg/day and 300 mg/day, respectively).

Overall, results from the secondary outcome variables supported the primary objective. Quetiapine XR was superior to placebo as assessed by the change from randomization to Week 6 in MADRS response rate, MADRS remission rate, HAM-D total score, HAM-D Item 1 (Depressed mood), HAM-A total score, HAM-A psychic anxiety subscore, CGI-S total score, and the proportion of patients with CGI-I ratings of "much/very much improved". The efficacy of quetiapine XR over placebo with regard to the HAM-A somatic anxiety subscale was not established. The quetiapine XR group showed a greater mean improvement in sleep quality than did the placebo group as assessed by change from randomization to Week 6 in

HAM-D sleep disturbance items (Items 4-6) (-2.9 for both quetiapine XR doses compared to -1.8 for placebo) and in the PSQI global score ($p<0.001$ for both doses).

There was no significant difference between quetiapine XR and placebo with regard to change from randomization to Week 6 in Q-LES-Q. Duloxetine was superior to placebo for this assessment, thus establishing assay sensitivity. In an evaluation of health-related quality of life, by Q-LES-Q Item 16, satisfaction with medication by Q-LES-Q Item 15 (satisfaction with medication), the efficacy of quetiapine XR over placebo was not demonstrated. Both the quetiapine and duloxetine groups showed greater improvement from baseline in health status, as assessed with the EQ-5D visual analogue scale score.

Quetiapine XR 150 or 300 mg/day and duloxetine showed similar effects on change from randomization to Week 6 in MADRS total score. However, quetiapine XR 150 mg/day was superior to duloxetine at Week 1: the quetiapine XR 150-mg/day and 300-mg/day groups exhibited LS mean changes versus duloxetine of -1.55 and -1.38 at Week 1 ($p=0.046$ and $p=0.078$, respectively), and duloxetine was not superior to placebo with regard to change from randomization to Week 1 in MADRS total score.

Quetiapine XR and duloxetine showed similar effects on change from randomization to Week 6 in MADRS response rate or change from randomization to Week 6 in MADRS remission rate, HAM-D total score, HAM-D Item 1 score, CGI-S total score, or proportion of patients with CGI-I scores of "much/very much improved", HAM-A total score, HAM-A psychic anxiety subscale score, and HAM-A somatic anxiety subscale score.

Safety results

The number (%) of patients who had at least 1 adverse event (AE) in any category is summarized in Table S4.

Table S4 Patients who had an adverse event in any category (safety analysis set)

Category of adverse event	PLA N=157 n (%)	QTP150 N=152 n (%)	QTP300 N=152 n (%)	DUL N=149 n (%)
Any adverse event	114 (72.6)	137 (90.1)	139 (91.4)	131 (87.9)
Serious adverse event	0 (0.0)	1 (0.7)	3 (2.0)	3 (2.0)
Serious adverse event leading to death	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Serious adverse event not leading to death	0 (0.0)	0 (0.0)	3 (2.0)	3 (2.0)
Drug-related adverse event[a]	78 (49.7)	124 (81.6)	125 (82.2)	112 (75.2)
Adverse events leading to discontinuation	9 (5.7)	33 (21.7)	23 (15.1)	27 (18.1)

[a] As judged by the investigator.
DUL Duloxetine. n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine XR.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as n/N*100.

Both the 150-mg/day and 300-mg/day doses of quetiapine XR were generally well tolerated. Most AEs were mild to moderate in all treatment groups. Serious AEs (SAEs) were infrequent in all treatment groups and none was considered to be drug-related. One death occurred during the study (quetiapine XR 150 mg/day) due to homicide, which was judged not to be drug-related. Larger proportions of patients in the quetiapine XR and duloxetine groups discontinued due to an AE than did patients in the placebo group. The incidence of drug-related AEs was higher in the quetiapine XR treatment groups compared to placebo.

The incidence of common AEs (occurring at an incidence of ≥2% in any treatment group) is shown by preferred term in Table S5. The table summarizes AEs occurring from the start of study treatment through the last study visit (Visit 8).

Table S5 Common (≥2%) adverse events by preferred term (safety analysis set)

	PLA N=157	QTP150 N=152	QTP300 N=152	DUL N=149
MedDRA preferred term[a]	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any adverse event	114 (72.6)	137 (90.1)	139 (91.4)	131 (87.9)
Dry mouth	14 (8.9)	51 (33.6)	59 (38.8)	31 (20.8)
Sedation	9 (5.7)	59 (38.8)	57 (37.5)	24 (16.1)
Somnolence	11 (7.0)	37 (24.3)	42 (27.6)	20 (13.4)
Dizziness	18 (11.5)	24 (15.8)	30 (19.7)	31 (20.8)
Headache	20 (12.7)	21 (13.8)	19 (12.5)	32 (21.5)
Constipation	10 (6.4)	9 (5.9)	14 (9.2)	17 (11.4)
Nausea	16 (10.2)	25 (16.4)	14 (9.2)	56 (37.6)
Fatigue	1 (0.6)	4 (2.6)	10 (6.6)	11 (7.4)
Irritability	7 (4.5)	4 (2.6)	10 (6.6)	2 (1.3)
Diarrhea	14 (8.9)	11 (7.2)	8 (5.3)	19 (12.8)
Dyspepsia	5 (3.2)	6 (3.9)	8 (5.3)	8 (5.4)
Vision blurred	3 (1.9)	8 (5.3)	8 (5.3)	4 (2.7)
Dysarthria	0 (0.0)	0 (0.0)	7 (4.6)	0 (0.0)
Nasal congestion	4 (2.5)	2 (1.3)	7 (4.6)	1 (0.7)
Nasopharyngitis	6 (3.8)	7 (4.6)	7 (4.6)	2 (1.3)
Weight increased	2 (1.3)	3 (2.0)	7 (4.6)	1 (0.7)
Anxiety	7 (4.5)	4 (2.6)	6 (3.9)	5 (3.4)
Back pain	3 (1.9)	7 (4.6)	6 (3.9)	6 (4.0)
Increased appetite	3 (1.9)	9 (5.9)	6 (3.9)	3 (2.0)
Musculoskeletal stiffness	1 (0.6)	2 (1.3)	6 (3.9)	2 (1.3)
Palpitations	3 (1.9)	2 (1.3)	6 (3.9)	2 (1.3)

Table S5 Common (≥2%) adverse events by preferred term (safety analysis set)

MedDRA preferred term[a]	PLA N=157 n (%)	QTP150 N=152 n (%)	QTP300 N=152 n (%)	DUL N=149 n (%)
Pharyngolaryngeal pain	1 (0.6)	3 (2.0)	6 (3.9)	2 (1.3)
Sinus congestion	1 (0.6)	3 (2.0)	6 (3.9)	1 (0.7)
Upper respiratory tract infection	11 (7.0)	3 (2.0)	6 (3.9)	6 (4.0)
Abnormal dreams	3 (1.9)	10 (6.6)	5 (3.3)	5 (3.4)
Dyspnea	1 (0.6)	3 (2.0)	5 (3.3)	0 (0.0)
Insomnia	13 (8.3)	11 (7.2)	5 (3.3)	24 (16.1)
Myalgia	3 (1.9)	5 (3.3)	5 (3.3)	3 (2.0)
Arthralgia	3 (1.9)	4 (2.6)	4 (2.6)	0 (0.0)
Gastroesophageal reflux disease	1 (0.6)	2 (1.3)	4 (2.6)	2 (1.3)
Nightmare	1 (0.6)	2 (1.3)	4 (2.6)	1 (0.7)
Pain	1 (0.6)	4 (2.6)	4 (2.6)	3 (2.0)
Restlessness	0 (0.0)	2 (1.3)	4 (2.6)	4 (2.7)
Vomiting	3 (1.9)	10 (6.6)	4 (2.6)	7 (4.7)
Chills	1 (0.6)	0 (0.0)	3 (2.0)	2 (1.3)
Cough	0 (0.0)	3 (2.0)	3 (2.0)	1 (0.7)
Disturbance in attention	0 (0.0)	6 (3.9)	3 (2.0)	5 (3.4)
Hypoesthesia	3 (1.9)	1 (0.7)	3 (2.0)	0 (0.0)
Lethargy	2 (1.3)	5 (3.3)	3 (2.0)	3 (2.0)
Muscle tightness	2 (1.3)	0 (0.0)	3 (2.0)	6 (4.0)
Pollakiuria	2 (1.3)	5 (3.3)	3 (2.0)	8 (5.4)
Tremor	2 (1.3)	2 (1.3)	3 (2.0)	8 (5.4)
Abdominal pain	2 (1.3)	3 (2.0)	2 (1.3)	0 (0.0)
Abdominal pain upper	4 (2.5)	1 (0.7)	2 (1.3)	5 (3.4)
Depression	2 (1.3)	0 (0.0)	2 (1.3)	3 (2.0)
Feeling jittery	0 (0.0)	0 (0.0)	2 (1.3)	4 (2.7)
Paresthesia	5 (3.2)	2 (1.3)	2 (1.3)	2 (1.3)
Stomach discomfort	1 (0.6)	2 (1.3)	2 (1.3)	3 (2.0)
Decreased appetite	1 (0.6)	5 (3.3)	1 (0.7)	8 (5.4)
Feeling hot and cold	1 (0.6)	0 (0.0)	1 (0.7)	3 (2.0)
Hot flush	3 (1.9)	1 (0.7)	1 (0.7)	6 (4.0)
Hyperhidrosis	1 (0.6)	0 (0.0)	1 (0.7)	11 (7.4)
Influenza	2 (1.3)	1 (0.7)	1 (0.7)	3 (2.0)
Muscle spasms	2 (1.3)	1 (0.7)	1 (0.7)	7 (4.7)
Restless legs syndrome	0 (0.0)	3 (2.0)	1 (0.7)	4 (2.7)

Table S5 Common (≥2%) adverse events by preferred term (safety analysis set)

MedDRA preferred term[a]	PLA N=157 n (%)	QTP150 N=152 n (%)	QTP300 N=152 n (%)	DUL N=149 n (%)
Tachycardia	0 (0.0)	4 (2.6)	1 (0.7)	1 (0.7)
Amnesia	0 (0.0)	3 (2.0)	0 (0.0)	0 (0.0)
Chest pain	4 (2.5)	3 (2.0)	0 (0.0)	3 (2.0)
Dizziness postural	0 (0.0)	3 (2.0)	0 (0.0)	3 (2.0)
Dysgeusia	3 (1.9)	4 (2.6)	0 (0.0)	3 (2.0)
Erectile dysfunction	1 (0.6)	1 (0.7)	0 (0.0)	5 (3.4)
Gastroenteritis	0 (0.0)	3 (2.0)	0 (0.0)	1 (0.7)
Gastroenteritis viral	4 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	2 (1.3)	1 (0.7)	0 (0.0)	3 (2.0)
Libido decreased	1 (0.6)	1 (0.7)	0 (0.0)	3 (2.0)
Memory impairment	1 (0.6)	3 (2.0)	0 (0.0)	0 (0.0)
Neck pain	1 (0.6)	0 (0.0)	0 (0.0)	3 (2.0)
Sinusitis	3 (1.9)	6 (3.9)	0 (0.0)	0 (0.0)
Tinnitus	2 (1.3)	3 (2.0)	0 (0.0)	2 (1.3)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.

DUL Duloxetine. MedDRA Medical Dictionary of Regulatory Activities. n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine XR.

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 QTP300 treatment group.

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

From the initiation of study treatment to the last study visit (which included the 2-week follow-up [TDSS] period), dry mouth, sedation, somnolence, dizziness, headache, and nausea were among the most common AEs in the quetiapine XR groups. The incidence rate across the quetiapine XR groups for these events was higher than that for placebo, although the incidence rates did not appear to be related to the dose of quetiapine XR received. The majority of these AEs were reported as mild to moderate for all groups. In the duloxetine treatment group, the most common AEs were nausea, headache, dry mouth, dizziness, insomnia, sedation, somnolence, diarrhea, and constipation.

The incidences of individual EPS-related AEs were low in the quetiapine XR groups (5.3% and 5.9% for 150 mg/day and 300 mg/day, respectively) with no dose-related pattern, and generally comparable to placebo (3.2%). The overall incidence of AEs related to EPS was highest in the duloxetine group (9.4%). The assessment of parkinsonian and akathisia symptoms as assessed by Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS) scores indicated that quetiapine XR treatment was similar to placebo, and an improvement or no change in symptoms was noted for the majority of patients in all active treatment groups at the end of the randomized treatment period.

There were no AEs related to QT prolongation reported during the study. There were 2 AEs potentially related to syncope during the study (preferred term, 'syncope'), both in the quetiapine XR 150-mg/day group. One of these was severe in intensity and not considered to be drug-related, and 1 was mild in intensity and considered to be drug-related. Neither event led to withdrawal from the study. There was 1 non-serious AE associated with neutropenia. One patient in the quetiapine XR 150-mg/day group had a neutrophil particle count of 1.12×10^9 cells/L at Week 4. No action was taken with regard to study drug, and this patient had a normal value at the end of treatment (Week 6). There were no AEs related to agranulocytosis. There were 4 AEs potentially related to diabetes: 1 in the quetiapine XR 150-mg/day group (hyperphagia), 2 in the quetiapine XR 300-mg/day group (hyperglycemia and polyuria), and 1 in the duloxetine group (thirst). Each was considered to be mild in intensity and no action was taken with regard to study treatment. The patient experiencing hyperglycemia had a shift to a clinically important high fasting glucose value at the end of the study. None of the other potentially diabetes-related events was associated with clinically important changes in glucose regulation parameters. AEs potentially related to nausea/vomiting occurred at a higher incidence in the duloxetine group (37.6%) than in the quetiapine XR 150-mg/day group (18.4%), the quetiapine XR 300-mg/day groups (10.5%), or in the placebo group (12.1%). The incidence of AEs potentially related to sexual dysfunction was low in both quetiapine XR groups and comparable to placebo (1.3% in all 3 groups). The incidence was higher in the duloxetine group (8.1%); these events occurred primarily in males. There was a higher incidence of AEs associated with somnolence in the quetiapine XR groups (64.5% at each dose) than in the placebo group. The majority were mild or moderate in intensity with onset during the first 4 days. The incidence, intensity, and time of onset of somnolence and sedation AEs in the quetiapine XR treatment groups were consistent with the AEs that were anticipated based on the known pharmacological profile of quetiapine. The incidence of AEs related to suicidality was low in all treatment groups (≤2%), and none of the AEs related to suicidality was considered to be drug-related. Based on AEs and MADRS Item 10 (suicidal thoughts) score, there was no clinical evidence to suggest a relationship between quetiapine XR treatment and increased suicidality.

Overall, the clinical laboratory results were consistent with those from previous studies in patients treated with quetiapine for other disorders. There were no notable differences among the treatment groups in any hematology assessments. Few patients had clinically important hematology values at the end of treatment, and there were no major differences across the 4 treatment groups. There were no notable differences between the treatment groups in mean change from baseline for most clinical chemistry assessments, including renal function, electrolytes, liver function, glucose regulation parameters (ie, fasting glucose, insulin, Homeostatic Model Assessment of insulin resistance [$HOMA_R$], Quantitative Insulin Sensitivity Check Index [QUICKI], and glycated hemoglobin), prolactin levels, or thyroid function tests. Triglycerides exhibited higher mean increases from baseline for the quetiapine XR groups than for the placebo group (mean changes from baseline were -2.5, 17.9, 16.0, and 5.1 for the placebo, quetiapine XR 150-mg/day, quetiapine XR 300-mg/day, and duloxetine groups, respectively). There were no notable differences between the groups regarding mean change in other lipid variables.

There were hemodynamic changes and weight gain results in the quetiapine XR groups that were consistent with the anticipated effects based on the pharmacological profile of quetiapine. No notable mean changes in ECG parameters were observed, and there were no treatment-emergent values related to QT or QTc prolongation in the quetiapine XR groups. The percentage of patients with a treatment-emergent shift from <3 to ≥3 metabolic risk factors was higher in the quetiapine XR groups (17.7% and 13.3% for the quetiapine XR 150- and 300-mg/day groups, respectively) than in the placebo group (6.4%).

Based on the mean change from baseline to the end of treatment in the CSFQ total score, sexual functioning improved slightly in all 4 treatment groups, with no apparent differences between the groups.