Drug product:	Seroquel XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate extended release		
Edition No.:	Final		
Study code:	D1448C00006		
Date:	10 December 2007		

A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL XR™) in Combination with an Antidepressant in the Treatment of Patients with Major Depressive Disorder with Inadequate Response to an Antidepressant Treatment (Pearl Study)

Study center(s)

This study was conducted in the USA (56 centers).

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	19 April 2006	Therapeutic confirmatory (III)
Last patient completed	18 July 2007	

Objectives

The **primary** objective of the study was to evaluate the efficacy of quetiapine fumarate extended-release in combination with an antidepressant versus an antidepressant in

combination with placebo in patients with Major Depressive Disorder (MDD) who have had an inadequate response to antidepressant monotherapy.[1]

Hereafter, quetiapine fumarate extended-release will be referred to as quetiapine XR (note that quetiapine fumarate extended-release was previously referred to as quetiapine fumarate sustained-release).

The **secondary** objectives were:

1. To evaluate if quetiapine XR in combination with an antidepressant improves health-related quality of life of patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;

2. To evaluate if quetiapine XR in combination with an antidepressant reduces anxiety symptoms in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;

3. To evaluate if quetiapine XR in combination with an antidepressant improves sleep quality in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;

4. To evaluate if quetiapine XR in combination with an antidepressant is effective in reducing suicidal ideation in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;

5. To evaluate if quetiapine XR in combination with an antidepressant improves somatic symptoms in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;

6. To evaluate if quetiapine XR in combination with an antidepressant improves satisfaction with medication in patients with MDD who have had an inadequate response to antidepressant monotherapy, compared to an antidepressant in combination with placebo;

7. To evaluate if quetiapine XR in combination with an antidepressant is as safe and well-tolerated as an antidepressant in combination with placebo in the treatment of patients with MDD who have had an inadequate response to antidepressant monotherapy;

8. To evaluate if quetiapine XR in combination with an antidepressant changes the plasma level of antidepressant.

This study also included the option for enrolled patients to provide a blood sample from which DNA was extracted and archived for future genetic research. The purpose of this research is

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[1] In order to clarify the primary and secondary objectives of the study in this report, minor revisions have been made to the original wording stated in the clinical study protocol.

to explore the effects of genetic polymorphisms on response to quetiapine XR and on susceptibility to MDD. The genetic research was optional for individual patients and centers and is not included in this study report.

Study design

This was an 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled, double-dummy, Phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to antidepressant monotherapy. The study comprised 3 periods: an enrollment and washout period of up to 14 days (for the discontinuation of all prohibited medications), a 6-week randomized treatment period, and a 2-week follow-up period. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment.

Target population and sample size

Male or female patients, 18 to 65 years old, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of MDD, Single Episode (296.2x) or MDD, Recurrent (296.3x) as confirmed by the Mini-International Neuropsychiatric Interview (MINI).

Patients should have been on treatment with 1 of the following antidepressants for at least 6 weeks prior to enrollment (at least minimum effective antidepressant dose according to the prescribing information), with at least 1 dose increase when permitted according to the prescribing information:

- amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine.

In addition, patients had to have a Hamilton Rating Scale for Depression (HAM-D) (17 item, hereafter referred to as HAM-D) total score ≥20 and a HAM-D Item 1 (depressed mood, hereafter referred to as HAM-D Item 1) score ≥2 at both enrollment and randomization.

It was planned to randomly assign 450 patients to obtain a total of 420 evaluable patients (140 per treatment group). The objective of the sample size calculation in this study was to demonstrate superior efficacy of quetiapine XR over placebo in combination with an antidepressant with respect to the primary outcome variable, change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 6. The planned sample size ensured a power of 90% and was attained by anticipating a difference of 3.5 units from placebo and a variability (standard deviation) of 9 for the change in the MADRS total score from randomization to Week 6.

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

The eligible patients were randomly assigned to one of the three treatment arms: quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo in combination with

ongoing antidepressant treatment. Tablets used in the study were: 50-mg and 300-mg quetiapine XR tablets, placebo tablets to match the 50-mg and 300-mg quetiapine XR tablets, and one ongoing antidepressant treatment in combination with quetiapine XR or placebo. Quetiapine XR 50-mg and 300-mg tablets (or placebo to match) were administered orally once daily in the evening.

Study treatment was given in tablets of the following doses (batch number): quetiapine XR 50 mg (LJ4701, LJ4706), quetiapine XR 300 mg (9049K, 9051K), placebo 50-mg match (CL879X), and placebo 300-mg match (CE891X).

Duration of treatment

Eligible patients underwent a washout period of up to 14 days for the discontinuation of all prohibited medications. Patients then entered a 6-week treatment period, when they were randomly assigned to blinded treatment in a 1:1:1 ratio to 150 mg/day quetiapine XR, 300 mg/day quetiapine XR, or placebo (each in combination with the ongoing antidepressant treatment). All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150-mg/day group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300-mg/day group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. The ongoing treatment with the antidepressant was maintained at the same dose throughout the study. During the 2-week follow-up period, no down-titration of quetiapine XR was performed since the dose of antidepressant was maintained.

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 the 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 the CGI-S score; the proportion of patients with a CGI-I score of "much/very much improved" at Week 6.
Secondary variable of particular interest
Change from randomization to Week 6 in the Q-LES-Q percent maximum total score.

Table S1 Outcome variables

Other secondary efficacy variables

Change from randomization to Week 6 in the Q-LES-Q overall quality of life (Item-16) score, HAM-A total score, HAM-A psychic anxiety subscale score, HAM-D anxiety items (Items 10 and 11) score, HAM-D sleep disturbance items (Items 4 to 6) score, PSQI global score, MADRS Item 10 (suicidal thoughts) score, HAM-A somatic anxiety subscale score, and Q-LES-Q satisfaction with medication (Item 15) score.

Pharmacokinetics

Change from randomization to Week 2 and Week 4 in the plasma concentration of antidepressant.

Safety variables

Laboratory values, physical examination, vital signs, weight, BMI, waist circumference, ECG, SAS total score, BARS global assessment (Item 4) score, CSFQ total score, AEs (including EPS-related), TDSS, MADRS Item 10 (suicidal thoughts) score ≥4 or an AE of or related to suicidality, and suicidality analysis.

AE Adverse event. BARS Barnes Akathisia Rating Scale. CGI-I Clinical Global Impression - Improvement. CGI-S Clinical Global Impression - Severity. CSFQ Changes in Sexual Functioning Questionnaire. ECG Electrocardiogram. EPS Extrapyramidal symptoms. 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 imputed using the last observation carried forward (LOCF) approach, as appropriate.

The primary efficacy outcome variable (change in the MADRS total score from baseline to Week 6) was analyzed using an analysis of covariance (ANCOVA) model that included baseline MADRS total score as covariate, treatment as fixed effect and center as random effect. The secondary efficacy outcome variable of particular interest (change in the Quality of Life Enjoyment Satisfaction Questionnaire [Q-LES-Q] percent maximum total score from baseline 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 the 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 the Q-LES-Q percent maximum total score from baseline 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.

Changes from randomization to each assessment in the MADRS total score as well as changes from randomization to Week 6 in the HAM-D total score, 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 versus all other scores as the second category) at Week 6 were analyzed utilizing logistic regression models. Changes from randomization to Week 6 in the MADRS Item 10 (suicidal thoughts) score, HAM-D anxiety items (Items 10 and 11) score, HAM-D sleep disturbance items (Items 4 to 6) score, Q-LES-Q overall quality of life (Item 16) score, Q-LES-Q satisfaction with medication (Item 15) score, changes from randomization to Weeks 2 and 4 in plasma concentration levels of antidepressants, as well as all safety assessments were presented by descriptive statistics.

The efficacy analyses were based on the modified intention-to-treat (MITT) analysis set (Full Analysis Set); this analysis set included all patients assigned to randomized treatment who took investigational product and who had a MADRS assessment at randomization and at least 1 valid MADRS assessment after randomization. The safety analyses were performed on the data from patients in the safety analysis set (all patients assigned to randomized treatment who took investigational product). The per-protocol (PP) analysis set included all patients in the MITT analysis set with no significant protocol violations or deviations. The treatment discontinuation signs and symptoms (TDSS) analysis set was used to summarize the TDSS results. This subset of the safety analysis set included patients who completed 6 weeks of double-blind treatment and who had 1 baseline (Week 6) TDSS assessment from the study treatment period and at least 1 TDSS assessment from the 2-week follow-up (TDSS) period. The pharmacokinetic (PK) analysis set included all patients assigned to randomized treatment who had a valid PK sample taken at randomization, at least 1 valid post-randomization PK sample taken, and no protocol violations or deviations affecting PK evaluations.

Patient population

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

Table S2 Analysis sets and patient baseline characteristics

	PLA	QTP150	QTP300	Total
Analysis sets				
N (randomized)	148	148	150	446
N safety[a]	148	148	149	445
N MITT[b]	143	143	146	432
N PP	121	121	122	364
N TDSS	106	102	83	291
N PK	75	72	68	215
Completed 6-week randomized treatment period	125	114	105	344
Completed study[c]	99	92	68	259

Table S2 Analysis sets and patient baseline characteristics

		PLA	QTP150	QTP300	Total
Demographic characteristics (MITT analysis set)					
Sex: n (%)	Male	45 (31.5)	34 (23.8)	40 (27.4)	119 (27.5)
	Female	98 (68.5)	109 (76.2)	106 (72.6)	313 (72.5)
Age: years	Mean (SD)	46.2 (10.9)	45.9 (11.0)	44.3 (11.3)	45.4 (11.1)
	Min to max	20 to 65	20 to 64	19 to 64	19 to 65
Race: n (%)	Caucasian	128 (89.5)	128 (89.5)	133 (91.1)	389 (90.0)
	Black	14 (9.8)	10 (7.0)	11 (7.5)	35 (8.1)
	Oriental	0	1 (0.7)	0	1 (0.2)
	Other	1 (0.7)	4 (2.8)	2 (1.4)	7 (1.6)
Baseline disease characteristics (MITT analysis set)					
DSM-IV diagnosis: n (%)					
296.2x MDD, Single Episode		10 (7.0)	8 (5.6)	14 (9.6)	32 (7.4)
296.3x MDD, Recurrent		133 (93.0)	135 (94.4)	132 (90.4)	400 (92.6)
MADRS total score	Mean (SD)	27.6 (5.5)	27.2 (5.2)	27.6 (5.0)	NC
HAM-D total score	Mean (SD)	24.2 (3.1)	24.0 (3.4)	24.0 (2.9)	NC
HAM-D Item 1 score	Mean (SD)	2.9 (0.6)	2.9 (0.6)	2.9 (0.6)	NC
HAM-A total score	Mean (SD)	17.9 (5.6)	17.7 (5.7)	18.7 (5.5)	NC
CGI-S score	Mean (SD)	4.4 (0.7)	4.4 (0.6)	4.5 (0.7)	NC
Q-LES-Q percent maximum total score	Mean (SD)	45.2 (13.6)	44.3 (13.8)	47.9 (14.8)	NC

[a] Number of patients who received at least 1 dose of investigational product.
[b] 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.
[c] Completed the randomized treatment period and the 2-week follow-up (TDSS) period.
CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. n Number of patients. NC Not calculated. PK Pharmacokinetic. 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 and pharmacokinetic 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=143	QTP150 N=143	QTP300 N=146
MADRS total score, LS mean change from baseline	-11.70	-13.60	-14.70[b]
Proportion with ≥50% MADRS response	46.2%	51.7%	58.9%[a]
Proportion with MADRS remission (total score ≤8)	24.5%	35.0%	42.5%[b]
HAM-D total score, LS mean change from baseline	-10.80	-12.63[a]	-13.53[b]
HAM-D Item 1 score, LS mean change from baseline	-1.35	-1.53	-1.60
HAM-A total score, LS mean change from baseline	-6.67	-7.43	-8.50[a]
CGI-S score, LS mean change from baseline	-1.23	-1.47	-1.52[a]
Proportion improved on CGI-I	46.9%	58.0%	58.2%[a]
Q-LES-Q percent maximum total score, LS mean change from baseline	11.32	10.37	11.82

[a] $p<0.05$ comparison with placebo.
[b] $p<0.01$ comparison with placebo.

CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. 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 total score and Q-LES-Q % maximum total score change from baseline, p-values were adjusted and compared with $\alpha=0.05$ using the Simes-Hommel procedure within the step-wise sequential testing strategy.

In patients with MDD, quetiapine XR at a dose of 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. Quetiapine XR 150 mg/day showed a greater mean reduction in depressive symptoms compared with placebo, but the difference did not reach statistical significance. The quetiapine XR 150-mg/day and 300-mg/day groups demonstrated a greater improvement compared with placebo in the MADRS total score by Week 1 of treatment, and this effect continued throughout the 6-week randomized treatment period. The mean change from baseline for both quetiapine XR treatment groups was superior to placebo at Week 1 (-5.95 in the placebo group; -9.06 for quetiapine XR 150 mg/day [$p<0.001$ vs placebo]; and -8.20 in the quetiapine XR 300 mg/day group [$p=0.002$ vs placebo]). Patients in the 300-mg/day group continued to demonstrate a statistically significant greater change in the MADRS total score compared with placebo throughout the 6 weeks of randomized treatment.

Overall, results from the secondary outcome variables supported the primary objective. Quetiapine XR 300 mg daily was superior to placebo as assessed by the change from randomization to Week 6 in the MADRS response rate, MADRS remission rate, HAM-D total score, HAM-A total score, HAM-A psychic anxiety subscale score, CGI-S 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-D Item 1 (depressed mood) score and the HAM-A somatic anxiety subscale score was not established. Quetiapine XR 150 mg/day showed superiority compared with placebo for the HAM-D total score change from randomization to Week 6. Both doses of quetiapine XR were also superior to placebo in improving sleep quality as assessed by the change from randomization to Week 6 in the PSQI global score.

Exploratory analysis of the interaction between quetiapine XR and the antidepressants and their associated metabolites, within the inherent limitations of obtaining appropriately timed PK sampling in an outpatient setting, revealed no apparent drug interactions requiring dose-adjustment of the antidepressant.

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=148 n (%)	QTP150 N=148 n (%)	QTP300 N=149 n (%)
Any adverse event	99 (66.9)	122 (82.4)	130 (87.2)
Serious adverse event	1 (0.7)	1 (0.7)	0
Serious adverse event leading to death	0	0	0
Serious adverse event not leading to death	1 (0.7)	1 (0.7)	0
Drug-related adverse event[a]	52 (35.1)	105 (70.9)	111 (74.5)
Adverse events leading to discontinuation	0[b]	17 (11.5)	29 (19.5)[c]

[a] As judged by the investigator.
[b] 1 Placebo patient (E1605429) is not included; the patient had an onset of AE (ECG abnormalities) prior to randomization, but was discontinued due to this AE during the randomized treatment period.
[c] 1 Quetiapine XR 300-mg/day patient (E1605422) is not included; the patient discontinued due to an AE, but the investigator did not specify which AE caused the patient to discontinue.
N Number of patients in treatment group. n Number of patients. 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. The overall incidence of AEs was highest in the quetiapine XR 300-mg/day group, followed by the quetiapine XR 150-mg/day and placebo groups. Most AEs were of mild to moderate

severity in all treatment groups. There were no deaths during the study. The number of serious AEs (SAEs) in the study was low (1 placebo patient and 1 quetiapine XR 150-mg/day patient); neither event was considered by the investigator to be possibly related to study medication. With the exception of 1 patient in the placebo group for whom an AE leading to discontinuation started prior to beginning study treatment, all of the AEs that led to discontinuation occurred in quetiapine XR–treated patients. The incidence of AEs considered by the investigator to be possibly related to study medication was higher in the quetiapine XR treatment groups compared with placebo and, as with the discontinuations due to AEs, appeared to be dose-related.

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

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

Adverse event[a]	PLA N=148 n (%)	QTP150 N=148 n (%)	QTP300 N=149 n (%)
Dry mouth	13 (8.8)	52 (35.1)	66 (44.3)
Somnolence	6 (4.1)	43 (29.1)	43 (28.9)
Sedation	6 (4.1)	25 (16.9)	33 (22.1)
Dizziness	8 (5.4)	17 (11.5)	21 (14.1)
Constipation	5 (3.4)	11 (7.4)	16 (10.7)
Nausea	12 (8.1)	13 (8.8)	15 (10.1)
Insomnia	10 (6.8)	16 (10.8)	12 (8.1)
Headache	20 (13.5)	21 (14.2)	11 (7.4)
Fatigue	7 (4.7)	23 (15.5)	10 (6.7)
Diarrhea	10 (6.8)	10 (6.8)	10 (6.7)
Increased appetite	8 (5.4)	8 (5.4)	10 (6.7)
Weight increased	1 (0.7)	3 (2.0)	9 (6.0)
Upper respiratory tract infection	5 (3.4)	7 (4.7)	6 (4.0)
Back pain	0	3 (2.0)	6 (4.0)
Irritability	9 (6.1)	9 (6.1)	5 (3.4)
Nasopharyngitis	2 (1.4)	5 (3.4)	4 (2.7)
Anxiety	1 (0.7)	5 (3.4)	4 (2.7)
Abnormal dreams	2 (1.4)	4 (2.7)	4 (2.7)
Disturbance in attention	4 (2.7)	3 (2.0)	4 (2.7)
Dyspepsia	3 (2.0)	2 (1.4)	4 (2.7)
Akathisia	1 (0.7)	2 (1.4)	4 (2.7)

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

Adverse event[a]	PLA N=148 n (%)	QTP150 N=148 n (%)	QTP300 N=149 n (%)
Restlessness	2 (1.4)	1 (0.7)	4 (2.7)
Hyperhidrosis	1 (0.7)	5 (3.4)	3 (2.0)
Decreased appetite	1 (0.7)	4 (2.7)	3 (2.0)
Muscle spasms	1 (0.7)	4 (2.7)	3 (2.0)
Arthralgia	0	4 (2.7)	3 (2.0)
Hypersomnia	0	3 (2.0)	3 (2.0)
Chills	1 (0.7)	2 (1.4)	3 (2.0)
Abdominal distension	1 (0.7)	1 (0.7)	3 (2.0)
Gastroesophageal reflux disease	0	1 (0.7)	3 (2.0)
Muscle twitching	1 (0.7)	0	3 (2.0)
Libido decreased	0	0	3 (2.0)
Musculoskeletal stiffness	0	0	3 (2.0)
Vision blurred	1 (0.7)	4 (2.7)	2 (1.3)
Sinusitis	5 (3.4)	2 (1.4)	2 (1.3)
Gastroenteritis viral	3 (2.0)	0	2 (1.3)
Depression	1 (0.7)	6 (4.1)	1 (0.7)
Vomiting	2 (1.4)	5 (3.4)	1 (0.7)
Pain in extremity	2 (1.4)	3 (2.0)	1 (0.7)
Fall	1 (0.7)	3 (2.0)	1 (0.7)
Abdominal pain upper	4 (2.7)	1 (0.7)	0

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
MedDRA Medical Dictionary of Regulatory Activities. N Number of patients in treatment group. n Number of patients. 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.

The pattern of common AEs observed in the quetiapine XR treatment groups generally conformed to that which was anticipated based on the known pharmacological profile of quetiapine. The most common AEs in the quetiapine XR groups were dry mouth, somnolence, sedation, fatigue, headache, dizziness, insomnia, constipation, and nausea, and generally occurred at a higher incidence compared with placebo. For the 2 quetiapine XR groups, most instances of nausea, insomnia, and headache started during the post-treatment period.

The incidence of extrapyramidal symptoms (EPS)-related AEs in the quetiapine XR treatment groups was low. The incidence of AEs potentially related to EPS was 3.4% in both the placebo and quetiapine XR 150-mg/day groups, and was 8.1% in the quetiapine XR 300-mg/day treatment group. The most common AEs potentially related to EPS were akathisia, restlessness, and tremor. Overall, the assessment of parkinsonian and akathisia symptoms as assessed by SAS and BARS scores indicated that quetiapine XR treatment was similar to placebo; almost all patients in each treatment group experienced no change or an improvement in score at the end of treatment. The percentage of patients whose BARS global assessment score worsened between baseline and the end of treatment was higher in the quetiapine XR groups compared with placebo, in a dose-dependent manner. This latter finding agrees with the higher incidence of akathisia AEs in the quetiapine XR groups (1.4% and 2.7% in the 150-mg/day and 300-mg/day groups, respectively) compared with placebo (0.7%). These results were not likely influenced by the use of anticholinergic medications because anticholinergic use was low during the randomized treatment period (≤3.5% in the quetiapine XR 150-mg/day group, ≤5.3% in the quetiapine XR 300-mg/day group, and ≤3.7% in the placebo group at any week).

The incidence of AEs related to suicidality was low in all treatment groups. No differences were observed among the 3 treatment groups in the change in the MADRS Item 10 score from randomization to Week 6.

A shift from normal to a clinically important low neutrophil count occurred in 1 patient in the placebo group and 1 patient in the quetiapine XR 150-mg/day group. The instance of neutropenia in the quetiapine XR–treated patient was reported as an AE. The patient had a normal neutrophil value at baseline and a potentially clinically important low value at Week 4, but the neutrophil level returned to normal at the end of the randomized treatment period. The AE of neutropenia resulted in the discontinuation of the patient from the study and was considered by the investigator to be possibly related to study medication. There were no cases of agranulocytosis.

AEs potentially related to diabetes were reported for 3 patients during the study: 2 in the placebo group (1 with polyuria; 1 with polyuria and thirst) and 1 in the quetiapine XR 300-mg/day group (thirst); none were reported for the quetiapine XR 150-mg/day group. All 4 events were of mild intensity, were not an SAE, and did not result in the discontinuation of the patient from the study; all the events were considered by the investigator to be possibly related to study medication. Other than polyuria or thirst, the patients showed no additional signs or symptoms indicative of DM. There were no notable laboratory values related to glucose regulation associated with any of these potentially diabetes-related AEs.

The incidence of AEs potentially related to sexual dysfunction was low (≤2%) in all 3 treatment groups. Based on the change from baseline to the end of treatment in the CSFQ total score, sexual functioning improved slightly in all 3 treatment groups, with no apparent differences among the treatment groups or between males and females.

The incidence of AEs that followed discontinuation of study treatment during the 2-week follow-up (TDSS) period included higher rates for quetiapine XR compared with placebo for

nausea, insomnia, diarrhea, anxiety, chills, and headache. Elicited responses for the TDSS scale about specific symptoms following treatment discontinuation generally confirmed the reported AEs. These results confirm the recommendation for gradual down-titration of quetiapine XR when patients discontinue treatment.

Overall, the clinical laboratory results in this study were consistent with the known pharmacological profile of quetiapine. There were no differences judged to be clinically relevant among the treatment groups in the changes from baseline for any hematology assessments. The most notable change in clinical chemistry parameters was an increase in triglycerides in the quetiapine XR 150-mg/day and 300-mg/day groups (39.5 and 35.6 mg/dL, respectively) compared with placebo (6.7 mg/dL). Increases in glucose and insulin levels occurred in the quetiapine XR groups (150 mg/day: 4.81 mg/dL and 2.20 μIU/mL; 300 mg/day: 5.86 mg/dL and 8.33 μIU/mL, respectively), that were larger than the increase in the placebo group (2.46 mg/dL and 1.40 μIU/mL, respectively). There was a high degree of interpatient variability in the changes to the end of treatment for lipids, glucose, and insulin; the degree of variability was similar between confirmed fasting and non-confirmed fasting values.

Among patients at baseline who either did not exhibit clinically important findings or exhibited clinically important low values, the incidence of a shift to a clinically important high glucose level was higher in the quetiapine XR 150-mg/day and 300-mg/day groups (6.4% and 8.7%) compared with the placebo group (4.8%). The incidence of shifts to clinically important high values for the glucose regulation parameters were similar between assumed fasting and confirmed fasting patients. A shift to a clinically important HbA1c level occurred during the study for 1 patient in each of the 3 treatment groups.

Few patients had clinically important hematology shifts at the end of treatment, and there were no major differences among the 3 treatment groups. The most notable clinical chemistry shifts at the end of treatment occurred for lipids. Patients in all 3 treatment groups exhibited shifts to clinically important high values of triglycerides, total cholesterol, and LDL cholesterol, as well as a shift to a clinically important low HDL cholesterol value. The shifts to clinically important high values of triglycerides (11%, 18%, and 22% of placebo and quetiapine XR 150-mg/day and 300-mg/day patients, respectively) and LDL cholesterol (8%, 6%, and 7% of placebo and quetiapine XR 150-mg/day and 300-mg/day patients, respectively) occurred in a dose-dependent manner in the quetiapine XR groups. The shifts to clinically important low values of HDL cholesterol (11%, 10%, and 12% of placebo and quetiapine XR 150-mg/day and 300-mg/day patients, respectively) in the quetiapine XR groups were also dose-dependent.

The incidence of patients with a treatment-emergent shift from <3 to ≥ 3 metabolic risk factors was higher in quetiapine XR–treated patients (approximately 17%) compared with placebo (6%). There were no cases of treatment-emergent hypothyroidism based on clinically important high thyroid-stimulating hormone (TSH) values in combination with clinically important low thyroxine (T4) values. One non-serious AE of hypothyroidism was reported in a patient treated with quetiapine XR 150 mg/day. The AE was not considered by the

investigator to be possibly related to study medication and the AE did not result in the patient being withdrawn from the study. Treatment-emergent shifts to potentially clinically important high prolactin values at the end of treatment occurred in 1 patient in the placebo group, 2 patients in the quetiapine XR 150-mg/day group, and 3 patients in the quetiapine XR 300-mg/day group. One of these instances of an elevated prolactin level at the end of treatment was reported as an AE of hyperprolactinemia (quetiapine XR 300 mg/day–treated patient).

The percentage of patients with a weight gain of ≥7% was highest in the quetiapine XR 300-mg/day group (8%); results in the quetiapine XR 150-mg/day group were comparable to placebo (1% to 2%). Across all treatment groups including placebo, there was a trend for a weight gain of ≥7% to occur more frequently in patients in the lower body mass index (BMI) categories. A weight decrease of ≥7% between baseline and the end of treatment, the incidence of which was low, occurred more frequently in the placebo group compared with the quetiapine XR groups (eg, 3% and 0%-1%, respectively).

There were no notable differences in the mean changes from baseline to the end of treatment in vital sign (including orthostatic changes) or ECG data between either dose of quetiapine XR and placebo. Small decreases from baseline in standing systolic and diastolic blood pressure (approximately 2 to 3 mmHg) were observed in all 3 treatment groups; a similar pattern was observed for supine systolic and diastolic blood pressure. Small increases from baseline in supine and standing pulse (approximately 2 to 4 bpm) were observed in the 2 quetiapine XR groups; the effect appeared to be dose-related. No notable mean changes in ECG parameters were observed. There were no instances when a QTc Fridericia value of ≥450 ms and a QTc increase of ≥60 ms were observed in the same patient in any treatment group. A potentially clinically important shift to QT prolongation (≥60 ms) occurred in 1 patient in the quetiapine XR 150-mg/day group (increase of 68 ms from a baseline QTc Fridericia value of 363 ms). No AEs potentially related to QT prolongation occurred during the study, except for 1 instance of a prolonged QTc interval in a patient assigned to the placebo group that occurred prior to randomization.