Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate extended release		
Edition No.:	Final		
Study code:	D1448C00003		
Date:	17 January 2008		

A Multicenter, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended Release (SEROQUEL XR) as Mono-Therapy in the Treatment of Adult Patients with Major Depressive Disorder (OPAL STUDY)

Study center(s)

This study was conducted at 35 sites in the United States.

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	29 May 2007	

Objectives

The **primary** objective of the study was to evaluate the efficacy of quetiapine extended-release (XR) compared with placebo in the treatment of patients with major depressive disorder (MDD), as assessed by the change from randomization to Week 8 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

Secondary objectives:

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

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

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

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

5. To evaluate if quetiapine XR improves somatic symptoms in the treatment of patients with MDD, compared with placebo;

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

7. To evaluate if quetiapine XR improves health status in the treatment of patients with MDD, compared with placebo;

8. To evaluate the safety and tolerability of quetiapine XR compared with placebo 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.

Study design

This was a 10-week, multicenter, double-dummy, randomized, parallel-group, placebo-controlled Phase III study of the efficacy and safety of quetiapine XR given as monotherapy in the treatment of patients with MDD. The study consisted of an up to 28-day enrollment period, an 8-week randomized treatment period, and a 2-week post-treatment period. All quetiapine XR patients initiated treatment on quetiapine XR 50 mg/day and were up-titrated to 150 mg/day at Day 3. Placebo patients received matched placebo according to the same treatment plan. After 2 weeks of treatment, patients with an inadequate response (defined as failure to achieve a ≥20% improvement from randomization in MADRS total score) were up-titrated to twice their original dose (300 mg/day quetiapine XR or matching placebo). Investigators were blinded to the criterion defining inadequate response (ie, the criterion for inadequate response was defined in a document separate from the study protocol and not shared with the investigator) and were blinded to dose increase. At the end of 8 weeks of randomized treatment, all investigational product was discontinued and patients underwent a 2-week post-treatment follow-up period.

Target population and sample size

Male and female patients, 18 to 65 years old inclusive, with 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 and a HAM-D Item 1 (depressed mood) score ≥2 at both enrollment and randomization to be eligible for the study. It was an aim of this study that approximately 40% of the patients would have randomization HAM-D total scores of ≥28.

The sample size calculation in this study was done to demonstrate superior efficacy of quetiapine XR over placebo with regard to the primary outcome variable, change in MADRS total score from randomization to Week 8. 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 8. For a two-sided hypothesis test with a 5% significance level (ie, α=0.05), a sample size of 140 evaluable patients per treatment group was required to ensure 90% power. Assuming based on earlier studies that 93% of all patients assigned to randomized treatments were expected to be evaluable patients (to be included in the modified intention-to-treat [MITT] group), a total of about 300 patients were required to obtain 140 evaluable patients per treatment group. A total of 310 patients were randomized, yielding 307 patients eligible for the safety analysis set and 299 patients eligible for the MITT analysis set.

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

Quetiapine XR 50-mg or 300-mg extended-release tablets were orally administered once daily in the evening. Placebo tablets matching quetiapine XR 50-mg tablets or placebo tablets matching quetiapine XR 300-mg tablets were administered once daily, in the evening.

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

Duration of treatment

An initial washout period of up to 28 days (depending on the medications involved) was followed by an 8-week, double-blind randomized treatment period. After 2 weeks of treatment, patients with an inadequate response were treated with double the randomized dose (ie, quetiapine XR 300 mg/day or placebo). The 8-week, double-blind treatment period was followed by a 2-week follow-up period.

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 8 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 (decrease in MADRS total score of ≥50%) at Week 1 and Week 8; MADRS remission at Week 8; change from randomization to Week 8 in the HAM-D total score and the HAM-D Item 1 score; change from randomization to Week 8 in the Clinical Global Impression - Severity (CGI-S) score; proportion of patients with Clinical Global Impression - Improvement (CGI-I) rating of 'very much improved' or 'much improved' at Week 8.

Secondary efficacy variable of particular interest

Change from randomization to Week 8 in Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) percent maximum total score.

Other secondary efficacy variables

Q-LES-Q overall quality of life score, Hamilton Rating Scale for Anxiety (HAM-A) total score, HAM-A psychic anxiety subscale score, HAM-D anxiety items score, HAM-D sleep disturbance items score, Pittsburgh Sleep Quality Index (PSQI) global score, MADRS Item 10 (suicidal thoughts) score, HAM-A somatic anxiety subscale score, Q-LES-Q satisfaction with medication score, and in EuroQoL Health Utility Index (EQ-5D) on each of the 5 domains and the visual analogue scale.

Pharmacokinetic variables

The relationship between plasma levels of quetiapine and metabolite, and change from randomization in total MADRS score will be analyzed at a later time, separate from the results presented in this Clinical Study Report.

Safety variables

Laboratory values, physical examination, vital signs, weight, waist circumference, CSFQ total score, ECG, SAS, BARS, AEs (including EPS-related), TDSS, MADRS Item 10 (suicidal thoughts) score ≥4 or an AE related to suicidality, and incidences of suicidality using Columbia-like 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. 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 two-sided tests. Where appropriate, model-based point estimates were presented together with two-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 8) was analyzed using an analysis of covariance (ANCOVA) model that included treatment, center, and randomization MADRS total score as explanatory variables. Randomization MADRS total score was treated as a covariate, center as a random effect, and treatment as a fixed effect.

Changes from randomization to each assessment in MADRS total score as well as changes from randomization to Week 8 in Quality of Life Enjoyment Satisfaction Questionnaire (Q-LES-Q) percent maximum total score, 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.

For the comparison of primary interest (change in MADRS total score from randomization) and the secondary variable comparison of particular interest (change in Q-LES-Q percent maximum total score from randomization), the overall Type-I error rate was controlled by using a sequential testing procedure. First, the primary outcome variable, change in MADRS total score from randomization to Week 8, was tested. If quetiapine XR was statistically significantly better than placebo, then the hypothesis related to the variable change in Q-LES-Q percent maximum total score from randomization to Week 8 was tested. No formal Q-LES-Q comparison was to be performed if the MADRS comparison was not significant as the adjusted p-value would be greater than alpha (i.e., 0.05).

MADRS response at Week 1 and Week 8 and remission rates at Week 8, 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 8 were analyzed utilizing logistic regression models. Changes from randomization to Week 8 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	QTP	Total
Analysis sets			
N (randomized)	156	154	310
N safety[a]	155	152	307
N MITT[b]	152	147	299
N PP	132	135	267
N TDSS	78	81	159

Table S2 Analysis sets and patient baseline characteristics

		PLA	QTP	Total
Adequate response[c]		102	107	209
Inadequate response[c]		35	22	57
Completed 8-week randomized treatment period		111	108	219
Completed study[d]		78	81	159
Demographic characteristics (MITT analysis set)				
Sex: n (%)	Male	54 (35.5)	52 (35.4)	106 (35.5)
	Female	98 (64.5)	95 (64.6)	193 (64.5)
Age: years	Mean (SD)	42.6 (11.7)	43.3 (10.5)	42.9 (11.1)
	Min to max	18 to 64	19 to 61	18 to 64
Race: n (%)	Caucasian	100 (65.8)	101 (68.7)	201 (67.2)
	Black	42 (27.6)	40 (27.2)	82 (27.4)
	Oriental	3 (2.0)	0	3 (1.0)
	Other	7 (4.6)	6 (4.1)	13 (4.3)
Baseline disease characteristics (MITT analysis set)				
DSM-IV diagnosis: n (%)				
296.2x MDD, Single Episode		21 (13.8)	9 (6.1)	30 (10.0)
296.3x MDD, Recurrent		131 (86.2)	138 (93.9)	269 (90.0)
MADRS total score	Mean (SD)	29.3 (5.3)	29.7 (6.2)	NC
HAM-D total score	Mean (SD)	25.6 (2.9)	25.4 (3.3)	NC
HAM-D Item 1	Mean (SD)	3.0 (0.5)	3.1 (0.5)	NC
HAM-A total score	Mean (SD)	19.3 (5.7)	18.6 (5.4)	NC
CGI-S total score	Mean (SD)	4.6 (0.7)	4.6 (0.7)	NC
Q-LES-Q % maximum total score	Mean (SD)	45.2 (15.1)	43.4 (15.0)	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] Patients with inadequate response after 2 weeks of treatment (defined as a failure to achieve ≥20% improvement from randomization in MADRS total score) were up-titrated to double their initial dose (300 mg quetiapine XR or double the placebo dose). Those with an adequate response remained at their initial dose (150 mg quetiapine XR or a matching placebo dose). This includes patients still receiving study drug at Week 2 (137 patients in the placebo group and 129 patients in the quetiapine XR group).
[d] Completed the randomization period and the 2-week follow-up period (TDSS).

CGI-S Clinical Global Impression Severity scale. DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition. 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. NC Not calculated. PP Per-protocol. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. 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 8 (LOCF, MITT analysis set)

Outcome variable	PLA N=152	QTP N=147
MADRS total score LS mean change from randomization	-13.1	-16.49[a]
Proportion with MADRS response (decrease in MADRS total score of ≥50%)	48.0%	61.9%[b]
Proportion with MADRS remission (total score ≤8)	25.0%	34.7%[c]
HAM-D total score LS mean change from randomization	-12.35	-14.75[b]
HAM-D Item 1 LS mean change from randomization	-1.40	-1.71[b]
CGI-S total score LS mean change from randomization	-1.24	-1.64[a]
Proportion improved on CGI-I	52.0%	63.3%[b]
Q-LES-Q % maximum total score LS mean change from randomization	11.93	13.80
HAM-A total score LS mean change from randomization	-7.70	-9.14[b]

[a] p<0.01 comparison with placebo.
[b] p<0.05 comparison with placebo.
[c] p=0.052 comparison with placebo.

CIG-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.

Based on the number of patients still receiving randomized treatment at Week 2, a total of 35 of 137 (26%) and 22 of 129 (17%) patients in the placebo and quetiapine XR groups, respectively, met the criterion for inadequate response (failure to achieve a ≥20% improvement from randomization in MADRS total score) and were up-titrated to double the initial randomized dose after 2 weeks of treatment.

In patients with MDD, quetiapine XR was superior to placebo in reducing the level of depressive symptoms as demonstrated by the statistically significant mean change from randomization to Week 8 in the MADRS total score. The quetiapine XR-treated group showed greater improvement by Week 1 of treatment (LS mean difference from placebo in change from randomization was -1.9, p=0.01), and the greater improvement compared with placebo was maintained throughout the 8-week randomized treatment period. In the evaluation of health-related quality of life with Q-LES-Q, the efficacy of quetiapine XR over placebo was not demonstrated. Overall, results from the secondary outcome variables supported the primary objective. For example, the quetiapine XR group demonstrated greater MADRS response, remission, reduction in the HAM-A total score, improvement in HAM-A psychic anxiety subscale score, and improvement in CGI-S score, in comparison to the placebo group. A greater proportion of quetiapine XR patients had a CGI-I score of

"much/very much improved" at Week 8 compared with the placebo group. The quetiapine XR group showed greater mean improvement in sleep quality than the placebo group as assessed by change from randomization to Week 8 in HAM-D sleep disturbance items (Items 4-6) score and in the PSQI global score. In the evaluation of health status with EQ-5D, the efficacy of quetiapine XR over placebo was not demonstrated.

Subgroup analyses for the primary variable indicated that the efficacy of quetiapine was not driven by any specific subgroup (ie, subgroups based on age, sex, race, or baseline disease severity [HAM-D ≥28 or <28]).

This study was not designed to compare the 150- and 300-mg doses of quetiapine XR. A reliable comparison of efficacy between the 2 quetiapine XR doses was not possible because the patients were not at the specified doses for the same length of time. However, the change from randomization to Week 8 in MADRS total score was evaluated among patients with and without an adequate or inadequate response. The change from randomization to Week 8 was -15.5 and -18.8 in placebo and quetiapine XR patients who had an adequate response, respectively, and was -6.2 and -8.7 in placebo and quetiapine XR patients who had had an inadequate response, respectively.

Safety results

Quetiapine XR was generally safe and well tolerated.

The number (%) of patients who had at least 1 adverse event (AE) in any category is summarized in Table S4. Most AEs were mild to moderate in the quetiapine XR and placebo treatment groups. Serious adverse events (SAEs) were infrequent in both treatment groups. No deaths occurred in the study. Larger proportions of patients in the quetiapine XR group experienced an AE and discontinued due to an AE than did patients in the placebo group. The incidence of drug-related AEs was higher in the quetiapine treatment group compared to placebo.

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

Category of adverse event	PLA N=155 n (%)	QTP N=152 n (%)
Any adverse event	96 (61.9)	125 (82.2)
Serious adverse event	2 (1.3)	3 (2.0)
Serious adverse event leading to death	0	0
Serious adverse event not leading to death	2 (1.3)	3 (2.0)
Drug-related adverse event[a]	44 (28.4)	101 (66.4)
Adverse events leading to discontinuation	4 (2.6)	15 (9.9)

[a] As judged by the investigator.

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.

The incidence of common AEs (occurring at an incidence of ≥2% in any treatment group) is shown by preferred term in Table S5. This table includes AEs collected from the start of treatment until the last treatment visit, a period of time that included the 2-week treatment discontinuation signs and symptoms (TDSS) follow-up period.

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

	PLA N=155	**QTP N=152**
MedDRA preferred term[a]	**n (%)**	**n (%)**
Any adverse event	**96 (61.9)**	**125 (82.2)**
Dry mouth	10 (6.5)	51 (33.6)
Sedation	4 (2.6)	35 (23.0)
Somnolence	8 (5.2)	31 (20.4)
Headache	16 (10.3)	22 (14.5)
Insomnia	4 (2.6)	14 (9.2)
Dizziness	6 (3.9)	13 (8.6)
Fatigue	0	11 (7.2)
Nausea	11 (7.1)	10 (6.6)
Diarrhea	6 (3.9)	10 (6.6)
Increased appetite	2 (1.3)	10 (6.6)
Constipation	2 (1.3)	9 (5.9)
Nasal congestion	3 (1.9)	9 (5.9)
Arthralgia	4 (2.6)	8 (5.3)
Vomiting	4 (2.6)	8 (5.3)
Irritability	2 (1.3)	6 (3.9)
Upper respiratory tract infection	6 (3.9)	6 (3.9)
Gastroesophageal reflux disease	0	5 (3.3)
Vision blurred	0	5 (3.3)
Weight increased	0	5 (3.3)
Abdominal pain upper	0	4 (2.6)
Depression	0	4 (2.6)
Dyspepsia	2 (1.3)	4 (2.6)
Nasopharyngitis	11 (7.1)	4 (2.6)
Rhinitis	1 (0.6)	4 (2.6)
Abdominal distension	0	3 (2.0)

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

MedDRA preferred term[a]	PLA N=155 n (%)	QTP N=152 n (%)
Akathisia	0	3 (2.0)
Anxiety	3 (1.9)	3 (2.0)
Back pain	2 (1.3)	3 (2.0)
Extrapyramidal disorder	1 (0.6)	3 (2.0)
Joint stiffness	0	3 (2.0)
Musculoskeletal stiffness	2 (1.3)	3 (2.0)
Muscle spasms	1 (0.6)	3 (2.0)
Myalgia	1 (0.6)	3 (2.0)
Sinusitis	4 (2.6)	2 (1.3)

[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. 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 QTP treatment group.
Note: Percentages are calculated as n/N*100.

During treatment and the post-treatment period combined, dry mouth, sedation, somnolence, headache, insomnia, dizziness, and fatigue were the most common AEs in the quetiapine XR group, and occurred at a higher incidence compared to placebo. The pattern of common AEs observed in the quetiapine XR treatment group generally conformed to that which was anticipated based on the known pharmacological profile of quetiapine, with the exception of the increased incidence of insomnia. Of those patients who reported insomnia, the AE had onset during the post-treatment period in 2 of the 4 placebo patients and 11 of the 14 quetiapine XR patients. The majority of the quetiapine XR patients who experienced an AE of insomnia during the post-treatment period had onset within the first 7 post-treatment days. Of those who reported headache, the AE occurred during the post-treatment period in 8 of 22 quetiapine XR patients and 0 of 16 placebo patients.

The incidence of AEs associated with extrapyramidal symptoms (EPS) was low overall but higher in the quetiapine XR group (0.6% and 4.6% in the placebo and quetiapine XR groups, respectively). The AEs potentially related to EPS included akathisia, EPS disorder, and restlessness, all of which were mild in intensity. Overall, 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 most patients in both treatment groups exhibited no change in these symptoms at the end of treatment. There were no AEs potentially related to QT prolongation or syncope during the study. There were no AEs potentially related to suicidality identified in this study and there was no clinical evidence to suggest a relationship between quetiapine XR treatment and increased suicidality. A non-serious AE of neutropenia was reported for 1 patient in the

quetiapine XR group. This patient had a low neutrophil count at randomization (1.69×10^9/L) which decreased to 1.11×10^9/L by Week 4. No action was taken with regard to study drug, and at the Week 8 (End of Treatment) visit, values had increased to 1.54×10^9/L. There were 2 AEs potentially related to diabetes reported during the study, polyuria in the placebo group and thirst in the quetiapine XR group, both of which were mild in severity. The thirst AE in the quetiapine XR group was not associated with a clinically important shift in fasting glucose levels. These potentially diabetes-related events were not considered related to study treatment, and no action was taken for either with regard to study medication.

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 between the treatment groups in the mean changes from baseline for any hematology or clinical chemistry assessments. Excluding the patient with an AE of neutropenia, whose values no longer met the criterion of a clinically important low value at the end of treatment, 4 patients in the quetiapine XR group and 3 patients in the placebo group had clinically important shifts to low neutrophil values at the end of treatment. One of the 4 quetiapine XR patients and 1 of the 3 placebo patients had low (but not clinically important) neutrophil counts at randomization.

There were no notable differences between treatment groups in mean change from baseline for any diabetes-related assessments, including glucose regulation parameters glucose, insulin, Homeostatic Model Assessment of insulin resistance ($HOMA_R$), Quantitative Insulin Sensitivity Check Index (QUICKI), and glycated hemoglobin (HbA_{1c}). Similar percentages of in the quetiapine XR group and the placebo group recorded clinically important elevated glucose values during the course of the study (5.6% in the placebo group and 4.0% in the quetiapine XR group). There were 1 and 4 patients in the placebo and quetiapine XR groups, respectively, recording treatment-emergent shifts to clinically important HbA1c levels during the study. Each of these patients had high HbA1c levels at randomization. The percentages of patients with a treatment-emergent shift from <3 to ≥3 metabolic risk factors were similar in the 2 treatment groups. The percentages of patients with a ≥7% weight increase between baseline and the end of treatment were low but higher in the quetiapine XR group compared to the placebo group. A weight decrease of ≥7% between baseline and the end of treatment occurred at a low incidence in both groups. 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; no AEs of hypothyroidism were reported. Treatment-emergent shifts to high prolactin values were seen in 1 patient each in the placebo and quetiapine XR groups, respectively.

An increase in mean heart rate of approximately 5 beats per minute (bpm), confirmed by ECG measurement of heart rate, was observed in the quetiapine XR group, compared with 2.2 bpm in the placebo group. Combined criteria for orthostatic changes in pulse and systolic blood pressure showed a higher percentage of quetiapine XR patients with an orthostatic increase in pulse rate. No other differential effect of quetiapine XR administration compared to placebo was observed for other orthostatic parameters. No notable mean changes in ECG parameters

were observed. No AEs or treatment-emergent clinically important values potentially related to QT prolongation occurred during the study.

Based on the change from baseline to the end of treatment in the Changes in Sexual Functioning Questionnaire (CSFQ) total score, sexual functioning improved in the quetiapine XR group compared with placebo (change of 2.8 and 1.4 for the quetiapine XR and placebo groups, respectively), with most of the improvement apparent for females. The incidence of AEs potentially related to sexual functioning was low and similar in both treatment groups (2 patients in each group).