Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate extended release		
Edition No.:	1		
Study code:	D1448C00004		
Date:	20 November 2007		

A Multi-Centre, Double-Blind, Randomised, Parallel Group, Placebo-Controlled and Active 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 (AMBER STUDY)

Study center(s)

There were 471 patients assigned to randomized treatment at 54 centers in Finland, Spain, Korea, Malaysia, China, Philippines, Canada, Mexico, and South Africa.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	09 May 2006	Therapeutic confirmatory (III)
Last patient completed	11 June 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 in patients with MDD, compared with placebo;

2. To evaluate the efficacy of quetiapine XR compared with escitalopram in patients with MDD;

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

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

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

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

7. To evaluate if quetiapine XR improves satisfaction with medication in 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 in the treatment of patients with MDD versus placebo. Escitalopram was added as an active control. This study consisted of an up to 28-day enrollment and washout period, an 8-week randomized treatment period, and a 2-week follow-up (treatment discontinuation signs and symptoms [TDSS]) period. All quetiapine XR patients initiated treatment on quetiapine XR 50 mg/day and were up-titrated to 150 mg/day at Day 3. All escitalopram patients initiated treatment on escitalopram 10 mg/day. After 2 weeks of treatment, patients in each treatment group with an inadequate response (defined as failure to achieve a ≥20% reduction in MADRS total score) were up-titrated to twice their original dose (300 mg/day quetiapine XR, 20 mg/day escitalopram, or 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 actual dose. At the end of the 8 weeks of randomized treatment, patients underwent a 2-week follow-up (TDSS) period including 1 week of down-titration in a blinded fashion. Patients on quetiapine XR 150 mg/day and escitalopram 10 mg/day received placebo for 1 week, whereas patients on quetiapine XR 300 mg/day and escitalopram 20 mg/day underwent a 1-week down-titration of quetiapine XR and escitalopram, to half of the 8-week dose (ie, to 150 mg/day and 10 mg/day, respectively). At the end of Week 9, all investigational product treatment was discontinued.

Target population and sample size

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

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. 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 demonstrate superior efficacy of quetiapine XR over placebo with regard to the primary analysis of the 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 Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 8. For a 2-sided hypothesis test at a 5% significance level (ie, α=0.05), a planned 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 treatment were expected to be evaluable patients (to be included in the modified intent-to-treat [MITT] group), a total of about 450 patients were required to obtain 140 evaluable patients per treatment group.

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

Quetiapine XR 50 mg or 300 mg sustained-release tablets were orally administered in doses of 150 mg (three 50-mg tablets) or 300 mg (one 300-mg tablet) 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.

Escitalopram 10-mg capsules (overencapsulated tablets) were administered in doses of 10 mg/day (1 capsule) or 20 mg/day (2 capsules) once daily, in the evening. Placebo tablets matching escitalopram 10-mg capsules (overencapsulated tablets) were administered once daily, in the evening.

Study treatment was given in tablets of the following doses (lot #): quetiapine XR 50 mg (LJ4707, LM4625), quetiapine XR 300 mg (33419D05, 41280I06), placebo 50-mg match (32195F05, 32200H05, 32201E05, 32202B05), placebo 300-mg match (CP297X, CP296X), escitalopram 10 mg (ST6055-001-FA02), and placebo 10-mg match (ST6062-001-FA01).

Duration of treatment

An initial washout period of 7 to 28 days (depending on the medications involved) was followed by an 8-week, double-blind 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 escitalopram 20 mg/day). The 8-week, double-blind treatment period was followed by a 2-week follow-up (TDSS) period that included 1 week of down-titration in a blinded fashion.

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 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 (depressed mood) score; change from randomization to Week 8 in the Clinical Global Impression - Severity (CGI-S) score; 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, and Q-LES-Q satisfaction with medication score.

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 score ≥4 or an AE of 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. 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 MADRS from baseline to Week 8) was analyzed using an analysis of covariance (ANCOVA) model with treatment, center and randomization MADRS total score as explanatory variables. Center was treated as a random effect while all other explanatory variables were treated as fixed effects.

Changes from randomization to each assessment in MADRS total score as well as changes from randomization to Week 8 in Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) percent maximum total score, HAM-D total score, HAM-D Item 1 (depressed mood) score, CGI-S score, 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 2 comparisons of primary interest (change in MADRS total score from randomization and change in Q-LES-Q percent maximum total score from randomization for quetiapine XR versus placebo), the overall type-I error rate (α=0.05) 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 the placebo group, 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 as the adjusted p-value would be greater than alpha (ie, 0.05).

To assess the robustness of the primary analysis results, changes in the MADRS total score from randomization to each assessment were analyzed using an ANCOVA model (LOCF, MITT), and the change from randomization to Week 8 in MADRS total score was analyzed using both an ANCOVA model (LOCF, PP) and a mixed-model repeated measures (MMRM) analysis (OC, MITT).

MADRS response 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 suicidal thought (Item 10) score, HAM-D anxiety items score (Items 10 and 11), HAM-D sleep disturbance items score (Items 4, 5, and 6), Q-LES-Q overall quality of life (Item 16) score, Q-LES-Q satisfaction with medication (Item 15) score, 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	ESC	Total
Analysis sets					
N (randomized)		157	157	157	471
N safety[a]		155	157	156	468
N MITT[b]		153	154	152	459
N PP		130	135	136	401
N TDSS		94	94	92	280
Completed 8-week randomized treatment period		117	107	118	342
Completed study[c]		73	81	69	223
Demographic characteristics (MITT analysis set)					
Sex: n (%)	Male	50 (32.7)	44 (28.6)	37 (24.3)	131 (28.5)
	Female	103 (67.3)	110 (71.4)	115 (75.7)	328 (71.5)
Age: years	Mean (SD)	39.7 (11.1)	40.1 (11.6)	40.3 (12.5)	NC
	Min to max	18 to 62	18 to 64	18 to 65	18 to 65
Race: n (%)	Caucasian	84 (54.9)	86 (55.8)	80 (52.6)	250 (54.5)
	Oriental	41 (26.8)	43 (27.9)	45 (29.6)	129 (28.1)
	Black	25 (16.3)	20 (13.0)	22 (14.5)	67 (14.6)
	Other	3 (2.0)	5 (3.2)	5 (3.3)	13 (2.8)
Baseline disease characteristics (MITT analysis set)					
DSM-IV diagnosis: n (%)					
296.2x MDD, Single Episode		37 (24.2)	40 (26.0)	32 (21.0)	109 (23.7)
296.3x MDD, Recurrent		116 (75.8)	114 (74.0)	120 (79.0)	350 (76.3)
MADRS	Mean (SD)	31.6 (5.4)	32.2 (5.6)	32.0 (5.6)	NC
HAM-D	Mean (SD)	26.6 (3.7)	27.1 (4.0)	27.2 (4.1)	NC
HAM-D Item 1	Mean (SD)	3.0 (0.5)	3.0 (0.5)	3.0 (0.5)	NC
HAM-A	Mean (SD)	19.8 (7.0)	20.8 (7.0)	20.6 (7.4)	NC
CGI-S	Mean (SD)	4.8 (0.9)	4.9 (0.8)	5.0 (0.9)	NC
Q-LES-Q % maximum total score	Mean (SD)	38.6 (14.3)	35.3 (16.0)	38.3 (14.3)	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] Including TDSS period.

CGI-S Clinical Global Impression Severity scale. ESC Escitalopram. 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. 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 8 (LOCF, MITT analysis set)

Outcome variable	PLA N=153	QTP N=154	ESC N=152
MADRS total score, LS mean change from randomization	-15.61	-17.21	-16.73
Proportion with MADRS response (total score ≥50% reduction from baseline)	51.0%	60.4%	59.9%
Proportion with MADRS remission (total score ≤8)	35.3%	35.7%	40.8%
HAM-D total score, LS mean change from randomization	-13.75	-14.99	-14.70
HAM-D Item 1 score, LS mean change from randomization	-1.41	-1.57	-1.65
HAM-A total score, LS mean change from randomization	-8.28	-9.44	-9.67
CGI-S score, LS mean change from randomization	-1.76	-1.83	-1.85
Proportion improved on CGI-I	58.8%	61.4%	64.2%
Q-LES-Q % maximum total score, LS mean change from randomization	13.55	13.46	16.00

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

A total of 26.1%, 13.0%, and 23.7% of patients in the placebo, quetiapine XR, and escitalopram groups, respectively, met the criterion for inadequate response (ie, failed to achieve a ≥20% reduction in MADRS total score after 2 weeks of randomized treatment). Those patients having an inadequate response were up-titrated to double the initial dose.

Although quetiapine XR showed greater improvements in reducing depressive symptoms with regard to the change from randomization to Week 8 in the MADRS total score, the efficacy of quetiapine XR over placebo was not established in the primary analysis using ANCOVA (least square [LS] mean change from randomization for quetiapine XR versus placebo of -1.6, p=0.174) (LOCF).

Separation between quetiapine XR and placebo in MADRS total score was observed by Week 2 (LS mean change from randomization quetiapine XR versus placebo of -2.3, p=0.011) and was maintained through Week 4 (LS mean change from randomization versus placebo of -2.8, p=0.005). Although greater mean changes throughout the 8-week randomized treatment period were observed, quetiapine XR did not demonstrate superiority over placebo. In comparisons between escitalopram and placebo, greater mean changes were also observed for escitalopram throughout the 8-week treatment period. Separation from placebo was demonstrated by Week 4 (LS mean change from randomization escitalopram versus placebo of -2.3, p=0.021); however, superiority of escitalopram over placebo was not demonstrated at any other timepoint. These results are supported by the lower percentage of patients in the quetiapine XR group with an inadequate response after 2 weeks of treatment compared to the placebo and escitalopram groups (13.0% vs. 26.1% and 23.7%, respectively).

Using the PP analysis set (LOCF), the results were similar to that of the primary analysis (LS mean change from randomization to Week 8 for quetiapine XR versus placebo of -1.7, p=0.175). In the MMRM analysis, quetiapine XR was shown to be superior to placebo in the change from randomization to Week 8 in the MADRS total score (LS mean change from randomization for quetiapine XR versus placebo of -2.67, p=0.004).

Similarly, greater improvements were seen for the escitalopram group in mean change in MADRS total score at Week 8 when compared with placebo (LS mean change from randomization for escitalopram versus placebo of -1.1, p=0.346); however, separation between escitalopram and placebo was not observed for any of the efficacy endpoints indicating a lack of assay sensitivity.

For patients with adequate and inadequate response (failure to achieve a ≥20% reduction in MADRS total score) after 2 weeks of treatment, the change from randomization in MADRS total score at Week 2 was -13.3, -14.9, and -14.9 in the placebo, quetiapine XR, and escitalopram groups, respectively, who had an adequate response, and -2.4, -4.1, and -2.5 in the placebo, quetiapine XR, and escitalopram groups, respectively, who had an inadequate response. The change from randomization at Week 8 in patients who had an adequate response was -18.3, -19.4, and -19.8 in the placebo, quetiapine XR, and escitalopram groups, respectively, and -10.3, -13.1, and -8.3 in the placebo, quetiapine XR, and escitalopram groups, respectively, for patients who had an inadequate response.

Secondary variables supporting the primary objective showed no differences between quetiapine XR and placebo in reducing the level of depressive symptoms with one exception. Separation between quetiapine XR and placebo in MADRS total score was observed by Week 2 (p=0.011) but was not sustained after Week 4. Although improvements were observed for other efficacy endpoints as early as Week 1, statistical superiority was not demonstrated. The efficacy of quetiapine XR over placebo was not established with regard to improvement of health-related quality of life, reduction of suicidal ideation, or satisfaction with medication.

Safety results

The proportion of patients who had at least 1 adverse event (AE) in any category is summarized in Table S4. Quetiapine XR was generally safe and well tolerated. Most AEs were mild to moderate in all treatment groups. Serious adverse events (SAEs) were infrequent in all treatment groups. No deaths occurred in the study. The incidence of AEs was higher in the quetiapine XR and escitalopram groups than in the placebo group. The incidences of both AEs leading to discontinuation and drug-related AEs were higher in the quetiapine XR group than in the escitalopram group.

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

	PLA N=155	QTP N=157	ESC N=156
Category of adverse event	**n (%)**	**n (%)**	**n (%)**
Any adverse event	114 (73.5)	136 (86.6)	127 (81.4)
Serious adverse event	1 (0.6)	4 (2.5)	3 (1.9)
Serious adverse event leading to death	0	0	0
Serious adverse event not leading to death	1 (0.6)	4 (2.5)	3 (1.9)
Drug-related adverse event[a]	81 (52.3)	125 (79.6)	106 (67.9)
Adverse events leading to discontinuation	7 (4.5)	25 (15.9)	11 (7.1)

[a] As judged by the investigator.
ESC Escitalopram. 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.

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)

	PLA N=155	QTP N=157	ESC N=156
MedDRA preferred term[a]	**n (%)**	**n (%)**	**n (%)**
Any adverse event	114 (73.5)	136 (86.6)	127 (81.4)
Dry mouth	13 (8.4)	60 (38.2)	22 (14.1)
Somnolence	6 (3.9)	56 (35.7)	13 (8.3)
Dizziness	22 (14.2)	53 (33.8)	29 (18.6)
Headache	49 (31.6)	41 (26.1)	49 (31.4)

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

	PLA N=155	QTP N=157	ESC N=156
MedDRA preferred term[a]	**n (%)**	**n (%)**	**n (%)**
Nausea	30 (19.4)	34 (21.7)	47 (30.1)
Insomnia	22 (14.2)	22 (14.0)	23 (14.7)
Constipation	7 (4.5)	20 (12.7)	13 (8.3)
Diarrhea	11 (7.1)	19 (12.1)	19 (12.2)
Fatigue	8 (5.2)	19 (12.1)	14 (9.0)
Sedation	5 (3.2)	17 (10.8)	8 (5.1)
Anxiety	4 (2.6)	12 (7.6)	7 (4.5)
Dyspepsia	9 (5.8)	12 (7.6)	5 (3.2)
Increased appetite	6 (3.9)	11 (7.0)	3 (1.9)
Myalgia	6 (3.9)	11 (7.0)	12 (7.7)
Abdominal pain upper	6 (3.9)	9 (5.7)	5 (3.2)
Hypersomnia	1 (0.6)	9 (5.7)	2 (1.3)
Irritability	8 (5.2)	9 (5.7)	8 (5.1)
Vomiting	3 (1.9)	9 (5.7)	6 (3.8)
Arthralgia	5 (3.2)	8 (5.1)	1 (0.6)
Hyperhidrosis	9 (5.8)	8 (5.1)	12 (7.7)
Influenza	4 (2.6)	8 (5.1)	3 (1.9)
Abdominal pain	5 (3.2)	7 (4.5)	6 (3.8)
Tachycardia	1 (0.6)	7 (4.5)	1 (0.6)
Palpitations	6 (3.9)	6 (3.8)	8 (5.1)
Vision blurred	5 (3.2)	6 (3.8)	4 (2.6)
Weight increased	0	6 (3.8)	2 (1.3)
Chills	1 (0.6)	5 (3.2)	1 (0.6)
Cough	2 (1.3)	5 (3.2)	5 (3.2)
Dyspnea	4 (2.6)	5 (3.2)	1 (0.6)
Hot flush	2 (1.3)	5 (3.2)	7 (4.5)
Musculoskeletal stiffness	3 (1.9)	5 (3.2)	3 (1.9)
Rash	0	5 (3.2)	1 (0.6)
Abdominal distension	4 (2.6)	4 (2.5)	5 (3.2)
Decreased appetite	3 (1.9)	4 (2.5)	5 (3.2)
Nasal congestion	1 (0.6)	4 (2.5)	0
Paraesthesia	2 (1.3)	4 (2.5)	4 (2.6)

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

MedDRA preferred term[a]	PLA N=155 n (%)	QTP N=157 n (%)	ESC N=156 n (%)
Restlessness	1 (0.6)	4 (2.5)	3 (1.9)
Thirst	0	4 (2.5)	1 (0.6)
Gastroenteritis	5 (3.2)	3 (1.9)	1 (0.6)
Pain in extremity	1 (0.6)	3 (1.9)	6 (3.8)
Akathisia	1 (0.6)	2 (1.3)	5 (3.2)
Nasopharyngitis	9 (5.8)	2 (1.3)	7 (4.5)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
ESC Escitalopram. 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 QTP treatment group.
Note: Percentages are calculated as n/N*100.

During treatment and the 30-day post-treatment period, dry mouth, somnolence, dizziness, nausea, fatigue, constipation, diarrhea, and sedation were the most common AEs in the quetiapine group and occurred at a higher incidence than 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 XR. In the escitalopram group, the most common AEs that occurred more frequently than placebo were nausea, dizziness, insomnia, dry mouth, diarrhea, and fatigue.

Those AEs occurring more frequently than in the placebo group during study treatment were dry mouth, somnolence, dizziness, fatigue, constipation, sedation, and diarrhea for quetiapine XR and nausea, dizziness, dry mouth, diarrhea, and insomnia for escitalopram. There were no discernable differences observed in the incidence of AEs after dose increases. Two occurrences each of dry mouth, gastroenteritis, nausea, and somnolence were reported after Week 2 in quetiapine XR patients with a dose increase to 300 mg. For escitalopram patients with a dose increase to 20 mg, 4 occurrences of diarrhea were reported.

The overall incidence of AEs was higher than placebo (27.7%) for those quetiapine XR (53.2%) and escitalopram (44.4%) patients abruptly discontinued from study treatment at the end of the randomized treatment period. For those groups of quetiapine XR and escitalopram patients experiencing a down-titration (to 150 mg and 10 mg, respectively), the incidence of AEs was similar to that of the placebo group. The most common AEs for the quetiapine XR group with no down-titration were nausea, insomnia, headache, hyperhidrosis, and anxiety. For the escitalopram group with no down-titration, the most common AEs were headache, insomnia, nausea, and myalgia.

The most common AE in the quetiapine group during the post-treatment period was headache. For the escitalopram group, the most common AEs during the post-treatment period were insomnia, nausea, headache, dizziness, and irritability.

Of special interest were AEs potentially related to EPS, QT prolongation, neutropenia/agranulocytosis, diabetes mellitus (DM), syncope, nausea/vomiting, sexual dysfunction, somnolence, and suicidality. Small increases in the incidence of EPS-related AEs and high incidences of AEs of nausea/vomiting and somnolence were observed. With the exception of somnolence which had the highest incidence in the quetiapine XR group, the incidence of EPS-related AEs and AEs of nausea/vomiting were higher in the quetiapine XR group compared to placebo, but were less than that for escitalopram.

Overall, the incidence of individual EPS-related AEs was 7.7% with the highest incidence observed in the quetiapine XR and escitalopram groups (5.2%, 8.3%, and 9.6% in the placebo, quetiapine XR, and escitalopram groups, respectively). The most common AEs potentially related to EPS were tremor, restlessness, and akathisia. Additionally, 1.9%, 3.2%, and 1.9% of patients in the placebo, quetiapine XR, and escitalopram groups experienced musculoskeletal stiffness. 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 an improvement or no worsening in symptoms was noted in most patients in all active treatment groups at the end of treatment.

AEs relating to nausea/vomiting were more frequent in the quetiapine XR and escitalopram groups than placebo (26.1% and 30.8% in the quetiapine XR and escitalopram groups compared with 20.6% in the placebo group). There was a higher incidence of AEs associated with somnolence in the quetiapine XR treatment group than in the placebo and escitalopram groups (45.9% compared with 7.1% and 14.7% in the placebo and escitalopram groups, respectively), with the onset of these events usually occurring in the first 4 days of treatment. Most of these AEs were mild to moderate in intensity.

The small increases in mean supine pulse rate (1.7 bpm) and weight (0.6 kg) in the quetiapine XR group were consistent with the anticipated effects based on the pharmacological profile of quetiapine. No notable differences were observed in the mean changes from baseline to the end of treatment in vital sign (including orthostatic changes) or ECG data between patients treated with quetiapine XR, escitalopram, and placebo. Combined criteria for orthostatic changes did not show any differential effect of quetiapine XR administration compared to placebo. The rates of AEs and discontinuations related to vital signs were low.

With the exception of a greater incidence in shifts to clinically important high levels of triglycerides in the quetiapine XR group compared to placebo and escitalopram, there were no notable differences between the treatment groups in the mean changes from baseline for any hematology assessments or clinical chemistry assessments, including renal and liver tests. There were no cases of treatment-emergent hypothyroidism based on clinically important high TSH values in combination with clinically important low T4 values.