Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine XR		
Study code:	D1448C00014		
Date:	22 April 2008		

A Multi-Center, 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 Elderly Patients with Major Depressive Disorder (SAPPHIRE STUDY)

Study center(s)

This study was conducted at 53 centers in Argentina, Estonia, Finland, Russia, Ukraine, and the United States.

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First subject enrolled	21 September 2006	Therapeutic confirmatory (III)
Last subject completed	28 December 2007	

Objectives

The **primary** objective of the study was to evaluate the efficacy of quetiapine XR (50 mg/day to 300 mg/day) versus placebo in elderly patients with major depressive disorder (MDD), as assessed by the change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 9.

Secondary objectives:

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

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

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

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

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

6. To evaluate if quetiapine XR improves somatic symptoms in patients with MDD, compared to placebo

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

An additional objective was to establish a panel of deoxyribonucleic acid (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 an 11-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled Phase III study of the efficacy and safety of quetiapine XR (flexibly dosed at 50 mg/day to 300 mg/day) as monotherapy in the treatment of elderly patients with MDD. The study comprised 3 periods: an enrollment period of up to 28 days, a 9-week randomized treatment period, and a 2-week follow-up period.

All quetiapine XR patients started on a 50 mg/day dose for 3 days, followed by up-titration to 100 mg/day on Day 4, 150 mg/day on Day 8, 200 mg/day on Day 15, and 300 mg/day on Day 22. From Day 4, retitration may have taken place at the judgment of the investigator if the dose was not tolerated (ie, the specifics of a dose reduction or increase was based on the investigator's judgement). From Day 8, dose reduction may have taken place if the dose was not tolerated, and up-titration continued if the patient's response to the dose was inadequate (defined as <20% reduction from baseline in MADRS total score). On Days 29 to 63, all quetiapine XR patients were treated with flexible dosing, from 50 mg/day to 300 mg/day, based on efficacy and tolerability. Patients randomized to the placebo group received matched placebo according to the same treatment plan. At the end of 9 weeks of randomized treatment, all investigational product was discontinued and patients underwent a 2-week post-treatment follow-up period.

Target subject population and sample size

Male or female patients, 66 years of age or older, with a documented clinical diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria of either 296.2x MDD, Single Episode, or 296.3x MDD, Recurrent. Diagnosis was to be confirmed by the Mini-International Neuropsychiatric Interview (MINI).

The patients had to have a Hamilton Rating Scale for Depression (HAM-D) total score ≥22 and HAM-D Item 1 score ≥2 at both enrollment and randomization to be eligible for the study.

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 9. 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 9. For a 2-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 (ie, to be included in the modified intention-to-treat [MITT] analysis set), a total of about 300 patients was 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/day to 300 mg/day or placebo was orally administered once daily in the evening. Tablets used in the study were 50-mg quetiapine XR tablets and placebo tablets to match the 50-mg quetiapine XR tablets.

Study treatment was given in tablets at the following doses (Lot numbers): quetiapine XR 50 mg (LM4622, LM4625, and MC4604) and matching placebo 50 mg (CN969X, CP020X, CP021X, and CP022X).

Duration of treatment

An initial washout period of up to 28 days (depending on the medications involved) was followed by a 9-week, double-blind, randomized treatment period. At the end of 9 weeks, patients underwent a 2-week follow-up period. No down-titration of investigational product was performed during the 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 9 in the MADRS total score

Secondary efficacy variables supporting the primary objective

MADRS response at Week 9; change in the MADRS total score from randomization to each assessment; MADRS remission at Week 9; change in the HAM-D total score and the HAM-D Item 1 score from randomization to Week 9; change in the CGI-S score from randomization to Week 9; CGI-I score at Week 9

Secondary efficacy variable of particular interest

Change in Q-LES-Q percent maximum total score from randomization to Week 9

Other secondary efficacy variables

Change in Q-LES-Q overall quality of life (Item 16) score from randomization to Week 9; change in Q-LES-Q satisfaction with medication (Item 15) score from randomization to Week 9; change in HAM-A total score from randomization to Week 9; change in HAM-A psychic anxiety subscale score from randomization to Week 9; change in HAM-D anxiety items score from randomization to Week 9; change in HAM-D sleep disturbance items score from randomization to Week 9; change in PSQI global score from randomization to Week 9; change in MADRS Item 10 (suicidal thoughts) score from randomization to Week 9; change in HAM-A somatic anxiety subscale score from randomization to Week 9; change in the pain VAS from randomization to Week 9

Safety variables

Physical examination, laboratory values, vital signs, ECG, AEs, TDSS scale, weight, BMI, waist circumference, SAS, BARS, AIMS, MADRS Item 10 score ≥4 or an AE of related to suicidality, and incidences of suicidality using Columbia-like analysis

AE Adverse event. AIMS Abnormal Involuntary Movement Scale. BARS Barnes Akathisia Rating Scale. BMI Body mass index. CGI-I Clinical Global Impression–Global Improvement. CGI-S Clinical Global Impression–Severity of Illness. ECG Electrocardiogram. 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. VAS Visual analogue scale.

Statistical methods

The efficacy analyses were based on the MITT analysis set, and the safety analyses were based on the safety analysis set (see Table S2 for definitions). No formal statistical tests were planned or conducted for any safety variables.

All hypotheses were tested with 2-sided tests with a significance level of 5% (ie, α=0.05) unless otherwise specified. Whenever analyses including statistical inference were performed, model-based point estimates were presented together with their 95% confidence intervals (CIs). Missing data were handled using the last observation carried forward (LOCF) approach, as appropriate.

The change from randomization to Week 9 in the MADRS total score was analyzed using a mixed-model analysis of covariance (ANCOVA). The model included treatment, center, and baseline MADRS total score as explanatory variables, where center was treated as a random effect, treatment group as a fixed effect, and randomization MADRS total score was a covariate.

Changes from randomization to each assessment in MADRS total score as well as changes from randomization to Week 9 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 of Illness (CGI-S) score, Hamilton Rating Scale for Anxiety (HAM-A) total score, HAM-A psychic anxiety subscale score, HAM-A somatic anxiety subscale score, Pittsburgh Sleep Quality Index (PSQI) global score, and pain visual analogue scale (VAS) score were analyzed similarly to the analysis used for the change from randomization in MADRS total score.

For the comparison of primary interest (change in MADRS total score from randomization at Week 9), a secondary variable supporting the primary objective (MADRS response rate at Week 9), and the secondary variable of particular interest (change in Q-LES-Q percent maximum total score from randomization at Week 9), the experiment-wise Type I error rate was set to 0.05, and a multiple testing procedure was used to adjust for multiplicity. If the null hypothesis for the first comparison (ie, change at Week 9 in MADRS total score) was rejected using a significance level of 0.05, then the hypothesis related to the second comparison (ie, MADRS response rate at Week 9) was tested. If the null hypothesis for the second comparison was rejected using a significance level of 0.05, then the third comparison (ie, change at Week 9 in Q-LES-Q percent maximum total score) was tested. This third and final comparison was also tested using a significance level of 0.05.

MADRS response at Week 1 and Week 9, MADRS remission rates (where remission is defined as MADRS total score ≤8) at Week 9, and the dichotomized Clinical Global Impression–Global Improvement (CGI-I) score ("very much/much improved" vs all other categories) at Week 9 were analyzed using logistic regression models.

Other MADRS remission rates (ie, MADRS total score ≤10 and MADRS total score ≤12), 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, and Q-LES-Q satisfaction with medication (Item 15) score were summarized using descriptive statistics.

The efficacy analyses were based on the MITT analysis set, and the safety analyses were based on 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 XR	Total
Analysis sets				
N (randomized)		172	166	338
N safety[a]		172	166	338
N MITT[b]		171	164	335
N PP		159	147	306
N TDSS		135	126	261
Completed 9-week randomized treatment period		131	127	258
Completed study[c]		114	110	224
Demographic characteristics (MITT analysis set)				
Sex: n (%)	Male	51 (29.8)	49 (29.9)	100 (29.9)
	Female	120 (70.2)	115 (70.1)	235 (70.1)
Age (years)	Mean (SD)	71.2 (4.9)	71.3 (4.6)	71.3 (4.8)
	Min to max	66 to 86	66 to 89	66 to 89
Age category (years) n (%)	≤75	137 (80.1)	133 (81.1)	270 (80.6)
	>75	34 (19.9)	31 (18.9)	65 (19.4)
Race: n (%)	Caucasian	168 (98.2)	162 (98.8)	330 (98.5)
	Black	0	2 (1.2)	2 (0.6)
	Other	3 (1.8)	0	3 (0.9)
Region	Europe	126	123	249
	North America	27	24	51
	South America	18	17	35
Baseline disease characteristics (MITT analysis set)				
DSM-IV diagnosis: n (%)				
	296.2x MDD, Single Episode	25 (14.6)	27 (16.5)	52 (15.5)
	296.3x MDD, Recurrent	146 (85.4)	137 (83.5)	283 (84.5)
MADRS total score	Mean (SD)	28.2 (6.2)	27.5 (6.1)	
HAM-D total score	Mean (SD)	25.2 (2.5)	25.4 (2.6)	
HAM-D Item 1	Mean (SD)	2.9 (0.6)	3.0 (0.6)	
HAM-A total score	Mean (SD)	20.1 (5.3)	19.4 (5.6)	
CGI-S total score	Mean (SD)	4.4 (0.6)	4.3 (0.5)	
Q-LES-Q % maximum total score	Mean (SD)	41.9 (11.4)	44.1 (12.1)	

[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 follow-up period.
CGI-S Clinical Global Impression-Severity of Illness. 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 of patients. N Number of patients in treatment group. PLA Placebo. PP Per-protocol. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP XR Quetiapine extended release. SD Standard deviation. TDSS Treatment discontinuation signs and symptoms.

All of the 338 randomly assigned patients received treatment and were included in the safety analysis set. In the safety analysis set, approximately 76% of patients completed the randomized treatment period and 66% of patients completed the study, including the follow-up period. The proportions of patients completing these periods were similar in the 2 treatment groups. In the quetiapine XR group, the most common reasons for withdrawal were adverse event (AE) (9.6%) and not willing to continue with the study (8.4%); in the placebo group, the most common reasons were not willing to continue with the study (9.9%) and condition under investigation not improved (7.0%). The treatment groups were well balanced with regard to demographic and baseline characteristics. The mean patient age was approximately 71 years, and 70% of the patients were female. Almost all (98.5%) of the patients in the study were Caucasian. The majority of patients (84.5%) had a DSM-IV diagnosis of 296.3x (MDD, Recurrent).

Efficacy results

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

Table S3 Efficacy results at Week 9 (LOCF, MITT analysis set)

Outcome variable	PLA N=171	QTP XR N=164
MADRS total score LS mean change from randomization	-8.79	-16.33[a]
Proportion with MADRS response (decrease in MADRS score of ≥50%)	30.41	64.02[a]
Proportion with MADRS remission (total MADRS score ≤8)	17.0	45.1[a]
HAM-D total score LS mean change from randomization	-8.62	-15.66[a]
HAM-D Item 1 LS mean change from randomization	-1.13	-1.84[a]
CGI-S total score LS mean change from randomization	-0.77	-1.73[a]
Proportion improved on CGI-I	39.18	71.34[a]
Q-LES-Q % maximum total score LS mean change from randomization	9.17	16.86[a]
HAM-A total score LS mean change from randomization	-5.20	-10.51[a]
PSQI global score LS mean change from randomization	-2.89	-6.42[a]
Pain VAS LS mean change from randomization	-9.01	-18.75[a]

[a] p≤0.001 comparison with placebo

CGI-I Clinical Global Impression-Global Improvement. CGI-S Clinical Global Impression-Severity of Illness. 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. N Number of patients in treatment group. PLA Placebo. PSQI Pittsburg Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP XR Quetiapine extended release. VAS Visual Analogue Scale.

In elderly patients with MDD, quetiapine XR is superior to placebo in reducing the level of depressive symptoms as demonstrated by the statistically significant difference in mean changes from randomization to Week 9 in the MADRS total score. The quetiapine XR-treated group showed greater improvement in MADRS total score and MADRS response by Week 1 of treatment, and the greater improvement compared with placebo was maintained throughout the 9-week randomized treatment period. Results from the secondary outcome variables supported the primary objective. At Week 9, compared with the placebo group, the quetiapine XR group demonstrated greater MADRS response; MADRS remission; and greater improvement in MADRS Item 10, HAM-D total score, HAM-D Item 1, HAM-D Items 10 and 11, HAM-D sleep disturbance (Items 4 to 6), HAM-A total score, HAM-A psychic and somatic subscale scores, and CGI-S total score; a greater proportion of patients had a CGI-I score of "much/very much improved"; and greater improvement in Q-LES-Q percent maximum total score, PSQI global score, and the pain VAS score.

Subgroup analyses of the primary efficacy variable, based on age, sex, race, region, and baseline disease severity, showed that the results were not unduly influenced by any particular subgroup.

Safety results

Quetiapine XR was well tolerated. Most AEs were of mild to moderate intensity in both treatment groups. Serious adverse events were infrequent in both treatment groups. No deaths occurred in the study. Larger proportions of patients in the quetiapine XR group discontinued due to an AE than did patients in the placebo group. The incidence of drug-related AEs was higher in the quetiapine XR treatment group compared to placebo.

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

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

	PLA **N=172**	**QTP XR** **N=166**
Category of adverse event	**n (%)**	**n (%)**
Any adverse event	105 (61.0)	134 (80.7)
Serious adverse event		
Serious adverse event leading to death	0	0
Serious adverse event not leading to death	2 (1.2)	4 (2.4)

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

Category of adverse event	PLA N=172 n (%)	QTP XR N=166 n (%)
Drug-related adverse event[a]	68 (39.5)	104 (62.7)
Adverse events leading to discontinuation	7 (4.1)	16 (9.6)

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

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 reported from the start of treatment until the last treatment visit, a period of time that included the 2-week follow-up period.

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

MedDRA preferred term[a]	PLA N=172 n (%)	QTP XR N=166 n (%)
Any adverse event	105 (61.0)	134 (80.7)
Somnolence	14 (8.1)	55 (33.1)
Headache	28 (16.3)	35 (21.1)
Dry mouth	18 (10.5)	34 (20.5)
Dizziness	26 (15.1)	32 (19.3)
Fatigue	7 (4.1)	13 (7.8)
Insomnia	10 (5.8)	13 (7.8)
Constipation	4 (2.3)	10 (6.0)
Diarrhea	12 (7.0)	9 (5.4)
Nausea	8 (4.7)	9 (5.4)
Weight increased	7 (4.1)	9 (5.4)
Sedation	2 (1.2)	8 (4.8)
Asthenia	1 (0.6)	6 (3.6)
Extrapyramidal disorder	1 (0.6)	6 (3.6)
Abdominal pain upper	4 (2.3)	5 (3.0)
Back pain	2 (1.2)	4 (2.4)
Dysgeusia	1 (0.6)	4 (2.4)

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

MedDRA preferred term[a]	PLA N=172 n (%)	QTP XR N=166 n (%)
Hypotension	0	4 (2.4)
Pain in extremity	2 (1.2)	4 (2.4)
Hypertension	4 (2.3)	2 (1.2)
Nasopharyngitis	6 (3.5)	2 (1.2)
Tachycardia	4 (2.3)	2 (1.2)
Edema peripheral	4 (2.3)	0 (0.0)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
Note: Common adverse event is defined as an event occurring at an incidence of ≥2% in any treatment group.
Note: Events sorted by decreasing frequency in the QTP XR treatment group.
Note: Percentages are calculated as n/N*100.
MedDRA Medical Dictionary for Regulatory Activities. n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP XR Quetiapine extended release.

During the study, including the 2-week follow-up period, somnolence, headache, dry mouth, dizziness, fatigue, insomnia, constipation, diarrhea, nausea, and weight increased were the most common AEs in the quetiapine XR group (occurring at an incidence of ≥5%), each of which occurred at a higher incidence than in the placebo group, except for diarrhea. 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, with the exception of the incidence of insomnia. The majority of insomnia AEs in the quetiapine XR group, however, occurred during the post-treatment period (ie, after randomized treatment had stopped). Similarly, the majority of nausea AEs in the quetiapine XR group occurred during the post-treatment period (ie, after randomized treatment had stopped).

The incidence of AEs potentially related to extrapyramidal symptoms (EPS) during the study (including the follow-up period) was higher in the quetiapine XR group (9.0%) compared to the placebo group (2.3%). During the randomized treatment period (ie, not including the follow-up period), the incidence of AEs potentially related to EPS was 7.2% in the quetiapine XR group and 2.3% in the placebo group. All AEs related to EPS were mild or moderate in intensity, with no serious adverse events (SAEs). The most common AEs potentially related to EPS were extrapyramidal disorder and akathisia. Extrapyramidal disorder was more common in the quetiapine XR group compared to the placebo group, but the incidences of akathisia were similar between the 2 treatment groups. Most patients in both treatment groups had either no change or an improvement in Simpson-Angus Scale (SAS) total, Barnes Akathisia Rating Scale (BARS) global, and Abnormal Involuntary Movement Scale (AIMS) (10-item) total scores. A higher proportion of patients in the quetiapine XR group had worsening SAS and AIMS total scores compared to the placebo group (the proportions of patients with worsening SAS total scores in the quetiapine XR and placebo

groups were 14.1% and 8.1%, respectively, and the proportions of patients with worsening AIMS total scores were 9.2% and 4.7%, respectively). The same proportion of patients in both treatment groups had worsening BARS global scores (1.2%).

There were no AEs potentially related to QT prolongation, neutropenia/agranulocytosis, syncope, sexual dysfunction, or cerebrovascular accidents (CVA) during the study. There was 1 AE potentially related to suicidality identified in the placebo group during randomized treatment. There was 1 AE potentially related to suicidality in the quetiapine XR group, which occurred 1 day after the patient's last dose of study medication. There was no clinical evidence to suggest a relationship between quetiapine XR treatment and increased suicidality. There was 1 AE potentially related to diabetes (blood glucose increased) reported in the quetiapine XR group during the study, which occurred in a patient who was being treated for type II diabetes prior to and during the study. The event was mild in intensity and was not considered related to study treatment. The incidence of AEs potentially related to nausea/vomiting was lower in the quetiapine XR group compared to placebo.

Overall, the clinical laboratory results were consistent with those from previous studies in patients treated with quetiapine for other disorders. Two patients in the quetiapine XR group (1.3%) had a clinically important shift to low neutrophil count at end of treatment. The incidence of patients with treatment-emergent clinically important triglyceride values was higher in the quetiapine XR group (13.9%) than in the placebo group (5.9%).

A higher proportion of patients in the placebo group had a treatment-emergent shift from <3 to ≥3 metabolic risk factors (13.3%) compared to the quetiapine XR group (5.6%). There were no patients in the quetiapine XR group with a ≥7% weight increase or decrease from randomization to end of treatment. In the placebo group, there was 1 patient with a ≥7% weight increase and 2 patients with a ≥7% weight decrease from randomization to end of treatment. 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, and no AEs of hypothyroidism were reported.