Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance:	Quetiapine XR		
Study code:	D1448C00015		
Date:	19 August 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 Monotherapy in the Treatment of Elderly Patients with Generalized Anxiety Disorder (CHROMIUM STUDY)

Study centers

556 patients were screened at 49 centers and 450 were randomized at 47 centers in Estonia, Poland, 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	29 September 2006	Therapeutic confirmatory (III)
Last subject completed	18 April 2008	

Objectives

The primary objective of the study was to evaluate the efficacy of quetiapine extended-release (XR) versus placebo in patients with generalized anxiety disorder (GAD), as assessed by the change from randomization in the Hamilton Rating Scale for Anxiety (HAM-A) total score at Day 64 (Week 9).

The secondary objectives were to evaluate the efficacy of quetiapine XR versus placebo by evaluating the HAM-A response rate in the treatment of anxiety symptoms in patients with GAD; to evaluate the efficacy of quetiapine XR versus placebo on the health-related quality of

life of patients with GAD; to evaluate the efficacy of quetiapine XR versus placebo in the treatment of anxiety symptoms in patients with GAD as measured by Clinical Global Impression - Severity of Illness (CGI-S), Clinical Global Impression – Global Improvement (CGI-I), and HAM-A psychic cluster scores; to evaluate the efficacy of quetiapine XR versus placebo by evaluating the remission rate in the treatment of anxiety in patients with GAD; to evaluate the efficacy of quetiapine XR versus placebo in the treatment of depressive symptoms in patients with GAD; to evaluate the efficacy of quetiapine XR versus placebo in improving somatic symptoms in the treatment of patients with GAD; to evaluate the efficacy of quetiapine XR versus placebo in improving sleep quality in patients with GAD; to evaluate if quetiapine XR improves satisfaction with medication in patients with GAD compared with placebo; and to assess the safety and tolerability of quetiapine XR in patients with GAD.

The genetic objective was to establish a panel of DNA samples from patients who provided separate consent for genetic research. (Genetic results were not available at the time of this report.)

Study design

This was an 11-week, multi-center, randomized, parallel-group, double-blind, placebo-controlled, Phase III study of the efficacy and safety of quetiapine XR flexible dosing (50 mg/day to 300 mg/day) as monotherapy compared to matching placebo in the treatment of elderly patients with GAD. The study included 3 periods: an enrollment period of up to 28 days, a 9-week randomized treatment period, and a 2-week post-treatment period.

The study schedule called for each patient to start with 50 mg of quetiapine XR (or placebo equivalent) per day and to have periodic stepwise increases to a maximum of 300 mg/day on Day 22. If the patient's HAM-A total score was not decreased by ≥20%, the dose should have been increased through all of the steps. If any dose was not tolerated, the investigator could down titrate. After 9 weeks (64 days), randomized treatment was discontinued; there was no down-titration of study medication.

Target subject population and sample size

Patients were male or female, 66 years of age or older, with a documented clinical diagnosis of GAD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria 300.02 as assessed by the Mini-International Neuropsychiatric Interview (MINI). Patients with/without co-morbid simple phobia or panic attacks (who did not meet criteria for DSM-IV Axis I Panic disorder) were eligible to enter the study. At enrollment and at randomization, patients were required to have a HAM-A total score ≥20 with both Item 1 and Item 2 scores each ≥2, a CGI-S score ≥4, and a Montgomery-Asberg Depression Rating Scale (MADRS) score ≤16.

The sample size was calculated to ensure 85% power to show a difference between quetiapine XR and placebo with respect to the primary efficacy outcome variable (change in HAM-A total score from randomization to Week 9). The appropriate sample size was calculated by assuming an anticipated difference of 2.275 units from placebo and a standard deviation (SD) of 7.5 for the change in HAM-A total score from randomization to Week 9.

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

Quetiapine XR 50 mg tablets or matching placebo tablets were orally administered in flexible doses of 50 to 300 mg quetiapine XR once daily, in the evening.

The batch numbers used in the study were LM4622, LM4625, LM4626, LJ4704, and MC4609 for quetiapine 50 mg tablets and CN969X, CP021X, CP020X, and DT834X for matching placebo tablets.

Duration of treatment

An enrollment period of up to 28 days was followed by a 9-week treatment period and a 2-week post-treatment period.

Criteria for evaluation (main variables)

Outcome variables for efficacy included HAM-A (total score, psychic cluster, somatic cluster, response, and remission), Quality of Life Enjoyment Satisfaction Questionnaire (Q-LES-Q % maximum total score, Item 15, and Item 16), CGI-S and CGI-I, MADRS total score, Visual Analogue Scale (VAS) for pain, and Pittsburgh Sleep Quality Index (PSQI) global score. For safety, adverse events (AEs), vital signs, suicidality (including MADRS Item 10 scores and suicidality classification using Columbia-type analysis), results from physical examinations (including weight and waist circumference measurements), laboratory tests, electrocardiograms, Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and treatment discontinuation signs and symptoms (TDSS) were evaluated. MADRS total score was also analyzed for safety.

Statistical methods

The primary efficacy outcome variable, change from randomization in the HAM-A total score at Week 9, was analyzed using an analysis of covariance (ANCOVA) model including the baseline HAM-A total score as a covariate, treatment as a fixed effect, and center as a random effect. Missing data for the primary outcome variable were imputed using last observation carried forward (LOCF) methodology. The overall experiment type I error rate was set to 0.05. A multiple testing procedure (MTP) was applied to the primary hypothesis (change in HAM-A total score), the additional hypotheses associated with the response rate (50% or greater reduction from randomization in HAM-A total score), and the change in the Q-LES-Q % maximum total score. The MTP was a stepwise sequential testing procedure designed to preserve the overall significance level of 0.05. First, the primary outcome variable, change in the HAM-A total score from randomization to Week 9, was tested. If the null hypothesis for this variable was rejected, then the hypothesis related to the HAM-A response rate at Week 9 was tested. If the null hypothesis for the HAM-A response rate was rejected, then the hypothesis related to the change in Q-LES-Q % maximum total score from randomization to Week 9 was tested.

The efficacy conclusions were based on the analysis of the modified intention-to-treat (MITT) analysis set, and the safety and tolerability analyses were based on the safety analysis set.

Patient population

The numbers of patients in each analysis set are presented in Table S1.

Table S1 Analysis sets and patient baseline characteristics

		PLA	QTP XR	Total
Analysis sets				
N (randomized)		227	223	450
N safety[a]		227	223	450
N MITT[b]		226	222	448
N PP[c]		213	210	423
N TDSS[d]		143	159	302
Completed 9-week randomized treatment period		168	178	346
Completed study[e]		140	155	295
Demographic characteristics (MITT analysis set)				
Sex: n (%)	Male	70 (31.0)	62 (27.9)	132 (29.5)
	Female	156 (69.0)	160 (72.1)	316 (70.5)
Age (years)[f]	Mean (SD)	70.6 (4.4)	70.3 (4.3)	70.4 (4.4)
	Min to max	65 to 87	66 to 86	65 to 87
Age category (years) n (%)	≤75	194 (85.8)	196 (88.3)	390 (87.1)
	>75	32 (14.2)	26 (11.7)	58 (12.9)
Race: n (%)	Caucasian	226 (100)	222 (100)	448 (100)
Region	Europe	182	178	360
	North America	44	44	88

Table S1 Analysis sets and patient baseline characteristics

		PLA	QTP XR	Total
Baseline disease characteristics (MITT analysis set)				
HAM-A total	Mean (SD)	25.1 (3.5)	25.2 (3.5)	NA
HAM-A psychic cluster score	Mean (SD)	13.8 (2.2)	13.8 (2.2)	NA
HAM-A somatic cluster score	Mean (SD)	11.3 (2.5)	11.4 (2.5)	NA
MADRS total	Mean (SD)	12.3 (2.3)	12.4 (2.6)	NA
CGI-S total	Mean (SD)	4.2 (0.5)	4.3 (0.5)	NA
Q-LES-Q % maximum total	Mean (SD)	50.02 (12.03)	50.19 (13.41)	NA
Pain VAS	Mean (SD)	41.4 (24.4)	41.6 (24.2)	NA

[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 HAM-A assessment and at least 1 valid HAM-A assessment after randomization.
[c] Number of patients in the MITT analysis set who did not have significant protocol violations or deviations.
[d] Number of patients in the safety and MITT analysis sets who completed 9 weeks of double-blind treatment (ie, still taking study drug at the Week 9 visit) and proceeded into the post-treatment period.
[e] Including post-treatment period.
[f] One patient's age at enrollment was less than the 66 years specified as the minimum age in the inclusion criteria. This patient was excluded from the PP analysis set.

CGI-S Clinical Global Impression – Severity of Illness. HAM-A Hamilton Rating Scale for Anxiety. MADRS Montgomery-Asberg Depression Rating Scale. MITT Modified intention-to-treat. n Number of patients in category. N Number of patients in treatment group. NA Not available. 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.

The 2 treatment groups were well balanced in demographic and baseline disease characteristics. The mean patient age was approximately 70.4 years with a range of 65 to 87 years. There were 87.1% patients who were 75 years of age or younger and 12.9% who were older than 75 years of age. All patients were Caucasian. The treatment groups were generally well balanced with regard to baseline disease characteristics. HAM-A total scores at baseline were similar in the 2 treatment groups within the MITT analysis set (means of 25.1 and 25.2 in placebo and quetiapine XR groups, respectively); HAM-A total scores in individual patients ranged from 20 to 39.

Efficacy results

The key efficacy results of the study are presented in Table S2.

Table S2 Efficacy results at Week 9 (LOCF, MITT analysis set)

Outcome variable	PLA N=226	QTP XR N=222
HAM-A total score, LS mean change from randomization[a]	-7.21	-14.97[b]
HAM-A response rate (decrease from randomization total score of ≥50%, percentage of patients)[a]	23.9%	68.5%[b]
Q-LES-Q % maximum total score, LS mean change from randomization[a]	4.94	14.82[b]
CGI-S, LS mean change from randomization	-0.59	-1.76[c]
HAM-A psychic cluster, LS mean change from randomization	-3.81	-8.88[c]
HAM-A somatic cluster, LS mean change from randomization	-3.37	-6.05[c]
HAM-A remission (total score ≤7, percentage of patients)	12.83	40.09[c]
MADRS total score, LS mean change from randomization[d]	-2.22	-6.94[c]
PSQI global score, LS mean change from randomization	-2.09	-6.25[c]

[a] To account for the testing of the primary efficacy variable (change in HAM-A total score) and the 2 secondary efficacy variables of particular interest (HAM-A response and change in Q-LES-Q % maximum total score), a stepwise sequential multiple testing procedure (MTP) was used in order to preserve the overall 0.05 significance level.

[b] Adjusted p<0.001 for the comparison with placebo. Adjusted p-value was determined using the MTP.

[c] Nominal p<0.001 for the comparison with placebo.

[d] Safety analysis set was used for the analysis of this variable; N values: 227 for placebo and 223 for quetiapine XR.

CGI-S Clinical Global Impression – Severity of Illness. HAM-A Hamilton Rating Scale for Anxiety. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Asberg Depression Rating Scale. MITT Modified intention-to-treat. MTP Multiple testing procedure. PLA Placebo. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP XR Quetiapine extended-release.

In elderly patients with GAD, quetiapine XR treatment was significantly better than placebo in reducing the level of anxiety symptoms as demonstrated by the statistically significant difference in mean changes from randomization to Week 9 in the HAM-A total score. The quetiapine XR-treated group showed greater improvement in HAM-A total score by Week 1 of treatment (least square [LS] mean change from randomization -4.18 vs -2.35 in the placebo group, nominal p<0.001). The greater improvement compared with placebo was demonstrated throughout and at the end of 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 HAM-A response and HAM-A remission; improvement in HAM-A psychic and somatic subscale scores, and CGI-S total score; a greater proportion of patients with a CGI-I score of "much/very much improved"; and greater improvement in Q-LES-Q % maximum total score, Q-LES-Q Item 15 score, Q-LES-Q Item 16 score, MADRS total score, PSQI global score, and the pain VAS score. In addition to improved HAM-A total scores at Week1 previously noted, early efficacy was evidenced by superiority of quetiapine XR to placebo for the following secondary endpoints at Week 1: CGI-S total score and HAM-A psychic and somatic anxiety subscale

scores. The number of patients demonstrating a HAM-A response rate at Week 1 was numerically greater in the quetiapine XR group than in the placebo group.

Subgroup analyses of the primary efficacy variable, based on compliance, age group, gender, baseline disease severity, and overall prescribed mean daily dose showed that the results were not unduly influenced by any particular subgroup. Both patients ≤75 years old and those >75 years old demonstrated numerically greater improvements with quetiapine XR than with placebo. The flexible dose design does not allow for a thorough evaluation of efficacy in different dose categories. However, a large number of the quetiapine XR patients (39%) reached and benefited from the 300 mg prescribed daily dose, based on the investigator's judgement of efficacy and tolerability.

Safety results

Quetiapine XR, flexibly dosed at 50 mg/day to 300 mg/day, was generally well tolerated. Of the 223 quetiapine XR-treated patients, 87 patients (39.0%) titrated to 300 mg/day of quetiapine XR. Of these 87 patients, 72.4% continued and completed the study on that dose. Most AEs were of mild to moderate intensity in the quetiapine XR and placebo treatment groups. Serious adverse events (SAEs) were infrequent in both treatment groups. There was 1 death in this study; a patient who was assigned to placebo died of cardiomyopathy 2 days after discontinuing the study. The proportion of patients discontinuing from the study due to an AE in the quetiapine XR group was low (5.4%) but higher than in the placebo group (1.3%). The incidence of AEs judged by the Investigator to be causally related to the study drug was higher in the quetiapine XR group than in the placebo group.

Quetiapine was well-tolerated in both age subgroups; however, a higher incidence of AEs was reported in patients over 75 years of age than in patients 75 years of age or younger.

The number (%) of patients who had at least 1 AE in any category is summarized in Table S3.

Table S3 Patients who had an adverse event in any category (safety analysis set)

Category of adverse event	PLA N=227 n (%)	QTP XR N=223 n (%)
Any adverse event	114 (50.2)	145 (65.0)
Serious adverse event	3 (1.3)	1 (0.4)
Serious adverse event leading to death	1 (0.4)	0
Serious adverse event not leading to death	2 (0.9)	1 (0.4)
Drug-related adverse event[a]	57 (25.1)	107 (48.0)
Adverse events leading to discontinuation	3 (1.3)	12 (5.4)

[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.
Note: AEs were summarized from first dose through 30 days after last dose.
n Number of patients in category. N Number of patients in treatment group. PLA Placebo. QTP XR Quetiapine extended-release.

Somnolence, dry mouth, and nausea were the most common AEs that occurred at a higher incidence in the quetiapine group than in the placebo group. Most patients who experienced nausea experienced it while receiving study treatment.

The incidence of AEs potentially associated with extrapyramidal symptoms (EPS) was higher in the quetiapine XR group (5.4%) compared with the placebo group (2.2%). In the quetiapine XR group, 11.8% of patients had worsening SAS total scores (compared with 8.8% in the placebo group), 3.2% had worsening BARS global scores (compared with 3.5% in the placebo group), and 10.4% had worsening AIMS total scores (compared with 7.1% in the placebo group).

There were no AEs potentially related to neutropenia/agranulocytosis, syncope, suicidality, sexual dysfunction, or cerebrovascular accident during the study. There was 1 AE of "electrocardiogram QT prolonged" reported in the quetiapine XR group during the study. There were 2 AEs potentially related to diabetes reported in the quetiapine XR group and 3 AEs reported in the placebo group. The incidence of nausea/vomiting was higher in the quetiapine XR group compared with the placebo group during the randomized treatment period.

There were no clinically notable differences in clinical laboratory results between treatment groups. The incidence of patients with treatment-emergent clinically important triglyceride values was low, and similar in the quetiapine XR and placebo groups.

A higher proportion of patients in the placebo group had a treatment-emergent shift from ≤2 to ≥3 metabolic risk factors compared with the quetiapine XR group. The percentage of patients with weight increases of ≥7% was low and similar in quetiapine XR and placebo groups. There was 1 case of possible treatment-emergent hypothyroidism, but no AEs of hypothyroidism were reported.

In this study, following abrupt discontinuation of quetiapine XR, some clinical evidence of withdrawal symptoms was noted based on observed AEs, but not based on the TDSS total scores.