Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine XR		
Study code:	D1448C00009		
Date:	24 March 2008		

A Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Study of the Efficacy and Safety of Sustained-release Quetiapine Fumarate (SEROQUEL®) Compared with Placebo in the Treatment of Generalized Anxiety Disorder (Titanium Study)

International co-ordinating investigator

Study center(s)

1364 patients were screened and 951 were randomized at 63 centers in the United States.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	19 April 2006	Therapeutic confirmatory (III)
Last patient enrolled	14 May 2007	

Objectives

The primary objective of the study was to evaluate the efficacy of quetiapine sustained-release (SR) versus placebo in the treatment of anxiety symptoms in patients with generalized anxiety disorder (GAD). [SEROQUEL SR (sustained-release SEROQUEL) will hereafter be referred to as SEROQUEL XR (extended-release SEROQUEL).]

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

GAD; to evaluate the efficacy of quetiapine XR versus placebo in the treatment of depressive symptoms in patients with GAD [This was described as efficacy but actually relates to safety.]; to evaluate the efficacy of quetiapine XR versus placebo in improving sleep quality in patients with GAD; to evaluate satisfaction with quetiapine XR versus placebo in patients with GAD; to assess the safety and tolerability of quetiapine XR in patients with GAD.

The pharmacokinetic (PK) objective was to study the relationship between plasma levels of quetiapine and metabolite and change from randomization in total Hamilton Rating Scale for Anxiety (HAM-A) score. (PK results will be provided in a separate report.) The genetic objective was to establish a panel of DNA samples from patients who provide separate consent for genetic research. Genetic results were not available at the time of this report.

Study design

This was a 10-week, multicenter, randomized, parallel-group, double-blind, double-dummy, placebo-controlled, Phase III study of the efficacy and safety of extended-release quetiapine fumarate (SEROQUEL XR) 50 mg/day, 150 mg/day, and 300 mg/day compared with placebo in the treatment of GAD.

Target population and sample size

Patients were male or female, 18 to 65 years of age, inclusive, with a diagnosis of GAD. Patients were required to have a HAM-A total score of ≥20 with both Item 1 and Item 2 scores ≥2, a Clinical Global Impression-Severity of Illness (CGI-S) score ≥4, and a Montgomery-Asberg Depression Rating Scale (MADRS) score ≤16.

The target sample size was calculated to ensure a 90% power in demonstrating superior efficacy of each of the 3 doses (50 mg/day, 150 mg/day, and 300 mg/day) over placebo with regard to the primary efficacy outcome variable (change in HAM-A total score from randomization to Week 8). The calculation assumed a difference of 2.75 units from placebo and a standard deviation of 7.5. Using a 2-sided test at an overall 5% significance level (ie, α=0.0167 for each dose comparison) yielded a planned sample size of 203 patients per treatment group and 812 patients total.

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

Quetiapine XR 50 mg, 150 mg, and 300 mg doses were orally administered once daily in the evening using 50 mg and 300 mg tablets. Matching placebos were used.

The batch numbers used in the study were 9003K, LJ4706, and MC4605 for quetiapine XR 50 mg tablets; CE888X, CL879X, and CP021X for placebo quetiapine XR 50 mg tablets; 9049K, 9051K, and LM4613 for quetiapine XR 300 mg tablets; and CE891X, CL888X, ST73042-001-FC01 for placebo quetiapine XR 300 mg tablets.

Duration of treatment

This study included an 8-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 and Satisfaction Questionnaire (Q-LES-Q: % maximum total score, Item 15, and Item 16); CGI-S and CGI-Improvement (CGI-I); and Pittsburgh Sleep Quality Index (PSQI). For safety, adverse events (AEs), vital signs, suicidality (including MADRS Item 10 scores), and results from physical examinations (including weight and waist measurements), laboratory tests, electrocardiograms (ECGs), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), Changes in Sexual Functioning Questionnaire (CSFQ), and Treatment Discontinuation Signs and Symptoms (TDSS) were evaluated.

Statistical methods

Changes in HAM-A total score from randomization were analyzed with analysis of covariance (ANCOVA), with the baseline HAM-A score as covariate and including treatment as a fixed effect and center as a random effect in the model. For comparisons between each dose of quetiapine XR and placebo, 95% confidence intervals (CIs) were reported. P-values were controlled for multiplicity only at Week 8. To account for the testing of each quetiapine XR treatment group compared to placebo for 2 outcome variables (change from baseline in HAM-A total score and in Q-LES-Q % maximum total score), a Bonferroni-Holm type multiple testing procedure (MTP) for groups of hypotheses was applied.

Patient population

The analysis of all safety and tolerability variables were performed using the safety analysis set, which included all randomized patients who took study drug. The modified intention to treat (MITT) population was the primary efficacy population, which included all randomized patients who took study drug and who had a randomization HAM-A total score assessment and at least 1 HAM-A total score post-randomization. The per protocol (PP) analysis set was a subset of the MITT analysis set and excluded those patients with significant protocol violations or deviations. The TDSS analysis set was a subset of the MITT analysis set and included patients who completed 8 weeks of double-blind treatment (ie, still on drug at the Week 8 visit) and proceeded into the post-treatment period. The numbers of patients in each analysis set are presented in Table S1.

Table S1 Analysis sets and completion status

	PLA	QTP XR 50	QTP XR 150	QTP XR 300
N randomized	235	234	241	241
N safety[a]	234	232	238	238
N MITT[b]	225	219	226	224
N PP	189	173	187	177
N TDSS	142	137	130	118
N completed 8-weeks randomized treatment period	165	162	154	139

Table S1 Analysis sets and completion status

	PLA	QTP XR 50	QTP XR 150	QTP XR 300
N completed TDSS follow-up period	128	119	117	104

[a] Number of patients who received at least 1 dose of study drug.
[b] Number of patients who took at least 1 dose of study drug and had a randomization HAM-A assessment and at least 1 valid HAM-A assessment after randomization.
PLA Placebo. QTP Quetiapine. XR Extended release. N Number of patients. MITT Modified intention to treat. PP Per Protocol. TDSS Treatment discontinuation signs and symptoms. HAM-A Hamilton Rating Scale for Anxiety.

The 4 treatment groups were well balanced in demographic and baseline characteristics. The patient ages within the MITT analysis group ranged from 18 to 65 years, with a mean of 39.9 years. For all treatment groups, the patients were primarily Caucasian (range 80% to 84%) and female (range 57% to 66%). The treatment groups were well balanced with regard to baseline disease characteristics. HAM-A total score at baseline was moderate (means ranged between 24.5 and 24.9) and well balanced across the 4 treatment groups within the MITT analysis set; HAM-A total scores in individual patients ranged from 20 to 40.

Efficacy results

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

Table S2 Efficacy results at Week 8 (LOCF, MITT analysis set)

Outcome variable	PLA N=225	QTP XR 50 N=219	QTP XR 150 N=226	QTP XR 300 N=224
HAM-A total score, LS mean change from randomization[a]	-11.10	-13.31[b]	-13.54[b]	-11.87
Q-LES-Q % maximum total score, LS mean change from randomization[a]	10.96	10.36	11.11	9.27
CGI-S, LS mean change from randomization	-1.44	-1.62	-1.70[c]	-1.45
CGI-I, proportion of patients with much/very much improved score	56.89%	66.21%[c]	67.26%[c]	58.04%
HAM-A psychic cluster, LS mean change from baseline	-6.47	-7.66[d]	-8.14[d]	-7.13
HAM-A somatic cluster LS mean change from baseline	-4.60	-5.66[b]	-5.41[d]	-4.76
HAM-A response (decrease from randomization total score of ≥50%), proportion of patients	50.7%	60.3%[c]	61.5%[c]	54.9%
HAM-A remission (HAM-A total score ≤7) proportion of patients	27.56%	36.07%	37.17%[c]	28.57%
PSQI	-3.31	-4.07[c]	-4.38[b]	-3.97[c]

[a] To account for the testing of each quetiapine XR treatment group compared to placebo for 2 outcome variables (change in HAM-A total score and change in Q-LES-Q % maximum total score), a Bonferroni-Holm procedure for groups of hypotheses was applied. Significance thresholds adjusted for multiplicity were p≤0.0167 for all quetiapine XR doses.
[b] p≤0.001 comparison with placebo.
[c] p≤0.05 comparison with placebo.
[d] p≤0.01 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. LOCF Last observation carried forward. LS Least square. MITT Modified intention-to-treat. N Total number of patients in treatment group. NA Not applicable. PLA Placebo. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. QTP Quetiapine. XR Extended release.

In patients with GAD, quetiapine XR 150 mg/day and 50 mg/day treatment were superior to placebo in reducing the overall level of anxiety symptoms.

For the primary endpoint (change from randomization to Week 8 in the HAM-A total score), quetiapine XR 50 mg/day and 150 mg/day were statistically significantly better than placebo after adjustment for multiplicity. Quetiapine XR 300 mg/day did not show statistically significant improvement compared to placebo.

Overall, the results from the secondary outcome variables at Week 8 were supportive of the results for the primary endpoint. At Week 8, quetiapine XR 50 mg/day and 150 mg/day were significantly better than placebo for the following secondary endpoints: CGI-I, HAM-A psychic cluster, HAM-A somatic cluster, and HAM-A response. In addition, at Week 8, all 3 quetiapine XR doses were significantly better than placebo for PSQI, and quetiapine XR 150 mg/day was significantly better than placebo for CGI-S and HAM-A remission. For Q-LES-Q % maximum total score, none of the quetiapine XR dose groups showed statistically significant improvement compared to placebo after adjustment for multiplicity.

At the Week 1 visit, the quetiapine XR 150 mg/day group had received 2 doses of quetiapine XR 50 mg/day and 4 doses of quetiapine XR 150 mg/day. At Week 1, patients in the quetiapine XR 300 mg/day group had received 2 doses of quetiapine XR 50 mg/day, 2 doses of quetiapine XR 150 mg/day, and 2 doses of quetiapine XR 300 mg/day. All 3 quetiapine XR groups were significantly better than placebo for the following secondary endpoints at Week 1: HAM-A total score, HAM-A psychic cluster, and CGI-S. In addition, the quetiapine XR 150 mg/day group was significantly better than placebo for HAM-A somatic cluster Week 1.

Safety results

The number (%) of patients who had at least 1 AE in any category is summarized in Table S3. The 50 mg/day, 150 mg/day, and 300 mg/day doses of quetiapine XR were generally well-tolerated. There was a higher incidence of AEs leading to discontinuation in the quetiapine XR groups compared to placebo. The largest portion of AEs leading to discontinuation included somnolence, sedation, dry mouth, fatigue, and dizziness, which is consistent with the known safety profile of quetiapine XR. 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. One death occurred approximately 2 months after the patient's final dose of study drug. The patient had been randomized to the quetiapine XR 300 mg/day group. The cause of death was unknown and no additional information could be obtained. This event was not considered to be related to study drug. The incidence of drug-related AEs was higher in the quetiapine XR treatment groups compared to placebo.

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

Category of adverse event	PLA N=234 n (%)	QTP XR 50 N=232 n (%)	QTP XR 150 N=238 n (%)	QTP XR 300 N=238 n (%)
Any adverse event	168 (71.8)	185 (79.7)	207 (87.0)	198 (83.2)
Serious adverse event	0	0	2 (0.8)	5 (2.1)
Serious adverse event leading to death	0	0	0	0
Drug-related adverse event[a]	127 (54.3)	161 (69.4)	185 (77.7)	181 (76.1)
Adverse events leading to discontinuation	15 (6.4)	37 (15.9)	43 (18.1)	58 (24.4)

[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: Adverse events from first dose of study drug through 30 days after last dose are included in this table.
N Total number of patients in treatment group. n Number of patients in category. PLA Placebo. QTP Quetiapine. XR Extended release

The most common AEs (occurring at an incidence of ≥5% in any randomized treatment group that also occurred at ≥2 times the placebo rate), included the following preferred terms: dry mouth, somnolence, sedation, and constipation.

The overall incidence of AEs was highest in the quetiapine XR treatment arms, with a higher incidence in the quetiapine XR 150 mg/day group compared with the other treatment groups. The most common AEs of severe intensity were somnolence, sedation, fatigue, and dry mouth; though overall, the majority of AEs were reported as mild to moderate in intensity. Also indicative of the overall pattern of AEs, the most common AEs considered by the investigator to be possibly related to study drug were dry mouth, somnolence, sedation, fatigue, and dizziness, with the highest percentages occurring in the quetiapine XR groups for dry mouth and somnolence.

Overall, the clinical laboratory results in this study were consistent with the clinical laboratory profile that has been observed in previous studies of patients treated with quetiapine immediate release (IR) and XR for other disorders. There were no differences between dose groups judged to be clinically relevant among the treatment groups in the changes from baseline for any hematology assessments. There were 2 cases of treatment-emergent clinically important shifts in total/free thyroxine in combination with clinically important high thyroid stimulating hormone (TSH) values (1 in the placebo group and 1 in the quetiapine XR 50 mg/day group). There was a moderate increase for insulin and a small increase for glucose in mean change from baseline to Week 8 (both fasting confirmed) in the quetiapine XR 300 mg/day group compared to the other treatment groups. There was a higher percentage of quetiapine XR 150 mg/day and 300 mg/day-treated patients with a treatment-emergent shift from ≤2 to ≥3 metabolic risk factors compared with the placebo group, but the quetiapine XR 50 mg/day group had a smaller percentage of patients meeting this criterion than the placebo group.

The percentage of patients with weight increases of ≥7% was higher in the quetiapine XR 300 mg/day group than in the other groups; no consistent pattern of ≥7% weight increases was observed based on patients' baseline body mass index (BMI) category in any treatment group.

Combined criteria for orthostatic changes in pulse and systolic blood pressure did not show any differential effect of quetiapine XR administration compared to placebo. There was no evidence of an increased risk of clinically relevant ECG changes in the quetiapine XR groups.

There was no evidence of increased risk of vomiting, diabetes mellitus, agranulocytosis/neutropenia, QT prolongation, sexual dysfunction, or suicidality in the quetiapine XR groups. The quetiapine XR 300 mg/day group had a slightly higher incidence of nausea compared to placebo, and the quetiapine XR 300 mg/day group had the only 2 nausea AEs considered severe in intensity by the investigator. A small increase in mean pulse rate was observed in the quetiapine XR groups compared to placebo. The incidences of somnolence-related AEs, syncope-related AEs, and extrapyramidal symptoms (EPS)-related AEs in the quetiapine XR groups were greater than in the placebo group (except incidence of EPS-related AEs in the 50 mg/day group was lower than placebo), but overall, the incidences were low and were anticipated based on the known pharmacological profile of quetiapine. No AEs potentially related to QT prolongation, neutropenia, or agranulocytosis were reported. Abrupt discontinuation of study treatment resulted in slightly higher TDSS total scores for patients who had received quetiapine XR 50 mg/day or 150 mg/day compared to those who had received placebo, which was driven mostly by symptoms of chills, insomnia, and vomiting. The overall percentage of patients experiencing AEs potentially related to withdrawal (up to 14 days after treatment discontinuation, safety analysis set) was higher in the quetiapine XR 150 mg/day and 300 mg/day groups compared to the other 2 treatment groups: 18.5% in each quetiapine XR 150 mg/day and 300 mg/day group and approximately 15% in each quetiapine XR 50 mg/day and placebo group. However, even the most common AE potentially related to withdrawal reported (insomnia) had a low overall incidence (2.2%).