Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine XR		
Study code:	D1448C00010		
Date:	24 March 2008		

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

Study center(s)

1344 patients were enrolled, and 854 were randomized at 64 centers in the United States.

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	17 April 2006	Therapeutic confirmatory (III)
Last patient enrolled	14 June 2007	

Objectives

The primary objective of the study was to evaluate the efficacy of quetiapine sustained release (SR) compared to 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 in 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 escitalopram 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 if quetiapine XR improves satisfaction with medication versus placebo in patients with GAD; 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 study was a 10-week, multicenter, randomized, parallel-group, double-blind, double-dummy, placebo-controlled, active-controlled study to assess the safety and efficacy of quetiapine XR (150 mg/day), quetiapine XR (300 mg/day), and escitalopram oxalate (LEXAPRO®, Forest Laboratories, Inc. [10 mg/day]) compared with placebo in the treatment of patients with 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 Hamilton Rating Scale for Anxiety (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 Montgomery-Asberg Depression Rating Scale (MADRS) score ≤16.

The sample size was calculated to ensure a 90% power in demonstrating superior efficacy of each of the 2 quetiapine XR doses (150 mg and 300 mg per day) over placebo with regard to the primary efficacy outcome variable (change in HAM-A total score from randomization to Week 8). The calculations assumed a difference of 2.75 units from placebo and a standard deviation of 7.5. Using a 2-sided test at a 5% significance level (ie, α=0.025 for each dose comparison) yielded a planned sample size of 186 patients per treatment group and 744 patients in total.

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

Quetiapine XR 150 mg and 300 mg doses of sustained-release tablets were orally administered once daily in the evening using 50 mg and 300 mg tablets. Escitalopram oxalate (10 mg once per day) was the active comparator. Matching placebos were used to achieve "double-dummy" blinding.

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 300 mg tablets; CE891X, CL888X, and ST73042-001-FC01 for placebo quetiapine XR 300 mg tablets; ST76055-001-FA02 and

ST76055-001-FA03 for escitalopram 10 mg capsules; and ST75022-001-FA02 for placebo escitalopram 10 mg capsules.

Duration of treatment

Patients entered 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, Clinical Global Impression-Global 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), MADRS, Simpson-Angus Scale, Barnes Akathisia Rating Scale, Changes in Sexual Functioning Questionnaire, and Treatment Discontinuation Signs and Symptoms (TDSS) were evaluated.

Statistical methods

Changes in HAM-A total score from randomization were evaluated with an analysis of covariance model (ANCOVA). For comparisons between each dose of quetiapine XR and placebo, 95% confidence intervals (CIs) were reported. P-values were controlled for multiplicity at Week 8 only. 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 for groups of hypotheses was applied. Nominal p-values were reported for the comparison of escitalopram to placebo.

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) analysis set was the primary efficacy population, which included all randomized patients who took study drug, had a randomization HAM-A total score assessment, and had 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 totals

	PLA	QTP XR 150	QTP XR 300	ESC 10
N randomized	215	219	207	213
N safety[a]	214	217	206	209
N MITT[b]	212	212	201	203
N PP	206	203	186	191
N TDSS	141	131	107	134
Completed 8-weeks randomized treatment period	169	156	126	154
Completed TDSS follow-up period	132	121	101	124

[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, had a randomization HAM-A assessment, and had at least 1 valid HAM-A assessment after randomization.
ESC Escitalopram. HAM-A Hamilton Rating Scale for Anxiety. N Total number of patients in treatment group. MITT Modified intention-to-treat. PLA Placebo. PP Per Protocol. QTP XR Quetiapine extended release. TDSS Treatment discontinuation signs and symptoms.

The 4 treatment groups were similar in mean HAM-A total score at baseline (24.6 to 25.3), percentage of males (range 29% to 36%), and mean age (range 36.6 to 40.4 years). For all groups, the patients were primarily Caucasian (range 79% to 82%), and the majority of the remainder was Black (range 10 to 15%).

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=212	QTP XR 150 N=212	QTP XR 300 N=201	ESC 10 N=203
HAM-A total score, LS mean change from randomization[a]	-10.72	-13.92[b]	-12.32[c]	-12.27[c]
Q-LES-Q % maximum total score, LS mean change from randomization[a]	8.36	11.83[c]	7.41	11.50[c]
Q-LES-Q Item 16 score, mean change from randomization	0.5	0.7	0.4	0.6
Q-LES-Q Item 15 score, mean change from randomization	0.0	0.0	-0.4	0.0
CGI-S, LS mean change from randomization	-1.29	-1.76[b]	-1.44	-1.51[c]
CGI-I percent of patients with “much/very much improved” score	51.18	65.09	57.21	60.59
HAM-A psychic cluster, LS mean change from baseline	-6.07	-8.16[b]	-7.30[c]	-7.29[c]
HAM-A somatic cluster, LS mean change from baseline	-4.65	-5.78[b]	-5.03	-5.01

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

Outcome variable	PLA N=212	QTP XR 150 N=212	QTP XR 300 N=201	ESC 10 N=203
HAM-A response (decrease from randomization total score of ≥50%), percentage of patients	46.2%	62.7%[b]	52.7%	53.7%
HAM-A remission (HAM-A total score ≤7), percentage of patients	27.36%	37.26%[c]	28.36%	31.53%
PSQI (LS mean change from randomization)	-3.12	-5.06[b]	-3.69	-3.04

[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 $p \leq 0.025$ for quetiapine XR 150 mg/day and $p \leq 0.050$ for quetiapine XR 300 mg/day.

[b] $p \leq 0.001$ comparison with placebo.

[c] $p \leq 0.050$ comparison with placebo.

[d] $p \leq 0.010$ comparison with placebo.

CGI-I Clinical Global Impression-Global Improvement. CGI-S Clinical Global Impression-Severity of Illness. ESC Escitalopram. 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 the treatment group. PLA Placebo. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP XR Quetiapine extended release.

In patients with GAD, quetiapine XR treatment was significantly better than placebo in reducing the level of anxiety symptoms. For the primary endpoint (change from randomization to Week 8 in the HAM-A total score), quetiapine XR 150 mg/day and 300 mg/day were significantly better than placebo after adjustment for multiplicity. Overall, the results from the secondary outcome variables were supportive.

For the secondary variable of special interest (change from randomization to Week 8 in Q-LES-Q % maximum total score), quetiapine XR 150 mg/day, but not 300 mg/day, was significantly better than placebo after adjustment for multiplicity.

At Week 8, both quetiapine XR doses were significantly better than placebo for the HAM-A psychic cluster secondary endpoint. In addition, quetiapine XR 150 mg/day, but not 300 mg/day, was significantly better than placebo for CGI-S, CGI-I, HAM-A somatic cluster, HAM-A response, HAM-A remission, and PSQI.

At the Day 4 visit, patients in the quetiapine XR 150 mg/day and 300 mg/day groups had received 2 doses of quetiapine XR 50 mg/day and 1 dose of quetiapine XR 150 mg/day. On Day 4, both quetiapine XR groups demonstrated significantly better results than the placebo group for the following endpoints: HAM-A total score and HAM-A psychic cluster. In addition, the quetiapine XR 150 mg/day group, but not the 300 mg/day group, was significantly better than the placebo group for the CGI-S and HAM-A somatic cluster on Day 4.

An active reference control arm, escitalopram 10 mg/day, was included in this study, which allowed for evaluation of assay sensitivity. Escitalopram was superior to placebo in treatment of GAD, and the results are consistent with the known pharmacology of escitalopram and

indicate that the study design was suitable for detecting effects on GAD at Week 8. Quetiapine XR 150 mg/day was significantly better than escitalopram 10 mg/day for HAM-A total score, HAM-A psychic cluster score, and HAM-A somatic cluster score at Week 8.

Safety results

Both the 150 mg/day and 300 mg/day doses of quetiapine XR were generally well tolerated. Most AEs were mild to moderate in all treatment groups. The number (%) of patients who had at least 1 AE in any category is summarized in Table S3. Serious AEs (SAEs) were infrequent in all treatment groups, and no deaths occurred in the study. Larger proportions of patients in the quetiapine XR and escitalopram groups 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 groups and the escitalopram group compared to the placebo group.

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

	PLA N=214	QTP XR 150 N=217	QTP XR 300 N=206	ESC 10 N=209
Category of adverse event	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any adverse event	172 (80.4)	203 (93.5)	193 (93.7)	177 (84.7)
Serious adverse event	2 (0.9)	1 (0.5)	2 (1.0)	3 (1.4)
Serious adverse events leading to death	0	0	0	0
Drug-related adverse event[a]	126 (58.9)	183 (84.3)	179 (86.9)	146 (69.9)
Adverse events leading to discontinuation	14 (6.5)	39 (18.0)	52 (25.2)	21 (10.0)

[a] As judged by the investigator.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as 100*n/N.
Note: AEs were summarized from first dose through 30 days after last dose.
AE Adverse event. ESC Escitalopram. N Total number of patients in treatment group. n Number of patients in category. PLA Placebo. QTP XR Quetiapine extended release.

AEs experienced by at least twice as many patients in any quetiapine XR group as in the placebo group and in ≥5% of patients in any treatment group were dry mouth, somnolence, sedation, constipation, dyspepsia, vomiting, and irritability.

The most common severe intensity AEs in the quetiapine XR treatment groups were sedation and somnolence. The most common AEs considered by the investigator to be possibly related to study drug were dry mouth, somnolence, sedation, nausea, dizziness, and headache, with the highest percentages occurring in the quetiapine XR groups for dry mouth, somnolence, sedation, and dizziness. The total percentage of patients with AEs was 80.4% in the placebo group, 84.7% in the escitalopram 10 mg/day group, 93.5% in the quetiapine XR 150 mg/day group, and 93.7% in the quetiapine XR 300 mg/day group.

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 for other psychiatric disorders. There were no notable differences judged to be clinically relevant among the treatment groups in the changes from baseline for any hematology assessments. One patient in the quetiapine XR 150 mg/day group had a clinically important high thyroid stimulating hormone value in combination with clinically important low thyroxine values at the end of treatment. There was a higher percentage of quetiapine XR-treated patients with a treatment-emergent shift from ≤2 to ≥3 metabolic risk factors than with the placebo group.

The percentages of patients with weight increases of ≥7% were higher in patients in the quetiapine XR-treated groups than in the other groups. Across both quetiapine XR treatment groups, there was a trend for weight gain ≥7% that occurred more often in patients in the lower body mass index categories.

A small increase in mean pulse rate was observed in the quetiapine XR groups compared with placebo. Combined criteria for orthostatic changes in pulse and systolic blood pressure did not show a notable 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 incidence of diabetes mellitus, neutropenia, sexual dysfunction, or suicidality in the quetiapine XR groups. The incidences of AEs related to nausea and vomiting for the quetiapine XR groups were greater than the placebo group; these events occurred both during and after treatment with quetiapine XR. The incidence of somnolence-related AEs, syncope-related AEs, and extrapyramidal symptoms-related AEs for quetiapine XR groups were greater than the placebo group, but these AEs were anticipated based on the known pharmacological profile of quetiapine. No AEs potentially related to QT prolongation or agranulocytosis were reported. The proportion of patients reporting AEs in the first 14 days following treatment discontinuation (no down titration) was higher in the quetiapine XR groups compared to placebo across all treatment groups. Abrupt discontinuation of study treatment resulted in TDSS scores for the quetiapine XR groups that were higher than the placebo group. Based on TDSS scores, the most prominent effects were vomiting; chills; nausea; trouble sleeping, insomnia; sweating more than usual; diarrhea; and bouts of crying or tearfulness.