Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine XR		
Study code:	D1448C00012		
Date:	31 March 2008		

A Multicenter, Double-blind, Randomized-Withdrawal, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Sustained Release (Seroquel SR™) as Monotherapy in the Maintenance Treatment of Patients with Generalized Anxiety Disorder Following an Open-Label Stabilization Period (PLATINUM STUDY)

International co-ordinating Investigator

Study center(s)

A total of 1811 patients were enrolled (screened), of which 1248 patients were enrolled in the open-label run-in period, 1224 patients were treated, and 433 patients were randomized at 128 sites in Asia, Europe, North America, and Australia.

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	17 March 2006	Therapeutic confirmatory (III)
Last patient completed	07 August 2007	

Objectives

The primary objective of this study was to evaluate the efficacy of quetiapine SR compared to placebo in increasing time from randomization to an anxiety event in patients with generalized anxiety disorder (GAD) [SEROQUEL XR (extended-release SEROQUEL) was previously referred to as SEROQUEL SR (sustained-release SEROQUEL)].

An anxiety event was defined as fulfilling at least 1 of the following: (a) Initiation of pharmacological treatment by the investigator to treat anxiety symptoms, (b) Initiation of pharmacological treatment by the patient for at least 1 week to treat anxiety symptoms, (c) Hospitalization for anxiety symptoms, (d) A Hamilton Rating Scale for Anxiety (HAM-A) total score ≥15 at 2 consecutive assessments 1 week apart or at the final assessment if the patient discontinued, (e) Clinical Global Impression – Severity (CGI-S) score of ≥5, or (f) Suicide attempt or discontinuation from study due to imminent risk of suicide.

The secondary objectives of this study were to evaluate the effect of quetiapine XR compared to placebo in health-related quality of life in patients with GAD during long-term treatment; to evaluate the efficacy of quetiapine XR compared to placebo in maintaining improvement of anxiety symptoms in patients with GAD during long-term treatment; to evaluate the effect of quetiapine XR compared to placebo on depressive symptoms in patients with GAD during long-term treatment [This was described as efficacy but actually relates to safety]; to evaluate the effect of quetiapine XR compared to placebo on quality of sleep in patients with GAD during long-term treatment; to evaluate the effect of quetiapine XR compared to placebo on suicidal ideation in patients with GAD during long-term treatment [This was described as efficacy but actually relates to safety]; to evaluate the effect of quetiapine XR compared to placebo on functional disability in patients with GAD during long-term treatment; and to evaluate if quetiapine XR compared to placebo was safe and well tolerated in patients with GAD during long-term treatment.

This study also included a genetic objective to allow enrolled patients the opportunity to provide a blood sample from which DNA will be extracted and archived for future genetic research. The purpose of this research was to explore the effects of genetic polymorphisms on response to quetiapine XR and on susceptibility to GAD. The genetic research was optional for individual patients and centers.

Study design

A multicenter, randomized-withdrawal, parallel-group, double-blind, placebo-controlled period following open-label run-in and stabilization periods. During the open-label run-in patients received quetiapine XR 50 mg/day on Days 1 and 2, and then the dose increased to 150 mg/day on Days 3 and 4. The dose of quetiapine SR could be increased to 300 mg/day on Day 5 or thereafter, based on the clinical judgement of the investigator. Dose adjustment was permitted at any time based on the clinical judgment of the investigator. Patients with a HAM-A ≤12 and CGI-S score ≤3 after 4 weeks or 8 weeks were entered into the open-label stabilization period (OLST). OLST continued for at least 12 weeks and up to 18 weeks prior to randomization. Patients meeting randomization criteria (ie, patients who remained stable for at least 12 weeks) were allocated to a double-blind treatment to continue with blinded quetiapine XR or switch to matching placebo at the same dose as taken at the last visit of the OLST. Safety during treatment withdrawal was assessed by comparing the placebo and active treatment groups with respect to adverse events (AEs) and pre-defined treatment discontinuation signs and symptoms (TDSS) during the first 2 weeks of randomized treatment. Patients could continue in the randomized treatment period (RTP) for up to 52 weeks.

Patients experiencing an anxiety event (relapse) were required to discontinue the study, and when the total number of required relapses occurred, the sponsor terminated the study.

Target patient population and sample size

Patients were male or female, 18 to 65 years of age (inclusive), with a diagnosis of GAD.

For inclusion in the randomized withdrawal period, the patients had to have a HAM-A score ≤12, a CGI-S score of ≤3, and a Montgomery-Asberg Depression Rating Scale (MADRS) score ≤16.

It was assumed that the risk of having an event in any time interval was reduced by 62.5% (hazard ratio [HR]=0.375) for patients treated with quetiapine XR in comparison to patients receiving placebo. In order to ensure 90% power to demonstrate that quetiapine XR, as compared with placebo, was effective in increasing the time to an anxiety event, 44 anxiety events were required. In support of the primary analysis, the same analysis was repeated censoring all patients who were withdrawn prior to Day 14 after randomization. An HR of 0.41 was assumed for anxiety events occurring on or after Day 14. It was planned to stop the recruitment when 46 late events were reached. The total number of events was 106 in this study. The total of 115 events was used to estimate the number of randomized patients needed. These calculations yielded a planned sample size of 1055 patients for the open-label phase to provide 575 patients for the randomized phase. Projections based on blinded data were done regularly to predict the number of patients needed to be entered into the study to reach the 46 late anxiety events.

Study drug 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. During the open-label phase patients started quetiapine XR 50 mg/day and were then increased to 150 mg/day (the targeted dose). The dose subsequently could be adjusted (to 50 mg/day or 300 mg/day) for efficacy or safety. Matching placebos were used during the randomized period.

The batch numbers used in the study were [redacted] for quetiapine XR 50 mg tablets; [redacted] for placebo quetiapine XR 50 mg tablets; [redacted] for quetiapine XR 300 mg tablets; and [redacted] for placebo quetiapine XR 300 mg tablets.

Duration of treatment

Sixteen to 26 weeks of open-label treatment and 0 to 52 weeks of randomized treatment.

Criteria for evaluation (main variables)

Efficacy

Outcome variables for efficacy included time from randomization to an anxiety event; number of patients with anxiety events; and change from randomization in HAM-A total score, CGI-S score, HAM-A psychic anxiety cluster score, HAM-A somatic anxiety cluster score, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) % maximum total score, Q-LES-Q Item 15, Q-LES-Q Item 16 score, Pittsburgh Sleep Quality Index (PSQI) global score, Sheehan Disability Scale (SDS) total score, SDS number of unproductive days, and SDS number of under-productive days.

Safety

For safety the following criteria were evaluated: physical examinations (including eye exams using ophthalmoscopy); laboratory values; vital signs; electrocardiograms (ECGs); AEs; Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS); MADRS scores; suicidality; total withdrawals due to AEs; discontinuation symptoms; weight and waist circumference.

Statistical methods

The main analysis for time to an anxiety event was performed with a Cox proportional-hazards model. The estimated hazard ratio between quetiapine XR and placebo was reported with a 95% confidence interval (CI). The null hypothesis of equivalent hazards was tested with a 2-sided Wald test with an overall significance level of 0.05. For the primary efficacy analysis, region was included as a stratification variable. A supporting analysis censored all anxiety events occurring up to and including 13 days after randomization.

In addition, the proportion of patients experiencing an anxiety event in each treatment group over the course of treatment was presented.

The mean of all changes for Q-LES-Q, MADRS, HAM-A, CGI-S, PSQI, SDS, and other continuous variables from randomization up to, but excluding, the visit where an anxiety event was recorded were analyzed using Analysis of Covariance (ANCOVA), with baseline as a covariate, and treatment and region as fixed effects. If no anxiety event was recorded for a patient, all visits after randomization with available data were used.

All statistical tests were 2-sided with an overall significance level of 5% (ie, α=0.05). Where appropriate, 95% CIs were presented. Descriptive statistics were provided for all variables.

Descriptive statistics of incidence rates were used to evaluate AEs (including serious AEs (SAEs), AEs leading to withdrawal, and deaths) and reasons for early withdrawal from study. Other safety analyses were by means of descriptive statistics, (mean, median, standard deviation, minimum and maximum value), frequency tables, and graphs as appropriate. Furthermore, total patient-years of exposure and incidence densities were calculated for common AEs. Incidence densities adjust for the time exposed to drug and were expressed as events per patient-year.

The open-label safety (OLS) analysis set included all patients who entered the open-label periods and received study drug. The randomized safety (RS) analysis set included all patients who received treatment during the RTP, classified according to actual treatment taken. The intention-to-treat (ITT) analysis set included all randomized patients who received study treatment during the RTP, classified according to their randomized treatment. The per-protocol (PP) analysis set was based on a subset of data from the ITT patients. The treatment discontinuation signs and symptoms (TDSS) analysis set was a subset of the ITT analysis set.

Patient population

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

Table S1 Number of patients by analysis set and treatment

Analysis set	PLA	QTP XR
OLS	NA	1224
RS	216	216
ITT	216	216
PP	180	185
TDSS	191	202

ITT Intention-to-treat. N Total number of patients in treatment group. OLS Open-label safety. PLA Placebo. PP Per protocol. QTP XR Quetiapine extended release. RS Randomized safety. TDSS Treatment discontinuation signs and symptoms.

Overall, the placebo and quetiapine XR groups were similar in baseline and demographic characteristics, including the percentage of males (36.6% and 32.9%, respectively) and age (median age 42 and 46 years, respectively). For both groups the patients were primarily Caucasian (81.9% and 84.7%, respectively) with representation from other races (Oriental: 9.3% and 7.4%, respectively and Black: 6.5% and 6.0%, respectively).

The primary reasons for discontinuation during the open-label period were AEs and not willing to continue. AEs resulting in discontinuation during the open-label period were consistent with the known safety profile for quetiapine. Demographic characteristics at randomization were similar to demographic characteristics at study entry.

Efficacy results

The primary efficacy results are summarized in Table S2.

Table S2 Analysis of time to occurrence of an anxiety event (ITT analysis set, randomized phase)

	Quetiapine XR (N=216) vs Placebo (N=216)
Time to anxiety event	
Hazard ratio	0.19
95% CI	0.12, 0.31
p-value	<0.0001
Time to anxiety event censoring events during the first 13 days **Quetiapine XR (N=166) vs Placebo (N=210)**	
Hazard ratio	0.27
95% CI	0.15, 0.47
p-value	<0.0001
Analysis of time to recurrence of an anxiety event, last open-label dose: 50 mg **Quetiapine XR (N=57) vs Placebo (N=64)**	
Hazard ratio	0.21
95% CI	0.08, 0.51
p-value	0.0006
Analysis of time to recurrence of an anxiety event, last open-label dose: 150 mg **Quetiapine XR (N=106) vs Placebo (N=91)**	
Hazard ratio	0.17
95% CI	0.08, 0.36
p-value	<0.0001
Analysis of time to recurrence of an anxiety event, last open-label dose: 300 mg **Quetiapine XR (N=53) vs Placebo (N=61)**	
Hazard ratio	0.22
95% CI	0.09, 0.51
p-value	0.0005

CI Confidence interval. ITT Intention-to-treat. N Number of patients in treatment group. XR Extended release.

The main secondary efficacy results are summarized in Table S3.

Table S3 Efficacy results: secondary variables, RTP (ITT analysis set, randomized phase)

Outcome variable		PLA	QTP XR	Estimated difference (95% CI)	p-value
HAM-A total score[a]	LS mean[b] (SE)	1.90 (0.24)	-0.14 (0.21)	Diff: 2.05 (1.43, 2.67)	<0.001
HAM-A psychic anxiety cluster score[a]	LS mean[b] (SE)	1.53 (0.17)	0.08 (0.15)	Diff: 1.45 (1.01, 1.89)	<0.001
HAM-A somatic anxiety cluster score[a]	LS mean[b] (SE)	0.38 (0.11)	-0.22 (0.10)	Diff: 0.61 (0.30, 0.91)	<0.001
Q-LES-Q % maximum total score[a]	LS mean[b] (SE)	-2.12 (0.73)	0.22 (0.63)	Diff: -2.34 (-4.25, -0.43)	0.017
Q-LES-Q 15[a]	LS mean[b] (SE)	-0.39 (0.06)	-0.09 (0.05)	Diff: -0.30 (-0.46, -0.14)	<0.001
Q-LES-Q 16[a]	LS mean[b] (SE)	-0.19 (0.05)	-0.01 (0.04)	Diff: -0.19 (-0.31, -0.06)	0.003
CGI-S score[a]	LS mean[b] (SE)	0.26 (0.05)	-0.03 (0.05)	Diff: 0.30 (0.16, 0.43)	<0.001
PSQI global score[a]	LS mean[b] (SE)	1.60 (0.23)	0.39 (0.20)	Diff: 1.21 (0.61, 1.82)	<0.001
SDS total score[a]	LS mean[b] (SE)	1.01 (0.38)	-0.19 (0.33)	Diff: 1.19 (0.21, 2.18)	0.017

[a] Change from randomization.

[b] Estimate of LS mean change from randomization to anxiety event or end of study was analyzed using an ANCOVA analysis with randomization value as a covariate and treatment and region as fixed effects.

CGI-S Clinical Global Impression – Severity. CI Confidence interval. HAM-A Hamilton Rating Scale for Anxiety. ITT Intention-to-treat. LS Least squares. N Number of patients in treatment group. PLA Placebo. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire. QTP XR Quetiapine extended release. RS Randomized safety. RTP Randomized treatment period. SDS Sheehan Disability Scale. SE Standard error.

When used as monotherapy in the maintenance treatment of patients with GAD, quetiapine XR at flexible doses of 50 mg, 150 mg, or 300 mg/day significantly increased the time to occurrence of an anxiety event compared with the placebo group, both for any anxiety event (HR=0.19) and with anxiety events prior to Day 14 after randomization censored (HR=0.27). The total number of patients with anxiety events was higher in the placebo group (84, 38.9%) than in the quetiapine group (22, 10.2%).

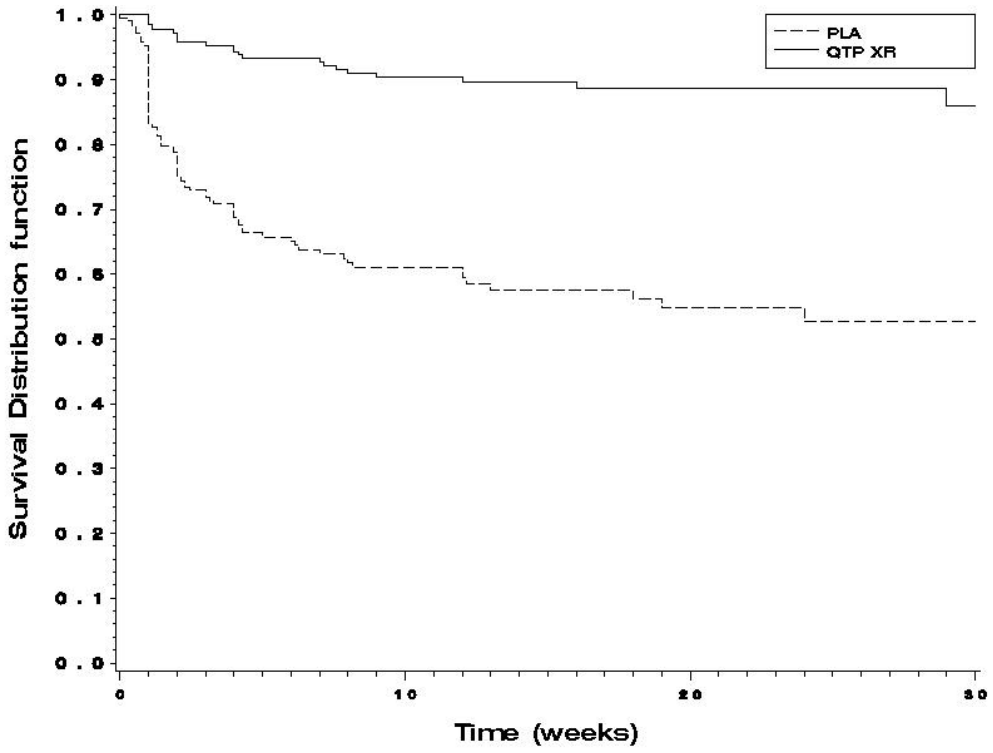
Based on the clinical judgement of the investigator, approximately 45% of patients were at a dose of 150 mg/day at randomization, with approximately 28% and 26% at a dose of 50 mg/day and 300 mg/day, respectively. Results when patients were grouped by the last dose of quetiapine XR taken during the open-label phase supported the primary endpoint with differences favoring the quetiapine XR group compared with the placebo group in time to occurrence of an anxiety event: 50 mg/day (HR=0.21); 150 mg/day (HR=0.17); and 300 mg/day (HR=0.22).

The demonstrated efficacy of quetiapine XR did not show restriction to any specific subgroup (sex, age, or race). The results in the primary ITT analysis set were supported by the results in the PP analysis set. Results were supported by additional robustness checks, including censoring early events (as described above) and censoring early events confirmed by rating scales. Quetiapine XR also significantly increased the time to occurrence of all-cause discontinuation compared with the placebo group.

The results of the symptom scale analyses supported the primary efficacy findings. Quetiapine XR was statistically superior to placebo at maintaining reduction in anxiety symptoms (HAM-A and CGI-S scores), improved health-related quality of life (Q-LES-Q scores), improved sleep quality (PSQI score), and improved level of functioning (SDS total score).

Kaplan-Meier curves for time to occurrence of an anxiety event are presented in Figure S1.

Figure S1 Time to occurrence of an anxiety event, Kaplan-Meier curves (ITT analysis set, randomized period)



ITT Intention-to-treat.

Safety results

During this study, 1224 patients with GAD received study drug during the open-label phase with a flexible dose of 50 mg, 150 mg, or 300 mg/day of quetiapine XR (mean of individual patients' median doses, 143 mg/day). Of these, 433 patients were randomized, with 1 patient discontinued prior to receiving randomized treatment, primarily due to termination of the study by the sponsor. A total of 432 patients received randomized, double-blind treatment with quetiapine XR or placebo, during which the mean of individual patients' median dose of quetiapine XR was 164 mg/day. Due to the efficacy of quetiapine XR at preventing or delaying anxiety events, randomized time of exposure was 56% greater in the quetiapine XR group (106.9 mean days in the quetiapine XR group compared with 68.6 mean days in the placebo group). Of the 216 patients in the quetiapine XR group, a total of 107 patients

received at least 12 weeks of randomized treatment with quetiapine XR, and a total of 44 patients received at least 24 weeks of randomized treatment with quetiapine XR (Table 11.3.1.4).

Although the exposure to study drug was considerably greater in the quetiapine XR group compared with the placebo group, the incidence of AEs was similar between randomized treatment groups. The number (%) of patients who had at least 1 AE in any category during the randomized treatment phase is summarized in Table S4. Quetiapine XR was generally well tolerated in the dose range of 50 mg to 300 mg daily when used as monotherapy for maintenance treatment in patients with GAD. Most AEs were mild to moderate in both treatment groups. SAEs were infrequent in both groups. No deaths occurred in the study. A similar proportion of patients in the quetiapine XR group discontinued due to an AE as patients in the placebo group (ie, prior to the sponsor termination of the study, after the required number of patients experienced an anxiety event). The incidence of drug-related AEs was higher in the quetiapine XR treatment group compared with the placebo group.

Table S4 Patients who had an adverse event in any category (open-label and RS analysis set, open-label and randomized periods)

Analysis set	RS		OLS
	PLA (N=216)	QTP XR (N=216)	Total QTP XR (N=1224)
Category of adverse event	n (%)	n (%)	n (%)
Any adverse event	111 (51.4)	112 (51.9)	1064 (86.9)
Serious adverse event	3 (1.4)	3 (1.4)	15 (1.2)
Serious adverse event leading to death	0	0	0
Serious adverse event not leading to death	3 (1.4)	3 (1.4)	15 (1.2)
Drug-related adverse event[a]	48 (22.2)	52 (24.1)	961 (78.5)
Adverse events leading to discontinuation	6 (2.8)	5 (2.3)	237 (19.4)

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

The most common AEs (≥2% in any randomized treatment group) that occurred ≥2 times the rate in the placebo group were weight increased, sinusitis, and sedation. The most common AEs during the open-label quetiapine XR treatment were dry mouth, sedation, somnolence, dizziness, fatigue, and constipation. For most quetiapine XR patients who experienced sedation or somnolence during the study, the first onset was reported in the first week after treatment initiation. Approximately 6.6% and 3.4% of patients discontinued due to sedation and somnolence, respectively, during open-label treatment with quetiapine XR

(Table 11.3.5.1.2) compared with 0% and 0.5%, respectively, during the randomization treatment (Table 11.3.5.1.1). The majority of the sedation and somnolence AEs resulting in discontinuation during open-label treatment were reported as severe.

During the randomized treatment phase, AEs potentially related to extrapyramidal symptoms (EPS), neutropenia, diabetes mellitus, sexual dysfunction, and suicidality were low (<4%) and similar between treatment groups. No patients in the quetiapine XR group experienced agranulocytosis, AEs potentially related to QT prolongation, or AEs potentially related to syncope during the randomized treatment phase. The incidence of AEs potentially related to somnolence was higher in the quetiapine XR group than in the placebo group. The incidence of AEs potentially related to nausea and vomiting was higher in the placebo group than in the quetiapine XR group, which was attributed primarily to withdrawal symptoms after discontinuation of open-label quetiapine XR at randomization.

During the open-label phase, quetiapine XR resulted in a mean decrease from baseline in MADRS total score, and during the randomized treatment phase, quetiapine XR was superior to placebo in maintaining this reduction in depressive symptoms ($p < 0.001$). Overall, for SAS, BARS, and AIMS, an improvement or no change in symptoms was noted in the majority of patients in both treatment groups. The superiority of quetiapine XR to placebo in reducing suicidal ideation in patients was not established.

A small increase in mean pulse rate (PR), confirmed by ECG measurement of heart rate (HR), was also observed in the quetiapine XR group. The change in HR was well tolerated, as there were few AEs related to this change.

There were no differences judged to be clinically relevant among the treatment groups in the changes from baseline for any hematology assessments. The most notable changes in clinical chemistry parameters were the mean increases in triglycerides during the open-label phase (consistent with the known profile for quetiapine), with subsequently greater mean decreases in the placebo group compared with quetiapine XR during the randomization phase, and shifts to clinically low values in high-density lipoprotein (HDL) cholesterol after randomization. There was also a moderate increase for insulin during the open-label phase, with subsequently greater mean decreases in the placebo group compared with quetiapine XR during the randomization phase. Interpretation of the observed changes in insulin was obscured by the large standard deviations in plasma concentrations.

Following abrupt discontinuation of quetiapine XR, some clinical evidence of withdrawal symptoms was noted in this study. Mean TDSS scores were higher in the placebo group compared with the quetiapine XR group at 1, 7, and 14 days after randomization. Worsening symptoms potentially related to withdrawal in the placebo group that were ≥1.5 times the rate of the quetiapine XR group were insomnia, anxiety, agitation, irritability, mood swings, difficulty concentrating, sweating, muscle tension, chills, nausea, tearfulness, diarrhea, and vomiting. This correlated to a higher incidence of AEs in the placebo group during the first week after randomization, in particular AEs of nausea, insomnia, headache, chills, and diarrhea. Few AEs in the placebo group were serious or led to discontinuation. Adverse

event-related symptoms following acute withdrawal of quetiapine XR were not considered clinically related to events of relapse into GAD.