Drug product:	Seroquel XR	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate XR		
Edition No.:	Final		
Study code:	D1441L00016		
Date:	19 February 2009		

A Multicenter, Randomized, Double-blind, Parallel-group, Placebo controlled Study of the Efficacy and Safety of Quetiapine Fumarate Extended-Release (SEROQUEL XR®) Compared with Placebo as an Adjunct to Treatment in Patients with Generalized Anxiety Disorder who Demonstrate Partial or No Response to Selective Serotonin Reuptake Inhibitor or Serotonin-Norepinephrine Reuptake Inhibitor Alone or in Combination with a Benzodiadepine (PALLADIUM STUDY)

Co-ordinating investigator

Not utilized for this study.

Study center(s)

This study was conducted at 54 centers in the United States (USA).

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	31 August 2007	Therapeutic confirmatory (IIIB)
Last patient completed	02 September 2008	

Objectives

The **primary** objective of this study was to evaluate the efficacy of quetiapine fumarate extended release (quetiapine XR) versus placebo when added to Food and Drug Administration (FDA)-approved selective serotonin reuptake inhibitor (SSRI)/ serotonin-norepinephrine reuptake inhibitor (SNRI) therapy in the treatment of anxiety symptoms

in patients with generalized anxiety disorder (GAD) with a documented history of partial or no response to SSRI/SNRI alone or in combination with a benzodiazepine.[1]

The **secondary** objectives were as follows:

1. To evaluate the effect of quetiapine XR versus placebo when added to FDA-approved SSRI/SNRI therapy alone or in combination with a benzodiazepine on the health-related quality of life in patients with GAD.

2. To evaluate early symptom improvement (onset of action) of quetiapine XR versus placebo when added to FDA-approved SSRI/SNRI therapy alone or in combination with a benzodiazepine in the treatment of anxiety symptoms in patients with GAD.

3. To evaluate the safety and tolerability of quetiapine XR when added to FDA-approved SSRI/SNRI therapy alone or in combination with a benzodiazepine in the treatment of anxiety symptoms in patients with GAD.

Study design

This was an 11-week, multicenter study that included a 1-week, single-blind, placebo run-in period, an 8-week, randomized, double-blind, parallel group, 2-arm, placebo-controlled treatment period, and a 2-week follow-up period. The goal of the study was to evaluate the efficacy and safety of quetiapine XR 150 or 300 mg/day compared with matching placebo as an adjunct to treatment in patients with GAD who demonstrated partial or no response to an SSRI or an SNRI alone or in combination with a benzodiazepine. Patients continued to maintain the same SSRI/SNRI therapy from the period beginning at enrollment through the end of double-blind treatment.

Target population and sample size

Patients were males or females, 18 to 65 years old inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of GAD (300.02) as assessed by the Mini-International Neuropsychiatric Interview (MINI).

Patients had a history during their current anxious episode of partial or no response to one of the following anxiolytics: duloxetine, escitalopram, paroxetine or venlafaxine XR. The anxiolytic dose was required to be at or above the minimum effective dose (unless there were tolerability issues) and to have been administered for at least 8 weeks.

Patients had to have a Hamilton Rating Scale for Anxiety (HAM-A; administered by use of the Structured Interview Guide for the Hamilton Anxiety Rating Scale [SIGH-A]) total score ≥20 with Item 1 (anxious mood) and Item 2 (tension) scores ≥2 at enrollment,

[1] In order to clarify the primary and secondary objectives of the study in this report, minor revisions have been made to the original wording stated in the clinical study protocol.

placebo run-in and randomization, and a Clinical Global Impression- Severity of Illness (CGI-S) score ≥4 at enrollment and randomization.

A total of 607 patients were screened, and 409 of these patients qualified for the study and were randomized: 200 patients in the placebo group and 209 patients in the quetiapine XR group. The objective of the sample size calculation in this study was to demonstrate superior efficacy of quetiapine XR over placebo along with FDA-approved SSRI/SNRI therapy alone or in combination with a benzodiazepine with respect to the primary outcome variable, change in HAM-A total score from randomization to Week 8. The planned sample size ensured a power of 90% and was attained by anticipating a difference of 2.5 points from placebo and a variability (standard deviation) of 7.5 for the change in the HAM-A total score from randomization to Week 8.

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

The eligible patients were randomly assigned to one of the two treatment arms: quetiapine XR 50 mg (1 x 50-mg quetiapine XR tablet and 2 x 50-mg matching placebo tablets) or placebo (3 x 50-mg matching placebo tablets) for 2 days, followed by quetiapine XR 150 mg (3 x 50-mg quetiapine XR tablets) or placebo (3 x 50-mg matching placebo tablets) in combination with ongoing FDA-approved SSRI/SNRI therapy alone or in combination with a benzodiazepine. Patients who met criteria for a dose increase at Weeks 3 or 4 received quetiapine XR 300 mg (1 x 300-mg quetiapine XR tablet) or placebo (1 x 300-mg matching placebo tablet) for the rest of the study. If they were not able to tolerate the increased dose, the dose for these patients was reduced to quetiapine XR 150 mg (3 x 50-mg quetiapine XR tablets) or placebo (3 x 50-mg matching placebo tablets). Tablets used in the study were: 50-mg and 300-mg quetiapine XR tablets, placebo tablets to match the 50-mg and 300-mg quetiapine XR tablets, and one ongoing FDA-approved SSRI/SNRI therapy alone or in combination with a benzodiazepine in combination with quetiapine XR or placebo. Quetiapine XR 50-mg and 300-mg tablets (or placebo to match) were administered orally once daily (with or without food) in the evening.

Study treatment was given in tablets of the following doses (batch number): quetiapine XR 50 mg (F13219), quetiapine XR 300 mg (F12527), placebo 50-mg match (F12903), and placebo 300-mg match (F12416).

Duration of treatment

Eligible patients underwent a washout period of up to 35 days for the discontinuation of all prohibited medications. Patients then entered an 8-week treatment period, when they were randomly assigned to blinded treatment in a 1:1 ratio to 150 mg/day quetiapine XR or placebo (each in combination with the ongoing FDA-approved SSRI/SNRI therapy, alone or in combination with benzodiazepine). All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. A dose increase to 300 mg quetiapine XR or matching 300 mg placebo was mandated at Week 3 (Day 22) or Week 4 (Day 29) in patients who continued to have a CGI-S score ≥4 and who were able to

tolerate the 150-mg dose. No dose increases were permitted after Week 4. Patients who were unable to tolerate the higher dose were returned to the 150-mg dose at any time at the discretion of the investigator. The ongoing treatment with FDA-approved SSRI/SNRI therapy (alone or in combination with a benzodiazepine) was maintained at the same dose throughout the study. Patients were encouraged not to take any medication for anxiety during the 14-day period of assessment for treatment discontinuation signs and symptoms.

Criteria for evaluation (main variables)

The main study variables were as follows:

- **Primary variable:** Change from randomization to Week 8 in the HAM-A total score.

- **Secondary variables supporting the primary objective:** Change from randomization to Week 8 in CGI-S score, Clinical Global Impression-Global Improvement (CGI-I) score, HAM-A psychic cluster score, HAM-A somatic cluster score, HAM-A response (decrease from randomization total score of ≥50%), and HAM-A remission (HAM A total score of ≤7).

- **Secondary variables:** Change from randomization to Week 8 in Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) % maximum total score, Q-LES-Q satisfaction with medication (Item 15) score, and Q-LES-Q overall life satisfaction (Item 16) score. Change from randomization to Week 1 in the HAM-A total score, HAM-A psychic cluster score, HAM-A somatic cluster score, CGI-S score, and HAM-A response (decrease from randomization total score of ≥50%).

- **Safety variables:** Adverse events (AEs) including extrapyramidal symptoms (EPS)-related AEs; incidence of suicidality (using a suicidality classification similar to the one established by Columbia University); laboratory values; physical examination; vital signs; electrocardiogram (ECG); weight; waist circumference; clinically significant weight gain (patients with ≥7% increase from randomization weight); Simpson-Angus Scale (SAS) score; Barnes Akathisia Rating Scale (BARS); global assessment score; Montgomery-Åsberg Depression Rating Scale (MADRS) total score; and Treatment Discontinuation Signs and Symptoms (TDSS).

Statistical methods

All hypotheses were tested with 2-sided tests. Where appropriate, model-based point estimates were presented together with 2-sided 95% confidence intervals. Missing data at Week 8 were handled using a last observation carried forward (LOCF) approach, as appropriate.

The primary efficacy outcome variable (change in the HAM-A total score from baseline to Week 8) was analyzed using an analysis of covariance (ANCOVA) model that included treatment, center, and baseline HAM-A total score as explanatory variables where center was treated as a random effect, treatment group as a fixed effect and baseline HAM-A total score as a covariate. The secondary efficacy outcome variable of particular interest (change in the Q-LES-Q % maximum total score from baseline to Week 8) was analyzed the same way as the primary variable. A step-wise sequential testing procedure was used for multiple comparisons across these 2 groups of efficacy variables to ensure that the overall significance level of 0.05 was preserved. First, the change in the HAM-A total score from randomization to Week 8 was tested for the quetiapine XR group versus the placebo group. If the quetiapine XR group was statistically significantly better than the placebo group, then the change in the Q-LES-Q % maximum total score from baseline to Week 8 was tested for the quetiapine XR group versus the placebo group. No correction of multiplicity was applied for any other variables.

Changes from randomization to each assessment in the HAM-A total score at Week 1, as well as changes from randomization to Week 1 and Week 8 in the HAM-A psychic cluster score, the HAM-A somatic cluster score, and the CGI-S score were analyzed similarly to the primary objective. HAM-A response at Week 1 and Week 8 and HAM-A remission rates at Week 8, as well as the CGI-I score ("much/very much improved" scores) at Week 8 were analyzed through logistic regression models. Changes from randomization to Week 8 in the Q-LES-Q Item 15 (satisfaction with medication) and Item 16 (overall quality of life) scores, Beck Anxiety Inventory (BAI) scores at enrollment, placebo run-in and randomization, as well as all safety assessments, were presented by descriptive statistics.

The efficacy analyses were based on the modified intention-to-treat (MITT) analysis set; this analysis set included all patients assigned to randomized treatment who took investigational product and who had a HAM-A total score assessment at randomization and at least 1 post-randomization HAM-A total score. The safety analyses were performed on the data from patients in the safety analysis set (all randomized patients who took at least 1 dose of double-blind study medication, classified according to the treatment actually received). The per-protocol (PP) analysis set included all patients in the MITT analysis set with no significant protocol violations or deviations that affected their efficacy assessments. The TDSS analysis set was used to summarize the TDSS results. This subset of the MITT analysis set included patients who completed 8 weeks of double-blind treatment and proceeded into the post-treatment period, and who had both a baseline TDSS assessment (defined as the assessment at the end of the 8-week treatment period) and at least 1 post-baseline TDSS assessment (ie, during the 2-week follow-up period).

Patient population

Analysis sets and patient baseline characteristics are presented in Table S1.

Table S1 Analysis sets and patient baseline characteristics

Analysis sets		PLA	QTP XR	Total
Randomized, N		200	209	409
Safety analysis set, N		200	209	409
MITT analysis set, N		198	204	402
PP analysis set, N		177	181	358
TDSS analysis set, N		159	141	300
Completed study, N		168	152	320
Demographic characteristics (MITT analysis set)				
Sex: n (%)	Male	48 (24.2)	58 (28.4)	106 (26.4)
	Female	150 (75.8)	146 (71.6)	296 (73.6)
Age (years)	Mean (SD)	44.2 (10.9)	44.6 (12.1)	44.4 (11.5)
	Min to max	19 to 65	20 to 65	19 to 65
Age category (years): n (%)	18 to 39	66 (33.3)	68 (33.3)	134 (33.3)
	40 to 65	132 (66.7)	136 (66.7)	268 (66.7)
Race: n (%)	Caucasian	177 (89.4)	181 (88.7)	358 (89.1)
	Black	18 (9.1)	18 (8.8)	36 (9.0)
	Asian	2 (1.0)	3 (1.5)	5 (1.2)
	American Indian or Alaskan Native	0	1 (0.5)	1 (0.2)
	Other	1 (0.5)	1 (0.5)	2 (0.5)
Baseline disease characteristics (MITT analysis set)				
		n = 198	n = 204	
HAM-A total score	Mean (SD)	24.6 (3.7)	24.5 (3.9)	NC
CGI-S score	Mean (SD)	4.3 (0.5)	4.3 (0.6)	NC
Q-LES-Q % maximum total score	Mean (SD)	53.55 (14.57)	53.16 (15.78)	NC
		n = 197	n = 204	
BAI (Visit 1)	Mean (SE)	24.9 (0.67)	25.3 (0.73)	NC
		n = 200	n = 209	
MADRS total score*	Mean (SD)	11.6 (2.9)	11.7 (2.8)	NC

* Data are from safety analysis set

BAI = Beck Anxiety Inventory. CGI-S = Clinical Global Impression – Severity of Illness. HAM-A = Hamilton Rating Scale for Anxiety. MADRS = Montgomery-Åsberg Depression Rating Scale. MITT = Modified intention-to-treat. N = Number of patients in treatment group. n = number of patients. NC = Not calculated. PLA = Placebo. Q-LES-Q = Quality of Life Enjoyment Satisfaction Questionnaire. QTP XR = Quetiapine extended release. SD = Standard deviation. SE = Standard error.

The placebo and quetiapine XR treatment groups were generally well-balanced in both their baseline demographics and baseline disease characteristics.

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=198	QTP XR N=204
HAM-A total score, LS mean change from randomization to Week 8	-9.61	-10.74
HAM-A total score, LS mean change from randomization to Week 1	-4.47	-6.45[a]
Proportion with HAM-A response at Week 1	11.5%	16.9%
Proportion with HAM-A response at Week 8	36.4%	41.2%
Proportion with HAM-A remission (total score≤7) at Week 8	17.17%	23.53%
HAM-A psychic anxiety subscale score, LS mean change from randomization to Week 1	-2.46	-3.70 [a]
HAM-A psychic anxiety subscale score, LS mean change from randomization to Week 8	-5.21	-6.09 [b]
HAM-A somatic anxiety subscale score, LS mean change from randomization to Week 1	-2.00	-2.74 [c]
HAM-A somatic anxiety subscale score, LS mean change from randomization to Week 8	-4.38	-4.63
CGI-S score, LS mean change from randomization to Week 1	-0.35	-0.56[a]
CGI-S score, LS mean change from randomization to Week 8	-1.13	-1.36[b]
Proportion with "much/very much improved" on CGI-I at Week 8	48.99%	55.88%
Q-LES-Q % maximum total score, LS mean change from randomization to Week 8	6.43	7.33
Q-LES-Q Item 16 score, LS mean change from randomization to Week 8	0.2	0.3
Q-LES-Q Item 15 score, LS mean change from randomization to Week 8	0.4	0.3

[a] $p<0.001$ comparison with placebo.
[b] $p<0.05$ comparison with placebo.
[c] $p<0.005$ comparison with placebo.

CGI-I = Clinical Global Impression Improvement scale. CGI-S = Clinical Global Impression Severity scale. HAM-A = Hamilton Rating Scale for Anxiety. LOCF = Last observation carried forward. LS = Least square. MITT = Modified intention-to-treat. PLA = Placebo. Q-LES-Q = Quality of Life Enjoyment Satisfaction Questionnaire. QTP XR = Quetiapine extended release.

Note: For the analyses of HAM-A total score and Q-LES-Q % maximum total score change from randomization, p-values were adjusted and compared with $\alpha=0.05$ using a step-wise sequential testing strategy.

The efficacy of quetiapine XR over placebo in reducing anxiety symptoms was not established as measured by change from randomization in the HAM-A total score at

Week 8. Both placebo and quetiapine XR showed some reduction in HAM-A total score at Week 8; although separation between the treatments was not observed.

Secondary variables supporting the primary objective showed inconsistent differences between placebo and quetiapine XR. Separation between quetiapine XR and placebo was observed at Week 8 for CGI-S scores and HAM-A psychic anxiety scores, but was not observed at Week 8 for CGI-I scores, HAM-A somatic anxiety scores, HAM-A response scores, and HAM-A remission scores. Regarding secondary variables of particular interest, there were no differences between quetiapine XR and placebo in improving quality of life as measured by the Q-LES-Q % maximum total score, improving satisfaction with medication as measured by Q-LES-Q Item 15, or improving overall life satisfaction as measured by Q-LES-Q Item 16.

Safety results

The number (%) of patients who had at least 1 adverse event (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=200 n (%)	QTP XR N=209 n (%)
Any adverse event	120 (60.0)	154 (73.7)
Serious adverse event	0	0
Serious adverse event leading to death	0	0
Serious adverse event not leading to death	0	0
Drug-related adverse event[a]	72 (36.0)	130 (62.2)
Adverse events leading to discontinuation	4 (2.0)	24 (11.5)

[a] As judged by the investigator.
N = Number of patients in treatment group. n = Number of patients. PLA = Placebo. QTP XR = Quetiapine extended release.
Note: All AEs occurred from start of study treatment to last dose plus 30 days.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as n/N x 100.

The overall incidence of AEs was higher in the quetiapine XR treatment group than in the placebo group, as was the incidence of drug-related AEs. Most AEs were of mild to moderate severity in all treatment groups. There were no deaths or serious AEs (SAEs) in the study. The number of patients withdrawing from the study due to an AE was higher in the quetiapine XR treatment group than in the placebo group.

The incidence of common AEs (occurring at an incidence of ≥2% in any treatment group) is shown by preferred term in Table S4.

Table S4 Common (≥2%) adverse events by preferred term (safety analysis set)

Adverse event[a]	PLA N=200 n (%)	QTP XR N=209 n (%)
Dry mouth	16 (8.0)	49 (23.4)
Somnolence	24 (12.0)	47 (22.5)
Sedation	5 (2.5)	26 (12.4)
Headache	21 (10.5)	24 (11.5)
Dizziness	9 (4.5)	22 (10.5)
Fatigue	8 (4.0)	20 (9.6)
Insomnia	3 (1.5)	15 (7.2)
Constipation	8 (4.0)	13 (6.2)
Nausea	12 (6.0)	12 (5.7)
Increased appetite	1 (0.5)	8 (3.8)
Upper respiratory tract infection	5 (2.5)	8 (3.8)
Weight increased	2 (1.0)	8 (3.8)
Nasopharyngitis	17 (8.5)	7 (3.3)
Abnormal dreams	2 (1.0)	6 (2.9)
Diarrhoea	6 (3.0)	6 (2.9)
Dyspepsia	3 (1.5)	6 (2.9)
Libido decreased	0 (0.0)	5 (2.4)
Paraesthesia	1 (0.5)	5 (2.4)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
MedDRA = Medical Dictionary of Regulatory Activities. N = Number of patients in treatment group. n = Number of patients. PLA = Placebo. QTP XR = Quetiapine extended release.
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 x 100.

The pattern of common AEs observed in the quetiapine XR treatment groups generally conformed to that which was anticipated based on the known pharmacological profile of quetiapine. The most common AEs in the quetiapine XR group were dry mouth,

somnolence, sedation, headache, dizziness, fatigue, insomnia and constipation, all of which occurred at a higher incidence than in the placebo group.

The incidence of AEs potentially related to nausea/vomiting was comparable between treatment groups: 7.5% in the placebo group and 7.2% in the quetiapine XR group.

The overall incidence of AEs potentially related to EPS (akathisia, psychomotor hyperactivity, restlessness and tremor) was low in both treatment groups: 2.0% in the placebo group and 3.8% in the quetiapine XR group.

There were no AEs potentially related to sexual dysfunction in the placebo group, compared to 6 (2.9%) in the quetiapine XR group. Three female patients and 2 male patients receiving quetiapine XR reported libido decreased, and 1 patient reported delayed ejaculation.

There were no AEs related to suicidality (MADRS, Item 10) in either treatment group. According to the Columbia Suicidality Classification by Classification Code, there were no suicide attempts, completed suicides, suicidal ideation or preparatory actions towards imminent suicidal behavior.

The incidence of AEs potentially related to diabetes mellitus (DM) was low (1.0%) in both treatment groups, with 2 patients each reporting AEs in the placebo and quetiapine XR groups.

There was a higher incidence of AEs potentially related to somnolence in the quetiapine XR group (35.9%) than in the placebo group (14.5%). The estimated median number of days to first onset of somnolence was 10 days for the placebo group and 3 days for the quetiapine XR group. All 17 patients who withdrew due to an AE of somnolence were in the quetiapine XR group.

The incidence of AEs that followed discontinuation of study treatment during the 2-week follow-up (TDSS) period was higher in the quetiapine XR group than in the placebo group for insomnia, agitation, anxiety, fatigue, irritability, headache and difficulty concentrating or paying attention.

No consistent pattern of differential change in weight or body mass index (BMI) dependent on the baseline BMI category was observed. Increases in weight and BMI were more prevalent in the quetiapine XR group, although these increases were small (approximately 1 kg). The percentage of patients with a weight gain of $\geq$7% was higher in the quetiapine XR group (4.3%) than in the placebo group (1.0%), but was generally low.

There were no clinically important overall mean changes in laboratory values, vital signs, or ECG results during the study. Overall, the clinical laboratory results in this study were consistent with the clinical laboratory profile that has been observed in previous studies in patients treated with quetiapine for other disorders.