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|---|---|---|---|
| Drug product: | SEROQUEL XR | **SYNOPSIS** | |
| Drug substance(s): | Quetiapine XR | | |
| Study code: | D1448C00011 | | |
| Date: | 17 March 2007 | | |

# An International, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Active-controlled Study of the Efficacy and Safety of Sustained-release Quetiapine Fumarate (Seroquel SR™) in the Treatment of Generalized Anxiety Disorder (SILVER Study)

**Study center(s)**

1054 patients were enrolled and 873 were randomized at 113 centers in Europe, Argentina, Canada, Mexico, and South Africa.

**Publications**

None at the time of the writing of this report.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | 18 May 2006 | Therapeutic confirmatory (III) |
| **Last patient enrolled** | 15 February 2007 | |

**Objectives**

The primary objective 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 paroxetine 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; 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 a 10-week, multicenter, randomized, parallel-group, double-blind, double-dummy, placebo-controlled, active-controlled Phase III study of the efficacy and safety of quetiapine XR 50 mg/day and 150 mg/day and paroxetine 20 mg/day compared with matching placebo in the treatment of GAD.

**Target population and sample size**

Patients were male or female, 18 to 65 years of age, 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-Åsberg 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 2 doses (50 mg/day and 150 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, $\alpha$=0.025 for each dose comparison) yielded a planned sample size of 186 per treatment group and 744 in total.

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

Daily oral doses of quetiapine XR were 50 mg and 150 mg using 50 mg tablets. Paroxetine hydrochloride (20 mg once per day) was the active comparator. Matching placebos were used.

The batch numbers used in the study were [redacted], and [redacted] for quetiapine 50 mg tablets; [redacted] for placebo quetiapine 50 mg tablets; [redacted] for paroxetine capsules 20 mg; and [redacted] for placebo paroxetine capsules 20 mg.

**Duration of treatment**

8-week treatment period and 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-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 an analysis of covariance (ANCOVA) model with the baseline HAM-A total score as the 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) was applied for groups of hypotheses. For Week 8 only, a nominal p-value was reported for the comparison of paroxetine to placebo.

The efficacy analyses were based on the modified intention-to-treat (MITT) analysis set, and the safety analyses were done on the data from patients in the safety analysis set (see the table below).

### Patient population

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 | PAR 20 |
| --- | --- | --- | --- | --- |
| N randomized | 217 | 221 | 218 | 217 |
| N safety[a] | 217 | 220 | 218 | 215 |
| N MITT[b] | 217 | 219 | 216 | 214 |
| N PP | 190 | 189 | 179 | 185 |
| N TDSS | 133 | 126 | 124 | 137 |
| N completed 8-week randomized treatment period | 176 | 164 | 163 | 173 |
| N completed TDSS follow-up period | 126 | 115 | 113 | 119 |

[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 XR Quetiapine extended release. PAR Paroxetine. 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 with respect to demographic and baseline characteristics. The mean patient age was approximately 41 years with a range of 18 to 65 years. Approximately 65% of the patients were female and approximately 94% of patients were Caucasian. HAM-A total score at baseline was moderate (means ranged between 26.6 and 27.3) and well balanced across the 4 treatment groups within the MITT analysis set; HAM-A total scores in individual patients ranged from 14 to 44.

### 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=217 | QTP XR 50 N=219 | QTP XR 150 N=216 | PAR 20 N= 214 |
|---|---|---|---|---|
| HAM-A total score, LS mean change from randomization[a] | -12.30 | -13.95[b] | -15.96[c] | -14.45[d] |
| Q-LES-Q % maximum total score, LS mean change from randomization[a] | 7.44 | 9.27 | 13.19[c] | 10.85[b] |
| CGI-S, LS mean change from randomization | -1.53 | -1.85[d] | -2.10[c] | -1.95[c] |
| HAM-A psychic cluster, LS mean change from baseline | -6.27 | -7.42[d] | -8.64[c] | -7.70[c] |
| HAM-A somatic cluster LS mean change from baseline | -6.00 | -6.54 | -7.37[c] | -6.74 |
| HAM-A Response (decrease from randomization total score of ≥50%), proportion of patients | 52.1% | 62.6%[b] | 70.8%[c] | 65.9%[b] |
| HAM-A Remission (HAM-A total score ≤7) proportion of patients | 27.19% | 32.42% | 42.59%[d] | 38.79%[b] |

[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 $p \leq 0.05$ for quetiapine XR 50 mg/day and $p \leq 0.025$ for quetiapine XR 150 mg/day.

[b] $p < 0.05$ comparison with placebo.

[c] $p < 0.001$ comparison with placebo.

[d] $p < 0.01$ comparison with placebo.

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. PAR Paroxetine. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP XR Quetiapine extended release.

In patients with GAD, quetiapine XR 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 50 mg/day and 150 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 50 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 following secondary endpoints: CGI-S, HAM-A psychic cluster, HAM-A response, and PSQI. In addition, quetiapine XR 150 mg/day, but not 50 mg/day, was significantly better than placebo for HAM-A somatic cluster and HAM-A remission.

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

An active reference control arm, paroxetine 20 mg/day, was included in this study, which allowed for evaluation of assay sensitivity. The results are consistent with the known pharmacology of paroxetine and indicate that the study design was suitable for detecting effects on GAD at Week 8. In comparisons based on 95% CIs, quetiapine XR 150 mg/day separated from paroxetine 20 mg/day, showing a larger effect for HAM-A total score and HAM-A psychic cluster scores at Week 8.

**Safety results**

The number (%) of patients who had at least 1 AE in any category is summarized in Table S3. Both quetiapine XR doses were generally well tolerated. Most AEs were mild to moderate in all treatment groups. Serious adverse events (SAEs) were infrequent in all treatment groups (<1.5%). There were no deaths among the patients assigned to randomized treatment; [redacted]. Larger proportions of patients in the quetiapine XR and paroxetine groups discontinued due to AEs than did patients in the placebo group. The incidence of drug-related AEs was higher in the quetiapine XR and paroxetine treatment groups compared with placebo.

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

| | PLA<br>N=217 | QTP XR 50<br>N=220 | QTP XR 150<br>N=218 | PAR 20<br>N=215 |
| --- | --- | --- | --- | --- |
| **Category of adverse event** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Any adverse event | 121 (55.8) | 156 (70.9) | 166 (76.1) | 156 (72.6) |
| Serious adverse event | 2 (0.9) | 3 (1.4) | 1 (0.5) | 0 |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Drug-related adverse event[a] | 75 (34.6) | 129 (58.6) | 143 (65.6) | 126 (58.6) |

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

| | PLA N=217 | QTP XR 50 N=220 | QTP XR 150 N=218 | PAR 20 N=215 |
|---|---|---|---|---|
| **Category of adverse event** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Adverse events leading to discontinuation | 9 (4.1) | 26 (11.8) | 35 (16.1) | 17 (7.9) |

[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 from first dose of study drug through 30 days after last dose are included in this table.
N Number of patients in treatment group. n Number of patients in category. PAR Paroxetine. 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 included the following preferred terms: dry mouth, somnolence, fatigue, dizziness, sedation, constipation, and myalgia.

The incidence of these AEs tended to be highest in the quetiapine XR 150 mg/day group compared with the other treatment groups. The most common AEs of severe intensity were somnolence, insomnia, headache, and fatigue; though overall, the majority of AEs were reported as mild to moderate in intensity. The most common AEs considered by the investigator to be possibly related to study drug were dry mouth, somnolence, fatigue, and dizziness, with the highest percentages occurring in the quetiapine XR groups for dry mouth and somnolence. The total percentage of patients with AEs in the paroxetine 20 mg/day group (72.6%) was in the same range as the quetiapine XR 50 mg/day and 150 mg/day groups (70.9% and 76.1%, respectively).

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 IR and XR for other disorders. There were no notable differences judged to be clinically relevant among the treatment groups in the changes from baseline for any hematology assessments. There were no cases of treatment-emergent hypothyroidism based on clinically important high thyroid stimulating hormone (TSH) values in combination with clinically important low thyroxine (T4) values. There was a higher percentage of quetiapine XR 150 mg/day-treated patients with a treatment-emergent shift from ≤2 to ≥3 metabolic risk factors (9.7%) than with the placebo (3.9%) group; but the quetiapine XR 50 mg/day group had a smaller percentage of patients (3.4%) than 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 and for the placebo group, there was a trend for weight gain ≥7% to occur more often in patients in the lower body mass index (BMI) categories.

A small increase in mean pulse rate was observed in the quetiapine XR 150 mg/day compared with placebo, but the other 2 treatment groups were similar to placebo. 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 nausea and vomiting, diabetes mellitus, neutropenia, sexual dysfunction, or suicidality in the quetiapine XR groups. The incidence of somnolence-related AEs, syncope-related AEs, and extrapyramidal symptoms (EPS)-related AEs for quetiapine XR groups were greater than for placebo, but the incidences were low and 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 2 weeks following treatment discontinuation was higher in the quetiapine XR groups compared to placebo, but was low across all treatment groups. Abrupt discontinuation of study treatment resulted in slightly higher TDSS total scores for patients who had received quetiapine XR than for those who had received placebo.