| | | | |
|---|---|---|---|
| Drug product | Seroquel tablets | **SYNOPSIS** | |
| Drug substance | Quetiapine fumarate | | |
| Document No. | | | |
| Edition No. | 01 | | |
| Study code | 5077IL/0099 | | |
| Date | 2 December 2002 | | |

**A Multicenter, Double-blind, Randomized, Placebo-controlled Trial of the Safety and Efficacy of SEROQUEL™ (Quetiapine Fumarate) as Add-on Therapy with Lithium or Divalproex in the Treatment of Acute Mania**

### Study center(s)

This study was conducted in the USA (38 centers).

### Publications

Sachs G, Mullen JA, Devine NA, Sweitzer DE. Quetiapine vs placebo as adjunct to mood stabilizer for the treatment of acute mania. Presented at the Third European Stanley Conference on Bipolar Disorder, Freiburg, Germany, 13 September 2002.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | 9 August 2000 | Therapeutic confirmatory (III) |
| **Last patient completed** | 26 November 2001 | |

### Objectives

The primary objective of the trial was to evaluate the effectiveness of quetiapine used as add-on therapy with lithium or divalproex for the treatment of symptoms of acute mania in patients with bipolar I disorder.

The secondary objectives of the trial were to evaluate the following:

- The effectiveness of quetiapine used as add-on therapy with lithium or divalproex to treat depressive symptoms in patients with acute mania

- The effectiveness of quetiapine used as add-on therapy with lithium or divalproex to treat agitation and aggression in patients with acute mania
- The effectiveness of quetiapine used as add-on therapy with lithium or divalproex to treat psychotic symptoms in patients with acute mania with psychotic features
- The effectiveness of quetiapine used as add-on therapy with lithium or divalproex to improve functional status in patients with acute mania
- The short-term safety and tolerability, including the incidence of extrapyramidal symptoms (EPS), of quetiapine when used as add-on therapy with lithium or divalproex in patients with acute mania

**Study design**

This trial was a multicenter, double-blind, randomized, parallel-group, placebo-controlled trial to compare the effects of quetiapine and a mood stabilizer (lithium or divalproex) with the effects of placebo and mood stabilizer during an acute treatment period (3 weeks) in in-patients being treated for acute mania.

**Target patient population and sample size**

Male and female patients aged at least 18 years, in a psychiatric facility for treatment of a bipolar disorder I acute manic episode as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association, 4$^{th}$ ed. (DSM-IV), treated at least 7 days in the prior month with lithium or divalproex and having a Young Mania Rating Scale (YMRS) total score of at least 20 and a score of at least 4 on 2 of the following YMRS items: Irritability, Speech, Content, and Disruptive/Aggressive Behavior.

A total of 89 evaluable patients per treatment group with acute mania, derived from an estimated 220 recruited patients, were required for 95% power of detecting a 6-point difference between groups in the change from baseline YMRS scores.

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

Quetiapine fumarate (SEROQUEL™), titrated from 100 to 400 mg orally twice daily, or placebo given adjunctively to patients being treated with either lithium (trough serum concentration: 0.7 to 1.0 mEq/L) or divalproex (trough serum concentration: 50 to 100 μg/mL).

**Duration of treatment**

21 days.

## Criteria for evaluation (main variables)

### Efficacy

- Primary variable: Change from baseline in YMRS Total score at Day 21
- Secondary variables: YMRS response, YMRS remission, changes from baseline in Clinical Global Impression – Bipolar Version (CGI-BP), Montgomery-Asberg Depression Rating Scale (MADRS), Positive and Negative Syndrome Scale (PANSS) total score, PANSS Positive subscale, PANSS Negative subscale, PANSS General Psychopathology subscale, PANSS Activation subscale, PANSS Supplemental aggression risk scale, and the Global Assessment Scale (GAS). Time to discharge was also used as a measure of improvement in functional status.

### Safety

Safety assessments included: adverse events, clinical laboratory assessments, weight/body mass index, vital signs, Modified Simpson-Angus score (SAS) and Barnes Akathisia Rating Scale score (BARS).

### Statistical methods

Efficacy variables (Change from baseline YMRS, MADRS, and PANSS scales) were analyzed with Analysis of Covariance (ANCOVA) using the baseline values and assigned mood stabilizer as covariates. Binary outcomes were analyzed with Cochran-Mantel-Haenszel techniques (stratified by assigned mood stabilizer), or Logistic Regression (to incorporate continuous baseline covariates) techniques. All statistical tests were 2-tailed with a significance level of 0.05. All analysis was executed in SAS version 8.1.

Populations for analysis included the safety population, all randomly assigned patients who received at least one dose of study drug; the modified-intent-to-treat population (MITT), all randomly assigned patients who took study medication and who had baseline and at least one set of post-baseline YMRS assessments; and the per-protocol population (PP), patients in the MITT population with no significant protocol violations or deviations. Patients from one study site were excluded from the MITT and PP.

### Patient population

Of the 270 patients screened for this study, 191 were randomly assigned to study treatment, and 190 received study treatment. One hundred eighty one had baseline YMRS data and at least 1 post-baseline YMRS assessment and were considered evaluable. The exclusion of 11 patients from Center 24 resulted in a total of 170 patients in the MITT population. With 81 patients in the MITT quetiapine treatment group and 89 in the placebo treatment group, the randomization goals were considered to be adequately satisfied.

The treatment groups were well-matched for demographic and baseline characteristics. Approximately two thirds of the patients had taken antipsychotics in the 4 weeks before enrollment, and 56% had taken lorazepam. Baseline mean YMRS scores were 31.5 for the quetiapine-treated patients and 31.1 for the placebo-treated patients. Baseline mean MADRS scores were 13.7 for the quetiapine-treated patients and 14.2 for the placebo-treated patients. The completion rate for the safety population was somewhat higher in the quetiapine group, but not statistically significantly different (62.2% vs 49.0%; p=0.0729).

### Efficacy results

A summary of efficacy findings is shown in Table S1.

**Table S1 Summary of efficacy findings**

| Assessment | Quetiapine N=81[a] | Placebo N=89[a] | P-value |
|---|---|---|---|
| YMRS Total score -- mean change from baseline | -13.76 | -9.93 | 0.0209 |
| YMRS Response -- proportion of patients | 54.3% | 32.6% | 0.0046 |
| YMRS Remission – proportion of patients | 23.5% | 15.7% | 0.2070 |
| CGI-BP Severity of Illness – mean change from baseline | -1.38 | -0.78 | 0.0013 |
| CGI-BP Global Improvement – proportion of patients scoring “much improved” or “very much improved | 50.6% | 31.5% | 0.0119 |
| PANSS Total score – mean change from baseline among patients with psychotic features at screening | -17.17 | -5.93 | 0.0060 |
| PANSS Positive subscale score – mean change from baseline among patients with psychotic features at screening | -7.56 | -3.25 | 0.0016 |
| PANSS Negative subscale score – mean change from baseline among patients with psychotic features at screening | -0.71 | 0.19 | 0.3944 |
| PANSS General Psychopathology subscale score – mean change from baseline among patients with psychotic features at screening | -8.92 | -2.63 | 0.0036 |
| PANSS Activation subscale score – mean change from baseline in entire MITT population | -4.08 | -2.81 | 0.0565 |
| PANSS Supplemental Aggression Risk subscale score – mean change from baseline in entire MITT population | -4.64 | -2.84 | 0.0204 |
| MADRS – mean change from baseline | -3.36 | -2.79 | 0.6495 |
| GAS – mean change from baseline | -15.3 | -11.5 | 0.0754 |
| Time to discharge – mean days for entire MITT population | 11.6 | 9.42 | 0.8568 |

a Numbers of patients in each treatment group are from the YMRS Total score comparisons.

Quetiapine-treated patients showed significantly more improvement on the primary endpoint, the change from baseline in YMRS score at Day 21. The results were confirmed for the PP population

Findings for secondary variables were supportive of the primary variable results. There was a significantly greater proportion of quetiapine-treated patients with at least a 50% reduction in YMRS score by Day 21. Among quetiapine-treated patients with full response to treatment, as a last-week median dose 97.7% had taken at least 200 mg daily; 90.9% had taken at least 400 mg; 59.1% had taken at least 600 mg; and 34.1% had taken at least 800 mg. The time to 50% reduction of YMRS score in the 54.3% of responding quetiapine-treated patients was an average of 8.4 days and in the 32.6% of responding placebo-treated patients was 9.1 days. The proportion of patients in full remission by Day 21 favored the quetiapine-treated group. The decrease in CGI-BP Severity of Illness scores was significantly higher for the quetiapine-treated patients. There was a significantly higher proportion of quetiapine-treated patients rated as "much" or "very much" improved on the CGI-BP Global Improvement scale than in the placebo-treated population.

Patients who were diagnosed at screening as having psychotic features (presence of delusions or hallucinations) were significantly improved on the change from baseline in YMRS score at Day 21 compared to placebo patients ($p = 0.0002$), and patients who were diagnosed as non-psychotic were not significantly improved in comparison with placebo patients ($p = 0.9983$). However, an ANCOVA analysis with a face-valid measure of baseline psychosis based on PANSS items (the sum of Delusions, Conceptual Disorganization and Hallucinatory Behavior), showed no statistically significant interaction with treatment, and the treatment effect remained significant ($p=0.0176$). Thus, the initial observation of a dependence of the therapeutic effect upon psychosis could not be confirmed.

Changes in MADRS scores for quetiapine-treated patients were not distinguishable from those of placebo-treated patients ($p = 0.6495$).

Quetiapine-treated patients diagnosed with psychotic features at screening showed significantly ($p \leq 0.006$) greater responses to treatment than did the placebo-treated group on the PANSS Total scale and all PANSS subscales except for the Negative scale.

For the entire MITT population, the PANSS Aggression Risk scale showed a statistically significant effect in favor of quetiapine ($p=0.0204$), and the PANSS Activation scale approached statistical significance ($p=0.0584$).

GAS scores showed mean responses in the therapeutic direction for both quetiapine-treated (15.3 points) and placebo-treated (11.5 points) patients ($p=0.0754$). The mean time to discharge from the treatment facility was 11.6 days for quetiapine-treated patients and 9.42 days for placebo-treated patients ($p = 0.8568$).

**Safety results**

No deaths were reported in this trial. The adverse events with incidence greater than 10% in quetiapine-treated patients were somnolence, headache, dry mouth, asthenia, postural hypotension, and dizziness. Postural hypotension occurred more often with the combination of quetiapine and divalproex (16%) than with quetiapine and lithium or placebo and either

mood stabilizer (2% to 3%). Tremor was observed more often with the combination of quetiapine and lithium (17.1%) than with the other 3 combinations (approximately 3.5%). Depression was reported as an adverse event in 4 (4.4%) quetiapine-treated patients and in no placebo-treated patients. Three of the quetiapine-treated patients experienced depression as serious adverse events. Fourteen of the 81 (17.3%) quetiapine patients and 12 of the 89 (13.5%) placebo patients met MADRS-defined criteria for emergent depression by Day 21. No patients discontinued treatment in association with depression.

**Table S2 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of incidence within the quetiapine group (safety population)**

| | Treatment | | | |
|---|---|---|---|---|
| | Quetiapine N=90 | | Placebo N=100 | |
| **COSTART preferred term** | **n** | **%** | **n** | **%** |
| Somnolence | 36 | 40.0 | 10 | 10.0 |
| Headache | 24 | 26.7 | 21 | 21.0 |
| Dry mouth | 17 | 18.9 | 4 | 4.0 |
| Asthenia | 10 | 11.1 | 3 | 3.0 |
| Postural hypotension | 10 | 11.1 | 3 | 3.0 |
| Dizziness | 9 | 10.0 | 6 | 6.0 |
| Constipation | 8 | 8.9 | 5 | 5.0 |
| Nausea | 8 | 8.9 | 7 | 7.0 |
| Pharyngitis | 8 | 8.9 | 3 | 3.0 |
| Tremor | 8 | 8.9 | 5 | 5.0 |
| Agitation | 7 | 7.8 | 5 | 5.0 |
| Dyspepsia | 6 | 6.7 | 5 | 5.0 |
| Hypertonia | 6 | 6.7 | 5 | 5.0 |
| Rhinitis | 6 | 6.7 | 3 | 3.0 |
| Akathisia | 5 | 5.6 | 7 | 7.0 |
| Twitching | 5 | 5.6 | 1 | 1.0 |

[a] This table uses a cut-off of 5% in the quetiapine group.

Body weight increased for both treatment groups. Quetiapine-treated patients exhibited a statistically significant (p=0.0031) mean increase of 1.60 kg more than the placebo treated group. There were no clinically significant findings for hematology, chemistry, vital signs or

ECG parameters in this study. While little difference was seen between groups for change in the SAS, the placebo-treated group had a larger proportion of patients showing increased BARS scores (approximately 18%) than did quetiapine-treated patients (approximately 4%). These findings are consistent with the previously-observed safety profile for quetiapine.

**Date of the report**

2 December 2002