AstraZeneca

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|---|---|---|---|
| Drug product: | SEROQUEL | **SYNOPSIS** | |
| Drug substance(s): | Quetiapine fumarate | | |
| Study code: | 5077US/0049 | | |
| Date: | 20 July 2005 | | |

# A Multicenter, Double-blind, Randomized, Placebo-controlled, Double-dummy Trial of the Use of Quetiapine Fumarate (SEROQUEL®) in the Treatment of Patients with Bipolar Depression

**Study centers**

This study was conducted in 39 centers in the USA.

**Publications**

Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J. A randomised, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005; 162:1351-50.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | 30 September 2002 | Therapeutic use (IV) |
| **Last patient completed** | 17 September 2003 | |

**Objectives**

**Primary:**

To evaluate the efficacy of quetiapine compared to placebo in the treatment for a major depressive episode in patients with bipolar disorder after receiving treatment for up to 8 weeks as assessed by comparing

1. The change from baseline to final assessment in the Montgomery-Asberg Depression Rating Scale (MADRS) total score

2. the percentage of patients with a ≥50% reduction from baseline in the MADRS total score at final assessment

3. the change from baseline to each assessment in the MADRS total score

4. the change from baseline to each assessment in the Hamilton Rating scale for Depression (HAM-D), HAM-D Item 1, and the Clinical Global Impression – Severity (CGI-S)

5. the Clinical Global Impression – Improvement (CGI-I)

**Secondary:**

1. to evaluate the incidence of treatment-emergent mania compared to placebo by comparing the percentage of patients who meet the criteria for treatment-emergent mania on the Young Mania Rating Scale (YMRS) or report an adverse event of mania or hypomania

2. to evaluate the effect of quetiapine on anxiety compared to placebo by comparing

   – the change from baseline to final assessment in the Hamilton Rating Scale for Anxiety (HAM-A) total score

   – the change from baseline to each assessment in the Hamilton Rating Scale for Anxiety (HAM-A) total score

3. to evaluate the safety and tolerability of quetiapine in the treatment of patients with bipolar depression by comparing

   – the incidence and nature of all adverse events

   – the incidence and nature of drug-related adverse events

   – patient withdrawal due to adverse events during double-blind treatment

   – the number of patients having clinically significant changes in vital signs from baseline to end of treatment

   – the change in Simpson-Angus Scale (SAS) total score

   – the change in Barnes Akathisia Rating Scale (BARS)

   – the incidence of adverse events related to extrapyramidal symptoms during double-blind treatment

**Exploratory**

1. to evaluate the efficacy of quetiapine on sleep quality by comparing the change in the Pittsburgh Sleep Quality Index (PSQI) from baseline to end of treatment

2. to evaluate the efficacy of quetiapine on the overall quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-Les-Q) from baseline to end of treatment.

**Study design**

This study was a randomized, multicenter, double-blind, placebo-controlled, double-dummy, parallel group, fixed-dose comparison of quetiapine vs placebo in the treatment of bipolar depression. Randomized treatment assignment was stratified in a 1:1:1 ratio for drug within bipolar diagnosis (bipolar I vs bipolar II).

**Target subject population and sample size**

Outpatients, aged 18 to 65 years, with a diagnosis of bipolar I or bipolar II disorder with a current major depressive episode of duration less than one year but greater than 4 weeks were enrolled in the trial. The patient's HAM-D (17-item scale) score had to be ≥20; the HAM-D item 1 (depressed mood) score had to be ≥2; the YMRS score had to be ≤12 at both Visit 1 and Visit 2 (randomization) for the patient to be eligible for entry into the trial. Approximately 530 patients were expected to be enrolled in the trial to obtain 504 evaluable patients.

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

Quetiapine fumarate was increased in a blinded manner to a total daily dose of 300 mg/day by Day 4 in the 300-mg/day treatment group and to a total daily dose of 600 mg/day by Day 8 in the 600 mg/day treatment group. Thereafter, oral doses of the study drug were administered in a blinded fashion once daily at bedtime (qhs) in a dose of 300 or 600 mg/day. One-time dose reductions for intolerability of 100 mg/day in both the 300 mg/day and in the 600 mg/day treatment groups were allowed at the discretion of the investigator after Day 8. Placebo was administered once daily with tablets matching in number and appearance to blinded quetiapine dosing. Study treatment was given in tablets of the following doses (lot #): quetiapine 25 mg (7527F), quetiapine 100 mg (7513H), quetiapine 200 mg (7541F), placebo 25 mg match (7553F), placebo 100 mg match (7550F), placebo 200 mg match (1509C).

**Duration of treatment**

Patients received double-blind, double-dummy treatment for up to 8 weeks (56 days), following an initial washout period of between 7 to 28 days (depending on the medications involved) and came in to the clinic on Day 57 for final assessments.

**Criteria for evaluation (main variables)**

**Efficacy**

- Primary variable: Montgomery-Asberg Depression Rating Scale (MADRS) Total score change from baseline at last assessment

- Secondary variables: Percentage of patients with a ≥50% reduction from baseline to final MADRS Total score, MADRS Total score change from baseline at each assessment, Hamilton Rating Scale for Depression (HAM-D), HAM-D Item 1, Clinical Global Impression Severity of Illness (CGI-S) score, Clinical Global Impression Improvement (CGI-I) score, Young Mania Rating Scale (YMRS) Total score, Hamilton Rating Scale for Anxiety (HAM-A), Pittsburgh Sleep Quality Index (PSQI), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)

### Safety

Safety assessments included: adverse events, patient withdrawal due to adverse events, adverse events of special interest (EPS, diabetes, mania/hypomania, suicidality), hematology and chemistry findings, vital signs, Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and specific inquiries of relevant data for metabolic syndrome, cardiac function, neutropenia/agranulocytosis and thyroid function.

### Statistical methods

All statistical tests were 2-sided. The primary analyses used last observation carried forward (LOCF) for the time period of interest. Analysis of Covariance (ANCOVA) was used for comparative analysis of continuous variables with the baseline score as the covariate and including treatment and diagnosis strata as fixed effects and center as a random effect in the model. The Simes-Himmel step up procedure was used to control for multiple comparisons with placebo for the MADRS change from baseline in order to preserve the overall experiment-wise error rate and conserve power. Cochran-Mantel-Haenszel Chi square tests (CMH) were used for categorical comparisons. Descriptive statistics were used for safety assessments except for SAS and BARS which were analyzed by CMH.

### Subject population

Baseline subject characteristics are shown in Table S1.

**Table S1 Patient population and disposition**

| | | Treatment group | | |
|---|---|---|---|---|
| | | **Quetiapine 300 mg (N=172)** | **Quetiapine 600 mg (N=170)** | **Placebo (N=169)** |
| **Demographic characteristics (ITT population)** | | | | |
| Sex (n and % of subjects) | Male | 79 (45.9) | 71 (41.8) | 64 (37.9) |
| | Female | 93 (54.1) | 99 (58.2) | 105 (62.1) |
| Age (years) | Mean (SD) | 36.6 (11.2) | 37.3 (11.4) | 38.3 (11.08) |
| | Minimum | 18 | 18 | 18 |
| | Maximum | 65 | 63 | 62 |

**Table S1 Patient population and disposition**

| | | Treatment group | | |
|---|---|---|---|---|
| | | **Quetiapine 300 mg (N=172)** | **Quetiapine 600 mg (N=170)** | **Placebo (N=169)** |
| Race (n and % of subjects) | Caucasian | 141 (82.0) | 144 (84.7) | 129 (76.3) |
| | Black | 23 (13.4) | 18 (10.6) | 26 (15.4) |
| | Oriental | 0 (0) | 1 (0.6) | 2 (1.2) |
| | Hispanic | 7 (4.1) | 5 (2.9) | 9 (5.3) |
| | Other | 1 (0.6) | 2 (1.2) | 3 (1.8) |
| **Baseline disease characteristics** | | | | |
| DSM-IV diagnosis [n and (%)] | | | | |
| Bipolar I disorder | | 116 (67.4) | 114 (67.1) | 112 (66.3) |
| Bipolar II disorder | | 56 (32.6) | 56 (32.9) | 57 (33.7) |
| Baseline MADRS | Mean (SD) | 30.3 (5.0) | 30.3 (5.3) | 30.6 (5.3) |
| Screening HAM-D | Mean (SD) | 24.3 (3.1) | 24.8 (3.6) | 24.7 (3.4) |
| Screening YMRS | Mean (SD) | 4.9 (2.8) | 4.8 (3.2) | 4.9 (3.2) |
| Baseline CGI-S | Mean (SD) | 4.4 (0.5) | 4.5 (0.6) | 4.4 (0.6) |
| Baseline HAM-A | Mean (SD) | 18.7 (7.3) | 18.7 (7.3) | 18.9 (7.2) |
| **Disposition (all enrolled)** | | | | |
| N (%) of patients | Completed | 121 | 98 | 107 |
| | Discontinued | 60 | 82 | 74 |
| N safety[a] | | 179 | 180 | 180 |
| N efficacy ITT[b] | | 172 | 170 | 169 |
| N efficacy PP | | 152 | 147 | 154 |

a Number of subjects who received at least one dose of study drug
b Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing, excluding 2 patients who enrolled at 2 separate sites.
ITT=Intention to treat; N=Number; PP=Per-protocol

The three groups were well-matched as to number and demographic and baseline disease characteristics. Adverse events were the main reason for withdrawal in quetiapine-treated patients, while lack of efficacy was the main reason for withdrawal in placebo-treated patients.

## Efficacy results

The comparison of change from baseline in total MADRS score supported the hypothesis that quetiapine at a dose of either 300 mg daily or 600 mg daily for up to 8 weeks of treatment of a

depressive episode in patients with bipolar disorder was superior to placebo in reducing the level of depressive symptoms. A treatment advantage for quetiapine over placebo was statistically significant by Day 8 and continued to be so through Day 57. Analysis of secondary outcome variables also supported the superiority of quetiapine over placebo in the treatment of depression in patients with bipolar disorder. For most secondary outcome variables the treatment advantage was apparent by Day 8 and continued through Day 57.

**Table S2 Efficacy results at final assessment (LOCF, ITT population)**

| Outcome variable | Quetiapine 300 mg (N=172) | | Quetiapine 600 mg (N=170) | | Placebo (N=169) | |
|---|---|---|---|---|---|---|
| | Day 8 | Day 57 | Day 8 | Day 57 | Day 8 | Day 57 |
| MADRS LS mean change from baseline | -8.67[a] | -16.39[a] | -8.78[a] | -16.73[a] | -4.89 | -10.26 |
| Proportion with ≥50% MADRS response | 17% | 58%[a] | 24%[a] | 58%[a] | 11% | 36% |
| HAM-D LS Mean change from baseline | -8.01[a] | -13.38[a] | -7.95[a] | -13.84[a] | -4.64 | -8.54 |
| HAM-D Item 1 LS mean change from baseline | -0.73[b] | -1.65[a] | -0.73[b] | -1.68[a] | -0.47 | -1.11 |
| CGI-S LS mean change from baseline | -0.58[a] | -1.63[a] | -0.56[a] | -1.66[a] | -0.26 | -0.95 |
| Proportion improved on CGI-I | 19%[c] | 64%[a] | 22%[b] | 56%[a] | 10% | 34% |

a $p<0.001$ comparison with placebo
b $p<0.01$ comparison with placebo
c $p<0.05$ comparison with placebo

## Safety results

Both the 300 mg and 600 mg once-daily doses of quetiapine were generally well-tolerated. Analysis of adverse events indicated that nervous and gastrointestinal events predominated, with dry mouth, sedation, somnolence, dizziness and constipation occurring at higher rates with quetiapine compared to placebo. Most adverse events were mild to moderate. Sedation and somnolence were the adverse events most associated with discontinuation by quetiapine-treated patients, with higher rates of discontinuation in the quetiapine 600 mg group. SAEs were infrequent in all treatment groups. Treatment emergent mania and hypomania were low in incidence and did not differ across the treatment groups. An increase in the incidence of EPS events was noted for both groups of quetiapine-treated patients. The incidence of adverse events associated with suicidality for quetiapine-treated patients was no different than that for placebo-treated patients. No cases of neutropenia or agranulocytosis following quetiapine

treatment were reported. Increases in weight, triglycerides, total cholesterol and LDL, and decreases in HDL were consistent with the known safety profile for quetiapine.

**Table S3 Adverse event overview (safety population)**

| Category of adverse event | Number (%) of subjects who had an adverse event in each category[a] | | | | | |
|---|---|---|---|---|---|---|
| | Quetiapine 300 mg (N=179) | | Quetiapine 600 mg (N=180) | | Placebo (N=180) | |
| Any adverse events | 166 | (92.7) | 165 | (91.7) | 148 | (82.2) |
| Serious adverse events | 6 | (3.4) | 9 | (5.0) | 16 | (8.9) |
| Serious adverse events leading to death | 0 | (0) | 0 | (0) | 0 | (0) |
| Discontinuations of study treatment due to adverse events | 29 | (16.2) | 47 | (26.1) | 15 | (8.3) |

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

**Table S4 Adverse event incidence of at least 5% sorted by decreasing order within the quetiapine 300 mg group (safety population)**

| Preferred term | Quetiapine 300 mg (N=179) | | Quetiapine 600 mg (N=180) | | Placebo (N=180) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Dry mouth | 79 | (44.1) | 73 | (40.6) | 14 | (7.8) |
| Sedation | 53 | (29.6) | 58 | (32.2) | 11 | (6.1) |
| Somnolence | 49 | (27.4) | 44 | (24.4) | 15 | (8.3) |
| Dizziness | 30 | (16.8) | 41 | (22.8) | 15 | (8.3) |
| Headache | 22 | (12.3) | 18 | (10.0) | 36 | (20.0) |
| Constipation | 21 | (11.7) | 20 | (11.1) | 8 | (4.4) |
| Fatigue | 16 | (8.9) | 21 | (11.7) | 13 | (7.2) |
| Nausea | 14 | (7.8) | 16 | (8.9) | 23 | (12.8) |
| Dyspepsia | 12 | (6.7) | 17 | (9.4) | 10 | (5.6) |
| Lethargy | 11 | (6.1) | 16 | (8.9) | 3 | (1.7) |
| Nasal congestion | 10 | (5.6) | 12 | (6.7) | 3 | (1.7) |
| Upper Respiratory Tract Infection NOS | 9 | (5.0) | 13 | (7.2) | 18 | (10.0) |
| Akathisia | 9 | (5.0) | 9 | (5.0) | 2 | (1.1) |
| Diarrhea NOS | 8 | (4.5) | 11 | (6.1) | 15 | (8.3) |
| Insomnia | 8 | (4.5) | 7 | (3.9) | 9 | (5.0) |

| Preferred term | Quetiapine 300 mg (N=179) | | Quetiapine 600 mg (N=180) | | Placebo (N=180) | |
| --- | --- | --- | --- | --- | --- | --- |
| | n | (%) | n | (%) | n | (%) |
| Appetite increase NOS | 7 | (3.9) | 10 | (5.6) | 3 | (1.7) |
| Vision blurred | 5 | (2.8) | 13 | (7.2) | 3 | (1.7) |
| Weight increased | 3 | (1.7) | 11 | (6.1) | 1 | (0.6) |
| Pain in extremity | 2 | (1.1) | 9 | (5.0) | 4 | (2.2) |

**Date of the report**

20 July 2005