AstraZeneca

Drug product	SEROQUEL™ tablets	**SYNOPSIS**	
Drug substance(s)	Quetiapine Fumarate		
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An International, Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of SEROQUEL™ (Quetiapine Fumarate) as Add-on Therapy with Lithium or Divalproex in the Treatment of Acute Mania

Study centers

This study was conducted at 44 clinical centers in Belgium (4 centers), Bulgaria (1 center), Canada (10 centers), Germany (6 centers), India (1 center), Rumania (2 centers), South Africa (8 centers), Spain (7 centers) and the United Kingdom (5 centers).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	08 November 2000	Therapeutic confirmatory (III)
Last patient completed	25 January 2002	

Objectives

The primary objective of the study was to evaluate:

- the effectiveness of quetiapine fumarate (SEROQUEL™, quetiapine) used as adjunct therapy with lithium or divalproex in the treatment of symptoms of acute mania in patients with bipolar disorder (acute mania).

The secondary objectives of the study 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 safety and tolerability, including the incidence of EPS, of quetiapine when used as add-on treatment with lithium or divalproex in patients with acute mania

Study design

This was a multicenter, double-blind, randomized, parallel-group, placebo-controlled study to compare the effects of quetiapine in combination with a mood stabilizer (lithium or divalproex) with the effects of placebo in combination with a mood stabilizer for a 3-week treatment period in patients hospitalized for an acute manic episode. The initial treatment period was immediately followed by an additional 3-week maintenance phase. Thus, the total treatment period was 6 weeks. Patients could be discharged from the hospital after Day 7 (ie, on Day 8) if the investigator believed that it was clinically appropriate to discharge the patient, that the patient was not suicidal or homicidal, and that the patient could reasonably be expected to continue in the study on an outpatient basis.

Target patient population and sample size

Male and female patients aged at least 18 years, hospitalized for treatment of a bipolar disorder I acute manic episode as defined by Diagnostic and Statistical Manual of the American Psychiatric Association, 4th ed. (DSM-IV), and having a Young Mania Rating Scale (YMRS) Total score of ≥20 and a score of ≥4 on 2 of the following YMRS items: Irritability, Speech, Content, and Disruptive/Aggressive behavior. Patients were also required to have a Clinical Global Impression – Bipolar (CGI-BP) Severity of Illness score of ≥4 on the Overall Bipolar Illness item.

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

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

Quetiapine or placebo administered orally twice a day, beginning on Day 1. Quetiapine doses were increased from 100 mg/day on Day 1 to 400 mg/day on Day 4 with dose adjustments thereafter to a maximum of 800 mg/day. Quetiapine or placebo were given as adjunct therapy to patients treated with a mood stabilizer, either lithium or divalproex.

Duration of treatment

42 days (6 weeks)

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Change from baseline in YMRS total score at Day 21.
- Secondary variables: change from baseline in YMRS total score at Day 42; YMRS response rates at Day 21 and Day 42; time to first YMRS response; maintenance of YMRS response at Day 42; YMRS remission at Day 21 and Day 42; change from baseline in Clinical Global Impression – Bipolar Version (CGI-BP) Severity of Illness score at Day 21 and Day 42; CGI-BP Global Improvement score at Day 21 and Day 42; change from baseline in Clinical Global Impression (CGI) Severity of Illness score at Day 21 and Day 42; CGI Global Improvement score at Day 21 and Day 42; changes from baseline at Day 21 and Day 42 in the following scores: Montgomery-Asberg Depression Rating Scale (MADRS), Positive and Negative Syndrome Scale (PANSS) Total, PANSS Positive subscale, PANSS Negative subscale, PANSS General Psychopathology subscale, PANSS Activation factor, PANSS Supplemental Aggression Risk scale, and Global Assessment Scale (GAS). Use of lorazepam during Days 2 to 10 and daily use of sleep medication was also assessed.

Safety

- Adverse events, changes in clinical laboratory test results, changes in body weight and body mass index, changes in vital signs, changes in electrocardiogram results, change in Modified Simpson-Angus (SAS) score, change in Barnes Akathisia Rating Scale (BARS) score, emergent depressive symptoms.

Statistical methods

Continuous efficacy variables (eg, changes from baseline in YMRS, MADRS and PANSS scales) were analyzed using analysis of covariance (ANCOVA) with baseline scores and assigned mood stabilizer as covariates. Binary variables (eg, YMRS response) 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 analyses were executed in SAS version 8.2.

Populations for analysis were as follows:

1. The safety population – all randomly assigned patients who took at least one dose of study drug.

2. The modified-intent-to-treat (MITT) population – all randomized patients who took study medication and who had a baseline YMRS assessment and at least one set of post-baseline YMRS assessments.

3. The per-protocol (PP) population – excluded patients with significant protocol violations or deviations, and any data collected after a patient was withdrawn, and also all data from noncompliant patients. The primary efficacy analysis was repeated on the PP population to test for homogeneity of treatment effect.

Patient population

Forty-four active centers screened 250 patients and randomized 211. Of the 211 patients assigned to study treatment, 2 patients randomized to placebo were withdrawn before receiving any study treatment. Subsequently, 209 patients (106 in quetiapine group and 103 in placebo group) took study medication and were analyzed for safety. Out of the safety population, 200 patients were analyzed for efficacy in a modified-intention-to-treat (MITT) population, ie, with 104 in the quetiapine-treated group and 96 in the placebo group. The study design called for 178 patients, 89 in each of the 2 treatment groups. With 104 patients in the MITT quetiapine-treated group and 96 patients in the placebo-treated group, the randomization goals were considered to be adequately satisfied.

The treatment groups in this study were well matched for demographic and baseline characteristics. All patients had moderate to severe bipolar disorder, with slightly more patients with severe bipolar disorder in the quetiapine group than in the placebo group. A majority of patients in each group were not diagnosed as having psychotic features at screening. The MITT population had an equal distribution of males and females, the mean age was 39.5 years and 73.5% of the patients were Caucasian.

Use of lorazepam or sleep medication was generally higher in the placebo-treated group than in the quetiapine group. The most common reason for withdrawal was progression of disease, 18 patients in quetiapine group and 17 patients in the placebo group. Two patients in the quetiapine group and 6 patients in the placebo group had treatment discontinued due to adverse events.

Efficacy results

A summary of efficacy findings is shown in Table S1.

Table S1 Summary of efficacy findings (MITT population, LOCF)

Assessment	Day 21					Day 42			
	Quetiapine N=104[a]	Placebo N=96[a]	Estim. diff/OR	95% CI	P-value	Quetiapine N=104[a]	Placebo N=96[a]	Estim. diff/OR	95% CI
YMRS total score – LSmean change from baseline	-15.2	-13.2	-2.0	-5.6 to 1.6	0.28	-17.1	-14.3	-2.8	-6.9 to 1.2
YMRS Response – proportion of patients	56.7%	50%	1.3	0.8 to 2.3	0.34	72.1%	57.3%	1.9	1.1 to 3.5
YMRS Response – maintenance at Day 42						91.5%	83.3%	ND	ND
YMRS Remission – proportion of patients	32.7%	31.3%	1.1	0.6 to 1.9	0.83	53.8%	45.8%	1.4	0.8 to 2.4
CGI-BP Severity of Illness – LSmean change from baseline	-1.6	-1.4	-0.2	-0.6 to 0.2	0.32	-1.8	-1.6	-0.2	-0.7 to 0.3
CGI-BP Global Improvement – proportion of patients scoring “much improved” or “very much improved	64.4%	54.2%	1.5	0.9 to 2.7	0.14	74.0%	58.3%	2.0	1.1 to 3.7
CGI Severity of Illness – LSmean change from baseline	-1.6	-1.3	-0.3	-0.7 to 0.1	0.20	-1.9	-1.6	-0.3	-0.8 to 0.2
CGI Global Improvement – proportion of patients scoring “much improved” or “very much improved	68.3%	54.2%	1.8	1.0 to 3.2	0.04	76.0%	59.4%	2.2	1.1 to 3.9
MADRS – LSmean change from baseline	-2.5	-1.7	-0.7	-2.5 to 1.0	0.41	-3.1	-2.1	-1.0	-3.0 to 1.0
PANSS Total score – LSmean change from baseline	-11.0	-11.7	0.7	-4.4 to 5.8	0.79	-14.5	-12.3	-2.2	-8.1 to 3.7
PANSS Total score – LSmean change from baseline among patients with psychotic features at screening	-9.6	-10.3	0.6	-8.5 to 9.7	0.89	-12.1	-8.9	-3.2	-13.4 to 7.0
PANSS Positive subscale score – LSmean change from baseline	-6.2	-6.4	0.2	-2.1 to 2.4	0.89	-7.6	-6.6	-1.0	-3.4 to 3.4
PANSS Positive subscale score – LSmean change from baseline among patients with psychotic features at screening	-6.6	-6.7	0.1	-4.0 to 4.2	0.96	-7.9	-5.9	-2.0	-6.6 to 2.6
PANSS Activation subscale score – LSmean change from baseline	-4.0	-3.4	-0.6	-2.4 to 1.1	0.47	-5.1	-3.7	-1.4	-3.3 to 0.6
PANSS Supplemental Aggression Risk subscale score – LSmean change from baseline	-4.8	-3.9	-0.8	-2.7 to 1.0	0.37	-6.2	-4.4	-1.8	-3.9 to 0.3
GAS – LSmean change from baseline	18.6	15.1	3.5	-2.7 to 9.0	0.22	23.1	18.4	4.7	-1.8 to 11.3

[a] Numbers of patients in each treatment group are from the YMRS total score comparisons. ND Not done. OR Odds ratio, presented only for proportions.

The results of this study showed that quetiapine therapy taken as adjunct to a mood stabilizer was not statistically significantly more effective than placebo taken adjunct to a mood stabilizer in reducing the symptoms of acute mania in patients with bipolar disorder. For the primary variable (change from baseline in YMRS total score at Day 21), and for all of the secondary variables supporting the primary one (ie, change from baseline in YMRS total score at Day 42, response rate, maintenance of response in YMRS at Day 42, time to response in YMRS, remission in YMRS, CGI-BP Severity of Illness, CGI-BP Global Improvement, CGI Severity of Illness, and CGI Global Improvement), there were no statistically significant differences between the 2 treatment groups. However, for the majority of these variables, there were numerical advantages for quetiapine-treated patients over placebo-treated patients at Day 21.

The numerical difference between the quetiapine and placebo groups at Day 21 with respect to change from baseline in YMRS total score had increased by Day 42. Other secondary efficacy variables confirmed that the numerical treatment advantages for quetiapine over placebo increased with duration of treatment.

The majority of quetiapine-treated patients who showed response at Day 21 maintained their response at Day 42.

The mean of the last-week median quetiapine dose for responders at Day 21 was 423 mg/day and for responders at Day 42 was 461 mg/day. 66% of patients who responded to quetiapine at Day 21 were taking doses between 400 mg/day and 800 mg/day, and 69% who responded at Day 42 were taking doses between 400 mg/day and 800 mg/day.

The secondary objectives of this study included evaluation of the effectiveness of quetiapine as adjunct therapy to mood stabilizer to treat psychotic symptoms in patients who had acute mania with psychotic features at screening. Patients with psychotic features at screening who received adjunct therapy with quetiapine showed similar responses to treatment compared with patients who received adjunct therapy with placebo in terms of PANSS Total score and PANSS Positive, Negative, and General Psychopathology subscale scores.

The decrease from baseline in MADRS scores (at Day 42) was similar between the two treatment groups, indicating a similar effect of each treatment on depression.

Quetiapine-treated patients showed similar improvements in the PANSS Activation subscale and the PANSS Supplemental Aggression Risk subscale as did placebo-treated patients.

Patients in both treatment groups showed a similar degree of improvement in GAS over time.

The response rate in YMRS total score in patients in the quetiapine group observed in this study (57% at Day 21, 72% at Day 42) was very similar to results in other similar studies assessing antipsychotics in the treatment of acute mania. Grossman et al (2001) assessed the efficacy of risperidone adjunct to a mood stabilizer for acute manic episodes in a placebo-controlled study and reported a response rate of 58% in improvement in YMRS total score in the risperidone group after 3 weeks of treatment. In another placebo-controlled study, Tohen

et al (2002), for example, evaluated the efficacy of olanzapine in combination with lithium/divalproex in a placebo-controlled study, and reported a response rate of 68% in patients receiving olanzapine adjunct to a mood stabilizer after 6 weeks of treatment.

Of note, however, is that the response rate in the placebo group (ie, mood stabilizer alone) in this study was high (50% at Day 21, 57.3% at Day 42) relative to previously-published data on the use of a mood stabilizer alone (40% reported by Grossman et al [2001] after 3 weeks, 44.7% reported by Tohen et al [2002] after 6 weeks). This relatively high placebo response rate cannot easily be accounted for. Baseline scores for key variables were similar between the 2 treatment groups, and although there was a numerically slightly higher use of lorazepam and sleep medication during the study in the placebo group compared with the quetiapine group, these differences were not statistically significant and are not considered sufficient to cause the relatively high response rate in the placebo group.

As a result of the high placebo response rate, the observed difference in YMRS total score was less than the delta used for the sample size calculation for this study. Hence, it is important to recognize that the lack of statistical significance in the primary endpoint was due to the small difference observed between treatments, and was not due to a lack of statistical power.

Another point to consider is the fact that the estimated difference between treatment groups in change from baseline in YMRS total score at Day 21 was greater in the PP population than in the MITT population, ie, 3.9 points compared with 2.0 points. The most common reason for exclusion from the PP population in both groups was a failure to achieve median serum levels of mood stabilizer within the therapeutic range. Although more patients in the quetiapine group than in the placebo group (26% vs 21%) were excluded from the PP population due to serum levels of mood stabilizer outside the therapeutic range, it is considered unlikely that this would explain the difference in treatment effect between the MITT and PP populations.

In both treatment groups a larger percentage of patients received lithium compared with divalproex (approximately 83% and 17%, respectively, in both groups). This is because at the time of study initiation, with the exception of Canada, divalproex was not licensed for use in acute mania in patients with bipolar disorder. Subsequently, only patients in Canadian centers could be assigned divalproex. For this reason, it is difficult to make any conclusions regarding the effect of mood stabilizer on the results of this study because the data are confounded by this large imbalance.

Safety results

The most common adverse events, summarized by COSTART preferred term, are shown in Table S2.

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

Costart preferred term	Treatment			
	QTP + LI / DVP n=106		PLA + LI / DVP n=103	
	No of pts	%	No of pts	%
Somnolence	30	28.3	9	8.7
Dry mouth	21	19.8	2	1.9
Constipation	11	10.4	6	5.8
Weight gain	11	10.4	4	3.9
Headache	10	9.4	5	4.9
Abdominal pain	9	8.5	4	3.9
Asthenia	9	8.5	5	4.9
Dizziness	9	8.5	7	6.8
Diarrhea	7	6.6	7	6.8
Insomnia	7	6.6	8	7.8
Tremor	7	6.6	10	9.7

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

The most common adverse events in quetiapine-treated patients were somnolence, dry mouth, constipation, weight gain, and headache; with the exception of headache; these types of adverse events are consistent with those seen when quetiapine is used as monotherapy for the treatment of schizophrenia. In the placebo-treated group, tremor, somnolence and insomnia were the most common adverse events. The majority of adverse events were transient and of mild intensity.

There was 1 death reported during this study in the placebo group. The patient died due to septicemia which was not considered to be related to study treatment.

Two patients in the quetiapine-treated group, compared with 6 patients in the placebo-treated group, had non-fatal, serious adverse events. No serious adverse events were reported in more than 1 patient in either treatment group.

Three patients in the quetiapine-treated group, compared with 6 patients in the placebo-treated group, had adverse events leading to withdrawal. Depression was the only adverse event leading to withdrawal in more than 1 patient (3 patients in the placebo-treated group compared with 0 patients in the quetiapine-treated group).

There was a low incidence of depression in both treatment groups: 2% in the quetiapine group and 4% in the placebo group. The proportion of patients developing emergent depression during the study was similarly low in each treatment group: 7% of quetiapine-treated patients compared with 8% of patients in the placebo group. Only 1 patient (1%) in each treatment group was hospitalized due to depression and 3% of patients in the placebo group (none in the quetiapine group) had study treatment discontinued due to depression.

The incidence of extrapyramidal symptoms was similar in the quetiapine and placebo groups. The mean change from baseline in SAS and BARS was similar in both treatment groups.

A higher proportion of patients in the quetiapine group than in the placebo group developed an increase in heart rate of ≥15 bpm. This is in line with the previous experience of quetiapine used as monotherapy for schizophrenia. There were no other clinically important findings in vital signs in this study. Generally, there were only minor differences between the 2 treatments in changes in hematology parameters throughout the study. Changes in body weight are described below.

A mean increase from baseline weight of 2.9 kg was observed in the quetiapine group at Day 42 (observed cases [OC]), compared with a mean increase of 0.6 kg in the placebo group (OC). Adverse events of weight gain were reported for 10.4% of quetiapine-treated patients compared with 3.9% of placebo-treated patients. Increases from baseline weight of 7% or more were observed in 21% of quetiapine-treated patients compared with 7% of placebo-treated patients. The weight change in the quetiapine-treated group was similar to that seen during monotherapy for patients treated with schizophrenia.

There were no clinically important effects of quetiapine treatment on glucose concentrations, and there were no clinically important differences between the treatment groups with respect to changes in glucose concentrations. Overall, with the exception of weight gain, there were few adverse events potentially related to diabetes.

There were no adverse events of clinical hypothyroidism reported. No patients in either group had a clinically significant decrease in free thyroxine in combination with a clinically significant increase in TSH. However, 4 patients in the quetiapine group, compared with 1 patient in the placebo group, had a clinically significant decrease in total thyroxine combined with a clinically significant increase in TSH. The observed changes in thyroxine are consistent with the known safety profile of quetiapine.

Overall, quetiapine was generally safe and well tolerated, and the pattern of adverse events did not reveal any safety concerns for the use of quetiapine in patients with acute mania associated with bipolar disorder. The safety profile was similar to that seen when quetiapine is used as monotherapy to treat schizophrenia.

Date of the report

29 November 2002