AstraZeneca

Drug product	SEROQUEL™ tablets	**SYNOPSIS**	
Drug substance	Quetiapine fumarate		
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An International, Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of SEROQUEL™ (Quetiapine Fumarate) and Lithium as Monotherapy in the Treatment of Acute Mania

Study center(s)

The study was conducted at 38 clinical sites in Bulgaria (6 sites), China (2 sites), Croatia (2 sites), Greece (4 sites), India (6 sites), Romania (5 sites), Russia (10 sites), and Turkey (3 sites).

Publications

None at the time this report was written.

Study dates

		Phase of development
First patient enrolled	3 April 2001	Therapeutic confirmatory (III)
Last patient completed	27 May 2002	

Objectives

The primary objective of the study was to evaluate the effectiveness of quetiapine fumarate (SEROQUEL™, quetiapine) used as monotherapy in the treatment of symptoms of acute mania in patients with bipolar I disorder.

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

- the effectiveness of quetiapine used as monotherapy to treat depressive symptoms in patients with acute mania
- the effectiveness of quetiapine used as monotherapy to treat agitation and aggression in patients with acute mania

- the effectiveness of quetiapine used as monotherapy to treat psychotic symptoms in patients with acute mania with psychotic features
- the effectiveness of quetiapine used as monotherapy to improve functional status in patients with acute mania
- the safety and tolerability, including the incidence of extrapyramidal symptoms (EPS), of quetiapine in patients with acute mania

Study design

This was a multicenter, double-blind, randomized, parallel-group, placebo-controlled, 12-week study to compare the efficacy and safety of quetiapine, lithium, and placebo in the treatment of mania in patients hospitalized for an acute manic episode. Patients could be discharged from the hospital after Day 7 (ie, 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 I disorder acute manic episode (acute mania) as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association, 4th ed. (DSM-IV) 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. Patients were also required to have a Clinical Global Impression – Bipolar (CGI-BP) Severity of Illness score of at least 4 on the Overall Bipolar Illness item.

A total of 89 evaluable patients with acute mania per treatment group, derived from an estimated 342 recruited patients, were required for 95% power of detecting a 6-point difference between groups in the change from baseline YMRS total scores.

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

Quetiapine, lithium, or placebo administered orally twice a day, beginning on Day 1. Quetiapine doses were started at 100 mg/day on Day 1 and increased to 400 mg/day on Day 4 in increments of 100 mg/day, with dose adjustments thereafter to a maximum of 800 mg/day. Lithium treatment began with a dose of 900 mg/day; from Day 5 to Day 84 onward the dose was then adjusted at the discretion of the investigator to achieve target trough serum lithium concentrations of 0.6 mEq/L to 1.4 mEq/L.

AstraZeneca supplied study medication as follows (tablet strength, formulation, batch number):

- Quetiapine: 25 mg (F12153, 72433B00); 100 mg (F12689, 74585A00); 200 mg (F12690, 74586I00)
- Quetiapine placebo: 25 mg (F7142, 72448E00); 100 mg (F7207, 73545B00); 200 mg (F7208, 73546J00)
- Lithium: 300 mg (F12792, 74753I00)
- Lithium placebo: 300 mg (F12793, 74667I00)

Duration of treatment

84 days (12 weeks)

Criteria for evaluation (main variables)

Efficacy

- Primary variable: change from baseline in YMRS total score at Day 21 (LOCF)
- Secondary variables: change from baseline in YMRS total score at Day 84; YMRS response rates at Days 21 and 84; time to first YMRS response; maintenance of YMRS response at Day 84; YMRS remission at Days 21 and 84; maintenance of YMRS remission at Day 84; change from baseline in Clinical Global Impression – Bipolar Version (CGI-BP) Severity of Illness score at Days 21 and 84; CGI-BP Global Improvement score at Days 21 and 84; change from baseline in Clinical Global Impression (CGI) Severity of Illness score at Days 21 and 84; CGI Global Improvement score at Days 21 and 84; changes from baseline at Days 21 and 84 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). Analyses of all secondary variables were based on the LOCF. Response was defined as a decrease from baseline in YMRS total score of at least 50%. Remission was defined as a YMRS total score $\leq$8 with a score $\leq$2 on each of the following 4 YMRS items: Irritability, Speech, Content, and Disruptive/Aggressive Behavior.
- Daily use of lorazepam.
- Rate of emergent depression.

Safety

- Adverse events

- Changes in clinical laboratory test results from baseline to Day 84
- Changes in body weight and body mass index from baseline to Day 84
- Changes in vital signs from baseline to Day 84
- Changes in electrocardiogram results from baseline to Day 84
- Change in Modified Simpson-Angus Scale score (SAS) from baseline to Day 84
- Change in Barnes Akathisia Rating Scale score (BARS) from baseline to Day 84
- Daily use of sleep medication and anticholinergic medications

Statistical methods

Efficacy variables (eg, changes from baseline in YMRS, MADRS, and PANSS scores) were analyzed using analysis of covariance (ANCOVA) with baseline scores as covariates. Binary variables (eg, YMRS response) were analyzed using Cochran-Mantel-Haenszel techniques or logistic regression (to incorporate continuous baseline covariates). 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 1 dose of study drug.

2. The modified-intent-to-treat population (MITT) – all randomized patients who took study medication and who had baseline and at least 1 set of post-baseline YMRS assessments.

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

Following the discovery of reported positive serum lithium concentrations for some quetiapine-treated and placebo-treated patients, a post hoc analysis population was defined for an additional analysis of the primary endpoint. This population excluded from the PP population any quetiapine-treated or placebo-treated patient who had a serum lithium concentration ≥0.5 mEq/L reported at any time after randomization.

Patient population

Of the 370 patients screened for this study, 302 were randomly assigned to study treatment. The exclusion of 2 patients who had no postbaseline YMRS assessments resulted in a total of

300 patients in the MITT population. The study design called for 267 patients, 89 in each of the 3 treatment groups. With 107 patients in the MITT quetiapine-treated group, 98 patients in the lithium-treated group, and 95 patients in the placebo-treated group, the randomization goals were considered to be adequately satisfied.

Similar proportions of quetiapine-treated and placebo-treated patients (97.2% and 94.8%, respectively) were included in the PP population, compared with 75.5% of lithium-treated patients. Nine quetiapine-treated patients and 5 placebo-treated patients who had at least 1 reported postbaseline serum lithium concentration ≥0.5 mEq/L were excluded from an additional, post hoc PP analysis performed to assess whether these patients influenced the primary efficacy results.

Patient withdrawal over the course of the study was highest for the placebo-treated group, which showed a statistically significant difference from the quetiapine-treated and lithium-treated groups at Day 21 and at Day 84. Lack of efficacy was the most frequent reason for withdrawal from each group: 9.3% of quetiapine-treated patients; 21.6% of placebo-treated patients; and 4.1% of lithium-treated patients. In all groups, most withdrawals occurred after Day 21.

The treatment groups were generally 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-treated group than in the lithium or placebo groups. YMRS total score at baseline ranged from 20 to 58 across the treatment groups, MADRS total score ranged from 0 to 23, and PANSS total score ranged from 35 to 118. Mean YMRS total score was similar across the 3 groups. Mean YMRS, MADRS, and PANSS total scores were similar across the 3 groups.

Before randomization, most (77% to 81%) patients did not use mood stabilizer; lithium use ranged from 12% to 17%. Approximately 70% of patients used antipsychotics (predominantly typical antipsychotics) before randomization, and 61% of patients used lorazepam. During the study, compliance was monitored by investigational staff for all treatments. Only 1 (lithium-treated) patient was considered noncompliant with study medication. Lorazepam use in the first 14 days of the study was generally higher in the placebo-treated group than in the quetiapine-treated or lithium-treated groups. In all 3 groups, the proportion of patients who used lorazepam decreased over time. After Day 14, the use of lorazepam was generally low (4 quetiapine-treated patients, 11 placebo-treated patients, and 9 lithium-treated patients). Overall, use of sleep medications was less frequent in the quetiapine-treated group than in either the placebo-treated or lithium-treated groups. Use of anticholinergic medication was low in all groups.

Efficacy results

A summary of efficacy findings from the quetiapine and placebo groups is shown in Table S1 (LOCF, MITT population). The efficacy findings from the lithium group are summarized in the text.

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

Assessment	Day 21			Day 84		
	Quetiapine (N=107)[a]	Placebo (N=95)[a]	P-value	Quetiapine (N=107)[a]	Placebo (N=95)[a]	P-value
YMRS Total score – LSmean change from baseline	–14.62	–6.71	<0.0001	–20.28	–9.00	<0.0001
YMRS Response -- proportion of patients	53.3%	27.4%	0.0002	72.0%	41.1%	<0.0001
YMRS Remission – proportion of patients	26.2%	12.6%	0.0162	62.6%	30.5%	<0.0001
YMRS Partial Remission – proportion of patients	46.7%	22.1%	NC	69.2%	33.7%	NC
CGI-BP Severity of Illness – LSmean change from baseline	–1.48	–0.66	<0.0001	–2.20	–0.89	<0.0001
CGI-BP Global Improvement – proportion of patients scoring “much improved” or very much improved	63.6%	30.5%	<0.0001	72.0%	36.8%	<0.0001
CGI Severity of Illness – LSmean change from baseline	–1.40	–0.60	<0.0001	–2.08	–0.82	<0.0001
CGI Global Improvement – proportion of patients scoring “much improved” or “very much improved	60.7%	33.7%	<0.0001	73.8%	37.9%	<0.0001
MADRS – LSmean change from baseline	–1.55	–0.05	0.0149	–1.49	1.21	0.0024
PANSS Total score – LSmean change, entire MITT population	–8.71	–2.12	<0.001	–11.78	–1.04	<0.001
PANSS Total score – LSmean change from baseline among patients with psychotic features at screening	–7.84	–5.28	0.4458	–13.45	–4.98	0.0309
PANSS Positive subscale score – LSmean change, entire MITT population	–4.29	–1.50	<0.001	–5.87	–1.07	<0..001
PANSS Positive subscale score – LSmean change from baseline among patients with psychotic features at screening	–5.26	–3.92	0.4299	–9.26	–4.37	0.0128
PANSS Activation subscale score – LSmean change from baseline in entire MITT population	–3.69	–1.00	<0.0001	–4.97	–0.49	<0.0001
PANSS Supplemental Aggression Risk subscale score – LSmean change from baseline in entire MITT population	–4.29	–1.50	<0.0001	–5.87	–1.07	<0.0001
GAS – LSmean change from baseline	17.96	5.59	<0.0001	26.35	9.26	<0.0001

[a] Number of patients in the MITT population.

NC Not calculated; test was not performed because it was not specified in the Statistical Analysis Plan.

Quetiapine showed a clinically relevant and statistically significant advantage over placebo with respect to the primary endpoint, the change from baseline in YMRS total score at Day 21.

The superiority of quetiapine compared with placebo at Day 21 was consistently confirmed by all analyses of secondary measures of mania, depression, agitation and aggression, and functional status: response rates; remission rates, the change from baseline in CGI-BP Severity of Illness Overall Bipolar Illness score, CGI-BP Global Improvement Overall Bipolar Illness score, change from baseline in CGI Severity of Illness score, CGI Global Improvement score, and changes from baseline in MADRS, PANSS Activation Factor, PANSS Supplemental Aggression Risk, and GAS scores.

The results of analysis of the primary endpoint in the post hoc analysis population that excluded from the PP population 9 quetiapine-treated and 5 placebo-treated patients because of their reported serum lithium concentrations (see Statistical methods, above) were entirely consistent with those observed for the MITT and PP populations.

The advantage of quetiapine over placebo with respect to change from baseline in YMRS total score increased from −7.92 on Day 21 to −11.28 on Day 84. Other secondary efficacy variables related to mania, depression, and functional status confirmed that the treatment advantages of quetiapine increased with the duration of treatment.

The vast majority of quetiapine-treated patients who showed response or remission at Day 21 maintained their response or remission at Day 84.

The mean of the last-week median quetiapine dose for responders at Day 21 was 586 mg/day and for responders at Day 84 was 618 mg/day. Ninety percent of patients who responded to quetiapine at Day 21 were taking doses from 400 to 800 mg/day, and 91% who responded at Day 84 were taking doses from 400 to 800 mg/day.

Lithium treatment also showed a statistical advantage compared with placebo at Days 21 and 84 with respect to the primary and most secondary efficacy variables. Quetiapine and lithium showed similar efficacy at Day 21 on all efficacy endpoints except remission. At Day 84, the 2 active treatments were similar with respect to all measures of on mania, including remission rates, functional status, MADRS scores, and PANSS Activation Factor and Supplemental Aggression Risk.

The secondary objectives of this study included evaluation of the effectiveness of quetiapine as monotherapy to treat psychotic symptoms in patients who had acute mania with psychotic features at screening. Patients with and without psychotic features at screening benefited from treatment with quetiapine, as shown by reductions in PANSS total and Positive subscale scores, but the observed effects in this study were larger for the patients without psychotic features.

Changes from baseline in PANSS total and Positive subscale scores for patients with psychotic features at screening did not show a statistically significant advantage for quetiapine over placebo at Day 21. However, at Day 84, quetiapine treatment showed a statistically significant advantage over placebo treatment. Lithium treatment was no more effective than

placebo treatment at Day 21 or at Day 84. Quetiapine and lithium had treatment effects of similar magnitude at Day 21.

In the MITT population as a whole, quetiapine treatment was significantly more effective than placebo treatment in reducing PANSS total and Positive subscale scores at Days 21 and 84. Lithium was also significantly more effective than placebo treatment in reducing PANSS total and Positive subscale scores at Days 21 and 84.

Safety results

The most common adverse events, as summarized by 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 group					
	Quetiapine (N=107)[b]		Placebo (N=97)[b]		Lithium (N=98)[b]	
	n	%	n	%	n	%
Dry mouth	26	24.3	2	2.1	6	6.1
Somnolence	21	19.6	3	3.1	9	9.2
Weight gain	16	15.0	1	1.0	6	6.1
Dizziness	13	12.1	2	2.1	7	7.1
Insomnia	10	9.3	20	20.6	16	16.3
Headache	8	7.5	4	4.1	12	12.2
Asthenia	7	6.5	1	1.0	4	4.1
Depression	6	5.6	1	1.0	1	1.0
Tremor	6	5.6	4	4.1	18	18.4
Diarrhea	5	4.7	4	4.1	5	5.1
Weight loss	2	1.9	1	1.0	6	6.1
Anorexia	1	0.9	4	4.1	9	9.2
Nausea	1	0.9	2	2.1	6	6.1
Vomiting	1	0.9	2	2.1	6	6.1

[a] This table uses a cut-off of 5% in the quetiapine-treated or lithium-treated group.
[b] Number of patients in the safety population.
COSTART Coding Symbols for a Thesaurus of Adverse Reaction Terms.

In the quetiapine-treated group, the most frequently reported adverse events were dry mouth, somnolence, weight gain, and dizziness; 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, insomnia was the most common adverse event. In the lithium-treated group, the most frequently reported adverse events were insomnia, headache, and tremor; tremor is a known effect of lithium treatment. Adverse events of postural hypotension were reported infrequently in all groups.

Two patients in the quetiapine-treated group had serious adverse events: 1 patient had an event of heart arrest and died due to kidney failure that occurred secondary to the heart arrest; the other patient had an event of atrial fibrillation (the patient did not have a reported history of cardiovascular disease). In the placebo-treated group, 2 patients had serious adverse events: 1 patient had events of GI perforation and peritonitis and died due to hypovalemic shock; the other patient had a pathological fracture. Fifteen patients had adverse events that led to withdrawal: 6 patients were treated with quetiapine, 4 were treated with placebo, and 5 were treated with lithium.

Two deaths were reported during this study, as noted in the preceding paragraph. One quetiapine-treated patient died from heart arrest and secondary kidney failure; the heart arrest was considered by the investigator to be directly related to study treatment, and the kidney failure was not. One placebo-treated patient died from hypovolemic shock secondary to a perforated ulcer; neither event was considered by the investigator to be related to study treatment.

Quetiapine-treated and lithium-treated patients showed statistically significant improvement from baseline in MADRS scores at Day 84 compared with placebo-treated patients. Emergent depression (defined as the occurrence of a MADRS score of at least 18, representing an increase from baseline of at least 4, on any 2 consecutive post-baseline visits or at the final visit) was observed in 6 quetiapine-treated patients, 8 placebo-treated patients, and 3 lithium-treated patients. Only 2 quetiapine-treated patients, 0 placebo-treated patients, and 1 lithium-treated patients had both emergent depression and depression reported as an adverse event. In addition, the Depression subscale of the CGI-BP Severity of Illness scale showed few shifts toward depression among the quetiapine-treated patients and incidences similar to those observed for placebo-treated patients.

Depression was reported as an adverse event for 6 quetiapine-treated patients, 1 placebo-treated patient, and 1 lithium-treated patient. None of the events was considered serious, and most were rated by the investigator as mild in intensity. Most of the events were not considered to be related to study treatment, and most patients remained in the study. Two of the 6 quetiapine-treated patients and the lithium-treated patient were withdrawn from the study because of depression.

The overall evaluation of depression did not suggest that quetiapine-treated patients were any more likely than placebo-treated patients to experience depression during this study.

The rates of adverse events related to EPS were similar in the quetiapine-treated and placebo-treated groups. While adverse events of tremor can represent EPS, most adverse events of

tremor occurred in the lithium-treated group and likely reflect the known effects of lithium treatment rather than EPS. The lack of differences in SAS total and BARS scores between quetiapine-treated patients and placebo-treated patients was consistent with the low rates of EPS in these groups.

There were no clinically important differences among the treatment groups with respect to vital signs (including orthostatic changes), ECGs, or hematology or clinical chemistry parameters.

A mean increase from baseline weight of 3.3 kg was observed in the quetiapine group at Day 84 (OC), compared with a mean increase of 0.3 kg (OC) in the placebo-treated group and a mean increase of 1.0 kg in the lithium group. Adverse events of weight gain were reported for 15% of quetiapine-treated patients, 1% of placebo-treated patients, and 6% of lithium-treated patients. Increases from baseline weight of 7% or more were observed in 39% of quetiapine-treated patients, 14% of placebo-treated patients, and 20% of lithium-treated patients. The weight change in the quetiapine-treated group was similar to that seen during monotherapy for patients with schizophrenia.

There were no clinically important effects of quetiapine treatment on glucose concentrations, and there were no clinically important differences among 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. One patient treated with lithium had a nonserious adverse event reported as diabetes mellitus; the patient did not have a reported history of diabetes, and the event did not lead to withdrawal.

There were no adverse events of clinical hypothyroidism reported. Mean decreases in free and total thyroxine were observed in the quetiapine group, without clinically significant increases in TSH concentration. The proportion of lithium-treated patients with clinically significant increases in TSH concentration was 15.6%, compared with 0.1% in the quetiapine-treated group and 0.1% in the placebo-treated group; increased TSH concentration is a known effect of lithium treatment. 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

10 December 2002