AstraZeneca

Drug product	SEROQUEL™ tablets	**SYNOPSIS**	
Drug substance	Quetiapine fumarate		
Document No.	805-1440-AK-0002		
Edition No.	1		
Study code	5077IL/0104		
Date	3 December 2002		

An International, Multicenter, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of SEROQUEL™ (Quetiapine Fumarate) and Haloperidol as Monotherapy in the Treatment of Acute Mania

Study center(s)

This study was conducted at 49 clinical sites in Argentina (12 sites), Chile (3 sites), China (2 sites), Croatia (3 sites), Estonia (3 sites), Indonesia (4 sites), Latvia (3 sites), Lithuania (5 sites), Philippines (4 sites), Poland (6 sites), and Taiwan (4 sites).

Publications

None at the time this report was written.

Study dates		**Phase of development**
First patient enrolled	7 January 2001	Therapeutic confirmatory (III)
Last patient completed	25 April 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 study was a 12-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study to compare the effects of quetiapine, haloperidol, and placebo during an acute treatment period in patients hospitalized for treatment of acute mania. Patients who were in a psychiatric unit for the treatment of an acute manic episode were eligible to participate in this study. Patients who were screened as outpatients and subsequently required hospitalization for treatment of an acute manic episode were also eligible for this study. Patients could be discharged from the hospital after Day 7 (ie, on Day 8).

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 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. Any patient treated with clozapine within 28 days before screening was excluded.

A total of 89 evaluable patients with acute mania per treatment group, derived from an estimated 342 recruited patients, were required for 95% power to detect 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 treatment began on Day 1 with a dose of 50 mg/day to 100 mg/day and was increased thereafter to reach a target dose of 400 mg/day on Day 4. On Day 5, the quetiapine dose could be adjusted, at the investigator's discretion, up to 600 mg/day. On Days 6 to 84, the quetiapine dose could be further increased, to a maximum of 800 mg/day, in the event of poor clinical response.

Haloperidol treatment began on Day 1 with a dose of 1 mg/day to 2 mg/day and was increased thereafter to reach a target dose of 4 mg/day on Day 4. On Day 5, the quetiapine dose could be adjusted, at the investigator's discretion, up to 6 mg/day. On Days 6 to 84, the quetiapine dose could be further increased, to a maximum of 8 mg/day, in the event of poor clinical response.

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)
- Haloperidol: 1 mg (F12789, 74668F00); 5 mg (F12790, 74579D00)
- Haloperidol placebo: 1 mg and 5 mg (F12791, 74666A00)

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.
- 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

Safety variables included adverse events and changes from baseline to Day 84 in clinical laboratory test results, weight and body mass index, vital signs, electrocardiogram results,

Modified Simpson-Angus (SAS) total score, Barnes Akathisia Rating Scale (BARS) score, daily use of sleep medication and use of 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 randomized patients who took at least 1 dose of study medication
2. The modified-intent-to-treat (MITT) population – 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 (PP) population – excluded patients with significant protocol violations or deviations; any data collected after a patient was withdrawn; and all data from noncompliant patients. The primary efficacy analysis was repeated on the PP population to test for homogeneity of treatment effect.

Patient population

Of the 353 patients screened for this study, 302 were randomly assigned to study treatment. The exclusion of 3 patients who had no postbaseline YMRS assessments resulted in a total of 299 patients in the MITT population. The study design called for 267 patients, 89 in each of the 3 treatment groups. With 101 patients in the MITT quetiapine-treated group, 100 patients in the placebo-treated group, and 98 patients in the haloperidol-treated group, the randomization goals were considered to be adequately satisfied.

The treatment groups in this study were generally well-matched for demographic and baseline characteristics; the quetiapine group included a higher proportion of patients with severe bipolar disease without psychotic features than did the placebo and haloperidol groups. Patients with psychotic features at screening represented approximately 40% of each treatment group. The 3 treatment groups were similar in their use of lorazepam, but fewer patients in the quetiapine group used sleep medications during the study.

Patient withdrawal was higher overall in the placebo-treated group than in the quetiapine-treated group, although the difference was not statistically significant. The predominant differences between groups were the higher rates of withdrawal in the placebo-treated group due to deterioration of condition and lack of efficacy. The rates of withdrawal due to adverse events in the quetiapine and placebo groups were approximately half those in the haloperidol group.

Efficacy results

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

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

Variable	Day 21			Day 84		
	Quetiapine (N=101)[a]	Placebo (N=100)[a]	P-value	Quetiapine (N=101)[a]	Placebo (N=100)[a]	P-value
YMRS total score –LS mean change from baseline	–12.29	–8.32	0.0096	–17.52	–9.48	<0.0001
YMRS response – proportion of patients	42.6%	35.0%	0.2717	61.4%	39.0%	0.0015
YMRS remission – proportion of patients	16.8%	16.0%	0.8739	50.5%	29.0%	0.0019
YMRS partial remission – proportion of patients	27.7%	24.0%	NC	61.4%	38.0%	NC
CGI-BP Severity of Illness – LSmean change from baseline	–1.02	–0.90	0.4421	–1.64	–1.02	0.0085
CGI-BP Global Improvement – proportion of patients scoring “much improved” or “very much improved	43.6%	35.0%	0.2150	50.5%	30.0%	0.0031
CGI Severity of Illness – LSmean change from baseline	–1.12	–0.79	0.0399	–1.78	–0.98	0.0005
CGI Global Improvement – proportion of patients scoring “much improved” or “very much improved	49.5%	37.0%	0.0743	57.4%	32.0%	0.0003
MADRS – LSmean change from baseline	–2.82	–0.93	0.0049	–3.31	–0.68	0.0084
PANSS total score – LSmean change from baseline among patients with psychotic features at screening	–5.49	–1.80	0.2772	–8.68	–1.61	0.0679
PANSS total score – LSmean change from baseline for entire MITT population	–9.48	–4.16	0.0060	–13.76	–3.99	<0.0001
PANSS Positive subscale score – LSmean change from baseline among patients with psychotic features at screening	–3.35	–1.28	0.1590	–4.92	–1.31	0.0353
PANSS Positive subscale score – LSmean change from baseline for entire MITT population	–4.31	–2.22	0.0075	–6.31	–2.42	<0.0001
PANSS activation factor score – LSmean change from baseline	–3.04	–1.60	0.0469	–4.36	–1.60	0.0011
PANSS Supplemental Aggression Risk subscale score – LSmean change from baseline	–3.44	–1.85	0.0405	–4.93	–2.06	0.0017
GAS –LSmean change from baseline	12.02	6.80	0.0230	20.33	8.79	0.0001

[a] Number of patients included in the MITT population.
LSmean Least-squares mean.
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 supported by analyses of secondary measures of mania: response rates, the changes from baseline in the CGI-BP Severity of Illness Overall Bipolar Illness and Mania item scores, the CGI-BP Global Improvement Overall Bipolar Illness score, and the CGI Global Improvement score. Quetiapine showed statistical superiority in the change from baseline in CGI Severity of Illness score. Remission rates were similar for the quetiapine and placebo groups. In addition, quetiapine was also statistically superior to placebo at Day 21 in the treatment of agitation and aggression as assessed by the changes from baseline in the PANSS activation factor and Supplemental Aggression Risk scale scores and in improving functional status as assessed by changes in GAS scores.

The superiority of quetiapine over placebo with respect to change from baseline in YMRS total score increased from –3.97 at Day 21 to –8.04 at Day 84. Statistically significant differences from placebo at Day 84 for other secondary efficacy variables related to mania, agitation and aggression, 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 559 mg/day and for responders at Day 84 was 532 mg/day. Eighty-four percent of patients who responded to quetiapine at Day 21 were taking doses from 400 to 800 mg/day, and 79% who responded at Day 84 were taking 400 to 800 mg/day.

Haloperidol treatment showed a statistical advantage compared with placebo at Days 21 and 84 with respect to the primary and all secondary efficacy variables tested, with the exception of changes from baseline in MADRS scores at Day 84. At Day 21, haloperidol showed an advantage over quetiapine with respect to changes from baseline in YMRS total scores and response rates. However, at Day 84, quetiapine and haloperidol were similar with respect to all measures of effect on mania, including remission rates, and on agitation, aggression, and functional status.

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 benefitted 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. At Day 84, changes from baseline in PANSS total scores also did not show a statistical advantage for quetiapine compared with placebo. However, there was a significant advantage for quetiapine with respect to changes in PANSS Positive subscale

scores. Haloperidol treatment was significantly more effective than placebo in reducing PANSS total and Positive subscale scores at Days 21 and 84. Quetiapine and haloperidol had similar effects for PANSS Positive subscale scores at Day 84.

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. Haloperidol 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 (incidence of 5% or more) adverse events, 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)

	Treatment group					
	Quetiapine (N=102)[b]		Placebo (N=101)[b]		Haloperidol (N=99)[b]	
COSTART preferred term	n	%	n	%	n	%
Insomnia	20	19.6	20	19.8	14	14.1
Somnolence	13	12.7	5	5.0	9	9.1
Agitation	8	7.8	9	8.9	8	8.1
Tremor	8	7.8	6	5.9	30	30.3
Dry mouth	7	6.9	4	4.0	4	4.0
Akathisia	6	5.9	6	5.9	33	33.3
Extrapyramidal syndrome	6	5.9	6	5.9	35	35.4
Postural hypotension	6	5.9	1	1.0	2	2.0
Headache	5	4.9	4	4.0	8	8.1

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

In the quetiapine-treated group, the most commonly reported adverse events were insomnia and somnolence; 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 commonly reported adverse event. In the haloperidol-treated group, the most commonly reported adverse events were extrapyramidal syndrome, akathisia, tremor, and insomnia; adverse events related to EPS are a known effect of haloperidol treatment. Adverse events of postural hypotension, were reported more frequently in the quetiapine-

treated group than in the placebo-treated and haloperidol-treated groups; postural hypotension is a known effect of quetiapine.

Serious adverse events were less frequent in the quetiapine-treated group (2.0%) than in the placebo-treated group (5.0%) and the haloperidol-treated group (6.1%). Adverse events that were considered serious were postural hypotension and abscess (1 patient each) in the quetiapine-treated group; agitation (4 patients) and hallucinations, insomnia, intentional injury, nervousness, delusions, and pneumonia (1 patient each) in the placebo-treated group, and hallucinations, tremor, akathisia, extrapyramidal syndrome, pathological fracture, accidental injury, lymphocytosis, leukopenia, and myocardial ischemia (1 patient each) in the haloperidol-treated group. Withdrawals due to adverse events were most frequent in the haloperidol group (10.1%) and compared to the quetiapine (4.9%) and placebo (6.9%) groups. There were no deaths reported during this study.

Quetiapine-treated patients showed statistically significant improvement from baseline in MADRS scores at Day 84 compared with placebo-treated patients, while haloperidol-treated patients did not. 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 2.9% of quetiapine-treated patients, 8.9% of placebo-treated patients, and 8.1% of haloperidol-treated patients. No quetiapine-treated patients had both emergent depression and depression reported as an adverse event, compared with 3.0% of placebo-treated patients, and 1.0% of haloperidol-treated patients. In addition, the Depression subscale of the CGI-BP Severity of Illness scale showed fewer shifts toward depression at Day 84 among quetiapine-treated patients than among placebo-treated patients.

Depression was reported as an adverse event for 2 quetiapine-treated patients, 4 placebo-treated patients, and 1 haloperidol-treated patient. None of the events was considered serious, and none of the events was considered to be related to study treatment. One quetiapine-treated patient and 3 placebo-treated patients were withdrawn from the study because of depression.

The overall evaluation of depression suggests that quetiapine-treated patients were no 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 (12.7% and 15.8%, respectively). In contrast, 59.6% of haloperidol-treated patients had at least 1 adverse event related to EPS reflecting the known effects of haloperidol treatment. The changes from baseline in SAS total and BARS scores were consistent with the low rates of EPS in quetiapine-treated and placebo-treated patients compared with haloperidol-treated patients. The lower liability for EPS during quetiapine treatment was also reflected in the less frequent use of anticholinergic medications by quetiapine-treated patients compared with haloperidol-treated patients.

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

A mean increase from baseline weight of 2.1 kg was observed in the quetiapine group at Day 84 (OC), compared with a mean decrease of 0.1 kg in the placebo-treated group and a mean increase of 0.2 kg in the haloperidol group. Adverse events of weight gain were reported for 2.9% of quetiapine-treated patients, 2.0% of placebo-treated patients, and 3.0% of haloperidol-treated patients. Increases from baseline weight of 7% or more were observed in 21.4% of quetiapine-treated patients, 9.5% of placebo-treated patients, and 7.4% of haloperidol-treated patients. The weight change in the quetiapine-treated group was similar to that seen during monotherapy for patients with schizophrenia.

The percentage of patients with potentially clinically significant low absolute neutrophil counts ($\leq 1.5 \times 10^9$ cells/L) at the end of treatment was slightly higher in the quetiapine group compared with the placebo group (5.3% vs 1.1%). In quetiapine-treated patients, the lowest absolute neutrophil count noted was 0.4×10^9/L (WBC count 2.5×10^9 cells/L. There were no serious adverse events of infection in quetiapine-treated patients with low absolute neutrophil counts.

Prolactin concentrations decreased from baseline in all 3 groups; the mean decrease was larger in the quetiapine-treated group than in the placebo-treated and haloperidol-treated groups.

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 quetiapine had a nonserious adverse event of hyperglycemia (reported term “elevated random glucose”) based on a change in glucose concentration from 89.0 mg/dL at baseline to 163.0 mg/dL at the final visit; the increased glucose concentration did not meet the predefined criterion for potential clinical significance (≥230 mg/dL).

There were no adverse events of clinical hypothyroidism reported, although 1 placebo-treated patient had an increased TSH concentration reported as an adverse event. Mean decreases in free and total thyroxine were observed in the quetiapine group, without clinically significant increases in TSH concentration. There were no patients with shifts to potentially clinically significant low free thyroxine concentrations; 2 quetiapine-treated patients had shifts to potentially clinically significant low total thyroxine concentrations, but neither had a corresponding shift to a potentially clinically significant high TSH concentration. 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

3 December 2002