Drug product:	Seroquel™ tablets	**SYNOPSIS**	
Drug substance(s):	Quetiapine Fumarate		
Study code:	D1440L00006		
Date:	12 October 2006		

A Double dummy & double blind, Multicenter, Randomized Study of the Efficacy and Safety of Seroquel (Quetiapine Fumarate) and Lithium as Monotherapy in the Treatment of Acute Mania in Patients with Bipolar Disorder

Study dates		**Phase of development**
First patient enrolled	1 September, 2005	Therapeutic confirmatory (III)
Last patient completed	21 June, 2006	

Objectives

The primary objective of the study was to evaluate the effectiveness of quetiapine fumarate used as monotherapy in the treatment of symptoms of acute mania in patients with bipolar disorder by evaluation of the change from baseline in YMRS total score at Day 28.

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

- The effectiveness of quetiapine used as monotherapy to treat symptoms in patients with acute mania by evaluation of YMRS response rate at Day 28 (LOCF)

- The effectiveness of quetiapine used as monotherapy to treat depressive symptoms in patients with acute mania by evaluation of change from baseline in MADRS total score at Day 28 (LOCF)

- The effetiveness of quetiapine used as monotherapy to treat psychotic symptoms in patients with acute mania by evaluation of change from baseline in PANSS total score at Day 28 (LOCF)

- Differences between the two treatment groups on day 28 for the efficacy parameters

- The safety and tolerability of quetiapine in patients with acute mania

Study design

This was a randomised, double blind, double dummy, multicentre, parallel-group, 4-week study to compare the efficacy and safety of quetiapine and lithium in the treatment of mania in patients hospitalised for an acute manic episode. The eligible patient was randomised into quetiapine or lithium group on Day 1.

Target patient population and sample size

Male and female patients aged above 18, hospitalised for the treatment of an acute manic episode of bipolar disorder (diagnosed based on CCMD-3) and having a Young Mania Rating Scale (YMRS) total score of at least 20.

A sample size of 60 evaluable patients per treatment arm was requested by China State Food and Drug Administration (SFDA) for clinical trials applying for new indication. Considering the rate of non-evaluable patients being 20%, the total sample size was planed to be 150 patients. The 150 patients were randomised in a ratio of 1:1 to two treatment groups, with 75 in each treatment arm.

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

Quetiapine was administered orally twice a day beginning on Day 1. The doses were started at 100 to 200 mg/day on Day 1 and were increased to 200 to 600 mg/day on Day 4. On Day 5-28, the quetiapine dose could be further increased, from a minimal of 300 mg/day to a maximum of 800 mg/day, in the event of poor clinical response. If the patient did not show a substantial clinical response by Day 8 and had good tolerance to study treatment, the dose of blinded study medication was increased to at least 600 mg/day.

Lithium carbonate manufactured by Hunan Qianjin Xiangjiang Pharmaceutical Co., Ltd began with a dose of 250 to 500 mg/day and it was increased to 500 to 2000 mg/day on Day 4. The dose was then adjusted at the discretion of the investigator to achieve target trough serum lithium concentration of 0.6mmol/L to 1.2mmol/L.

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

- Quetiapine: 25 mg (F12804; ADM 21033K04, ADM 22075D04); 100 mg (F12689; ADM 220777I04, ADM 22075D04); 200 mg (F12690; ADM 22368F04, ADM 23817H04)
- Quetiapine placebo: 25 mg (F12636; ADM 11270A03); 100 mg (F12637; ADM 23826G04, ADM 31894C05, ADM 11271I03); 200 mg (F12638; ADM 11272F03, ADM 23819B04)
- Lithium: 250 mg (F13250; ADM 32563D05)
- Lithium placebo: 250 mg (F13251; ADM 32564A05)

Duration of treatment

28 days(4 weeks)

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Change from baseline in YMRS total score at Day 28 (LOCF)
- Secondary variables: YMRS response rate at Day 28 (LOCF), which was defined as the proportion of patients showing a reduction 50% in YMRS total score at Day 28 (LOCF); Change from baseline in MADRS total score at Day 28 (LOCF); Rates of emergent depression at Day 28 (LOCF), which was defined as a MADRS total score ≥18, representing an increase ≥4 above baseline on 2 consecutive post-baseline visits or at the final study visit; Change from baseline in PANSS total score at Day 28 (LOCF)

Safety

Safety variables included adverse events and clinical significant change from baseline to Day 28 in laboratory test results, vital signs.

Statistical methods

The primary efficacy endpoint of change from baseline in YMRS total score at Day 28 (LOCF) was estimated for each treatment group. In addition, the differences between two treatment groups were also estimated using an analysis of covariance (ANCOVA) model with factors of treatment, centre and baseline score. The results were presented in terms of least-squares means and associated 95% confidence intervals.

Analysis on the secondary efficacy endpoints of change from baseline in MADRS and PANSS total score at Day 28 (LOCF), respectively, were performed using the same method as the change in YMRS total score.

YMRS response rate at Day 28 (LOCF) was estimated for each treatment group. In addition, the differences between two treatment groups were also estimated using logistic regression model with factors of treatment, centre and baseline YMRS score. The results were presented in terms of odds ratios and associated 95% confidence intervals.

Safety endpoints were summarized in the safety population by treatment received. The incidence and severity of adverse events were summarized by body system and preferred term for each of the two randomized treatment group. Change from baseline data to Day 28 in laboratory results and vital signs were summarized using descriptive statistics. The number and proportion of patients with clinically significant findings were presented. No inferential statistics were performed for treatment comparisons on safety endpoints.

Populations for analysis were as follows:

1. The safety population – all randomized patients who took at least 1 dose of study medication

2. The Intent-to-treat (ITT) 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 184 patients screened for this study, 155 were randomly assigned to study treatment. The exclusion of 1 patients who had no post baseline YMRS assessments resulted in a total of 154 patients in the ITT population. The study design called for 150 patients, 75 in each of the 2 treatment groups. With 77 patients in the ITT quetiapine-treated group, and 77 patients in the lithium-treated group, the randomization goals were considered to be adequately satisfied.

In the safety population, 78 patients was included in the quetiapine-treated group, while 77 patients was included in the lithium-treated group. The demographic and baseline characteristics in the safety population is similar with the ITT population, see Table 11.1.4.1.

The treatment groups in this study were generally well-matched for demographic and baseline characteristics; the quetiapine group (74.4%) and lithium group (70.1%) included a similar proportion of patients with bipolar disease without psychotic features. The 2 treatment groups were similar in their use of lorazepam and sleep medications during the study.

Patient withdrawal was higher overall in the lithium-treated group (15 of 77 patients (19.5%)) than in the quetiapine-treated group (5 of 78 patients (6.4%)). The predominant differences between groups were the higher rates of withdrawal in the lithium-treated group due to adverse events and informed consent withdrawn. The rates of withdrawal due to lack of efficacy in the quetiapine and lithium groups were approximately 1.3% to 3.8%.

Table S1 Patient population and disposition

		Quetiapine		Lithium		Total	
Population							
N randomised (N planned)		78	(75)	77	(75)	155	(150)
Demographic characteristics							
Sex (n and % of patients)	Male	34	(43.6)	40	(51.9)	74	(47.7)
	Female	44	(56.4)	37	(48.1)	81	(52.3)
Age (years)	Mean (SD)	32.9	(11.41)	33.6	(11.55)	NC	NC
	Range	18 to 63		18 to 59		18 to 63	
Race (n and % of patients)	Chinese	78	100%	77	100%	155	100%
Baseline characteristics							
Mean (SD) YMRS total score		29.4	5.87	29.8	5.69	NC	NC
Mean (SD) MADRS total score		5.0	3.68	4.8	4.14	NC	NC
Mean (SD) PANSS total score		51.9	9.68	51.1	10.65	NC	NC
Disposition							
N (%) of patients who	Completed	73	(93.6)	62	(80.5)	135	(87.1)
	discontinued	5	(6.4)	15	(19.5)	20	(12.9)
N analysed for safety[a]		78		77		155	
N analysed for efficacy (ITT)		77		77		154	
N analysed for efficacy (PP)		73		55		128	

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number; PP=Per-protocol
NC Not calculated; test was not performed because it was not specified in the Statistical Analysis Plan.

Efficacy

A summary of efficacy results for the quetiapine and lithium groups (LOCF, ITT population) is shown in Table S2.

Table S2 Summary of efficacy findings (LOCF, ITT population)

Assessment	Quetiapine (n=77)[a]	Lithium (n=77)[a]	P-value[b]
YMRS Total score – mean change from baseline	-18.2	-15.9	P=0.1052
YMRS Response – proportion of patients	77.9%	59.7%	P=0.0665
MADRS Total score – mean change from baseline	-3.5	-2.6	P=0.0805

Assessment	Quetiapine (n=77)[a]	Lithium (n=77)[a]	P-value[b]
Emergent Depression – proportion of patients	0.0%	1.3%	NC
PANSS Total score – change from baseline	-13.5	-10.3	P=0.6462

[a] Number of patients in the ITT population.
NC Not calculated; test was not performed because it was not specified in the Statistical Analysis Plan.

Quetiapine showed a clinically relevant improvement with respect to the primary endpoint, the change from baseline in YMRS total score at Day 28. Most of quetiapine-treated patients (77.9%) showed response, which has a significant statistical difference (p=0.0132) with lithium-treated patients (59.7%). The similarity of quetiapine compared with lithium at Day 28 was consistently confirmed by all other analyses of secondary measures of mania, depression, psychotic symptoms in the changes from baseline in YMRS, MADRS, and PANSS total score at Day 28.

The results of analysis of the primary endpoint in the post hoc analysis population that excluded from the PP population 5 quetiapine-treated and 22 lithium-treated (see Statistical methods, above) were entirely consistent with those observed for the ITT and PP populations. The reasons for the exclusion in quetiapine-treated group were treatment duration ≤ 8 days, no post-baseline YMRS assessment, and use of prohibited drugs during the study, while those in lithium-treated group were treatment duration ≤ 8 days, median serum lithium level < 0.6 mmol/L, incorrect enrolment, and use of prohibited drugs during the study.

Change from baseline in YMRS total score in quetiapine-treated and lithium-treated patients is −18.2 and −15.9 on Day 28, respectively, with no significant statistical difference. Other secondary efficacy variables related to mania, depression, and functional status confirmed that the treatment similarity of quetiapine and lithium with the duration of treatment.

The mean of the last-week median quetiapine dose for responders at Day 28 was 800 mg/day. 98.3% patients who responded to quetiapine at Day 28 were taking doses from 400 to 800 mg/day.

In the ITT population as a whole, quetiapine treatment was not significantly different from lithium treatment in reducing PANSS and MADRS total scores at Days 28.

Safety results

A summary of adverse events in each category of seriousness is presented in Table S3.

Table S3 Number (%) of patients who had at least 1 adverse event in any category (safety analysis set)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]					
	Quetiapine (n=78)		Lithium (n=77)		Total (n=155)	
	n	%	n	%	n	%
Safety population	78	100.0	77	100.0	155	100.0
Any adverse events	61	78.2	53	68.8	114	73.5
Serious adverse events						
Serious adverse events leading to death	0	0	0	0	0	0
Serious adverse events not leading to death	0	0	1	1.3	1	0.6
Study drug related adverse event	49	62.8	35	45.5	84	54.2
Discontinuations of study treatment due to adverse events	0	1.3	4	5.2	4	2.6
Other significant adverse events	3	3.8	6	7.8	9	5.8

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

The most common adverse events, as summarized by preferred term, are shown in Table S4.

Table S4 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

MedDRA (preferred term)	Number (%) of patients who had an adverse event					
	Quetiapine (n=78)		Lithium (n=77)		Total (n=155)	
	n[b]	%	n[b]	%	n[b]	%
Constipation	27	34.6	10	13.0	37	23.9
Dizziness	12	15.4	5	6.5	17	11.0
Diarrhoea	8	10.3	5	6.5	13	8.4
Alanine amino-transferase increase	7	9.0	3	3.9	10	6.5
Palpitations	7	9.0	3	3.9	10	6.5
Aspartate amino-transferase increase	6	7.7	3	3.9	9	5.8
Pharynglaryngeal pain	5	6.4	0	0	5	3.2
Upper respiratory tract infection	5	6.4	5	6.5	10	6.5

MedDRA (preferred term)	Number (%) of patients who had an adverse event					
	Quetiapine (n=78)		Lithium (n=77)		Total (n=155)	
Dry mouth	4	5.1	0	0	4	2.6
Asthenia	3	3.8	1	1.3	4	2.6
Insomnia	3	3.8	3	3.9	6	3.9
Nasopharyngitis	3	3.8	9	11.7	12	7.7
Nausea	3	3.8	13	16.9	16	10.3
Pharyngitis	3	3.8	1	1.3	4	2.6
Somnolence	3	3.8	3	3.9	6	3.9
Tachycardia	3	3.8	0	0	3	1.9
Vision blurred	3	3.8	0	0	3	1.9
Vomiting	3	3.8	10	13.0	13	8.4

[a] Events with a total frequency of ≥3% across all treatment groups are included in this table.
[b] Number of patients in the safety population.
MedDRA: Medical Dictionary for Regulatory Activities

In the quetiapine-treated group, the most frequently reported adverse events were constipation, dizziness, and diarrhoea; these types of adverse events are within the prescription information of quetiapine used as monotherapy for the treatment of schizophrenia. In the lithium-treated group, the most frequently reported adverse events were nausea, conspitation, and vomiting; these types of adverse events are the known effects of lithium treatment. Adverse events of postural hypotension and EPS were reported infrequently in both groups.

1 patient in the lithium-treated group had serious adverse events: 1 patient had an event of acute arrest of hemopoiesis due to bone marrow failure (the patient did not have a reported history of acute arrest of hemopoiesis). 3 patients had adverse events that led to withdrawal, all of which were treated with lithium.

No deaths was reported during this study, as noted in the preceding paragraph.

Quetiapine-treated and lithium-treated patients showed statistically significant improvement from baseline in MADRS scores at Day 28 compared with baseline. 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 1 lithium-treated patient. There was no depression reported as an adverse event for either quetiapine-treated patients or lithium-treated patient.

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

The rates of adverse events related to EPS were similar in the quetiapine-treated (2 patients (2.6%)) and lithiumj-treated (4 patients (5.2%)) groups. While adverse events of tremor can represent EPS, 2 adverse events of tremor occurred in the lithium-treated group and likely reflect the known effects of lithium treatment rather than EPS.

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 1.45 kg was observed in the quetiapine group at Day 28 and a mean increase of 0.25 kg in the lithium group. Adverse events of weight gain were reported for 2.6% of quetiapine-treated patients and none of lithium-treated patients. Increases from baseline weight of 7% or more were observed in 9.2% of quetiapine-treated patients and 5.2% of lithium-treated patients at Day 28. 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**.** 1 patient treated with lithium (blood insulin increased)and 1 patient treated with quetiapine (blood insulin decreased) had a non-serious adverse event reported as diabetes mellitus, respectively; these 2 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, while 1 patient treated with lithium reported free thyroxine increased. Mean decreases in total thyroxine were observed in the quetiapine group and mean decreases in free thyroxine were observed in the lithium group, without clinically significant increases in and TSH concentration. The proportion of lithium-treated patients with clinically significant increases in TSH concentration was 23.8%, compared with 6.1% in the quetiapine-treated; 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 was used as monotherapy to treat schizophrenia.