AstraZeneca

Drug product:	Seroquel	**SYNOPSIS**	
Drug substance(s):	Quetiapine		
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A Randomized, Parallel Group, Open Trial Examining the Safety, Efficacy and Tolerability of Fast Titration, 800mg/day by day 4, of Quetiapine Fumarate Compared to Standard Titration, 400mg/day by day 4, in the Treatment of Bipolar 1 Manic Episode.

Study Coordinator

[redacted]

Study centre(s)

[redacted]

[redacted]

Study dates		**Phase of development**
First subject enrolled	12/4/2005	Therapeutic confirmatory (III)
Last subject completed	27/2/2006	

Objectives

Primary Objectives

Compare the safety and tolerability of a fast titration of quetiapine to standard titration according to label.

Secondary Objectives

Assess the efficacy, safety and tolerability of a fast titration of quetiapine to standard titration according to label.

Study design

A randomised, parallel group, open , trial examining, Safety and efficacy of Quetiapine Fumarate (SEROQUEL™) in the Treatment of Bipolar I Manic episode after initial dose titration up to 800mg/day within 4 days followed by a flexible dosing regimen within the dose range of 400 to 800 mg during 3 weeks of treatment compared to standard titration 400mg/day by day 4.

Target subject population and sample size

Male or female subjects, aged 18 years or older, hospitalised with DSM-IV diagnosis of bipolar I and fulfilling eligibility criteria as outlined in the protocol, were considered for entry into the study. The episode leading to hospitalisation must be an episode of mania with or without psychotic features. Both at screening and at randomisation to treatment, subjects must had a Young Mania Rating Scale (YMRS) score of at least 20; and a Clinical Global Impression-(CGI) Severity of Illness score of at least 4. Subjects were to be inpatients for the first 7 days of the study.

A total of 150 patients should have been randomized into the study, 75 patients in each titration group. The sample size was calculated to estimate the difference in proportion of patients withdrawn due to Adverse Events during the first week between the two-titration groups with a two-sided 95% confidence interval, 75 patients per group will give a ±10% precision, assuming 10% will withdraw due to Adverse Events.

At the end of the study period only 49 patients had been included. Being that the study had only exploratory objectives and that continuing with that inclusion rate two more years would have been necessary for the total sample inclusion, the decision of closing the study when expected with the available patients at that time was taken.

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

The titration of the investigational product is according to the following scheme:

Group		Day 1	Day 2	Day 3	Day 4	Day 5 to 21
Daily Dose (mg)	A	200	400	600	800	FLEXIBLE DOSE 400-800mg
	B	100	200	300	400	FLEXIBLE DOSE 400-800mg

No antipsychotic medication was permitted during the trial except for the previous treatment that was switched to quetiapine by day 3.

Duration of treatment

21 days

Criteria for evaluation (main variables)

Safety

Primary endpoint (outcome variable):

(1)Proportion of subjects who withdraw from the trial due to adverse events by end of week 1 as well as total Adverse Events reported by end of week 1

Secondary safety endpoints (outcome variables):

(1)Adverse Events

(2)Changes in Vital Signs

(3)ECG (normal/abnormal)

(4)Change from baseline in Barnes Akathisia rating scale score

(5)Change from baseline in Simpson-Angus score

Secondary efficacy endpoints (outcome variables):

(1)Change from baseline in PANSS total and subscale scores

(2)Change from baseline in YMRS score

(3)Change from baseline in CGI severity of illness score

Statistical methods

The study is exploratory and is not powered to address any pre-defined hypothesis. Formal statistical testing will thus be an exception, and focus will instead be on descriptive statistics and estimation as appropriate.

All data collected in the study will be appropriately summarized for each treatment group using tabulations, graphs and summary statistics.

Subject population

Table S1 Subject population and disposition

		Fast titration		Standard titration		Total	
Disposition							
N (%) of subjects who	Completed	17	(68.0)	16	(66.7)	33	(67.3)
	Discontinued	8	(32.0)	8	(33.3)	16	(32.7)
N analysed for safety		25		24		49	
N analysed for efficacy (ITT)		20		22		42	
Protocol violation: Inclusion criteria No. 4		0		1		1	
Protocol violation: Non-compliance to treatment regimen		5		1		6	

Demographic or baseline characteristic		**Treatment group**					
		Fast titration (n=25) (ITT n=20)		**Standard titration (n=24) (ITT n=22)**		**Total (n=49) (ITT n=42)**	
Demographic characteristics							
Sex (n and % of subjects)	Male	9	(36.0)	11	(45.8)	20	(40.8)
	Female	16	(64.0)	13	(54.2)	29	(59.2)
Age (years)	Mean (SD)	41.76	(12.19)	40.00	(10.92)	40.90	(11.50)
	Range	21 to 65		19 to 62		19 to 65	
Race (n and % of subjects)	Caucasian	24	(96.0)	24	(100.0)	48	(98.0)
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline characteristics							
Height (cm)	Mean (SD)	163.38	(9.89)	164.88	(10.92)	164.13	(10.33)
Weight (kg)	Mean (SD)	74.56	(15.04)	75.92	(15.61)	75.22	(15.18)
PANNS Positive Subscale (ITT)	Mean (SD)	23.80	(5.80)	24.09	(7.47)	23.95	(6.65)
PANNS Negative Subscale (ITT)	Mean (SD)	11.40	(5.34)	9.50	(3.80)	10.40	(4.64)

		Fast titration		Standard titration		Total	
PANSS General Psychopathology Subscale (ITT)	Mean (SD)	40.15	(8.98)	37.14	(11.83)	38.57	(10.55)
PANSS Supplementary Items (ITT)	Mean (SD)	11.00	(3.82)	8.91	(4.22)	9.88	(4.12)
PANSS Total Score (ITT)	Mean (SD)	75.35	(15.93)	70.73	(20.07)	72.93	(18.15)
YMRS (ITT)	Mean (SD)	35.00	(8.01)	35.09	(8.62)	35.05	(8.23)
CGI Severity of Illness (ITT)	Mean (SD)	5.35	(0.75)	5.05	(0.79)	5.19	(0.77)

Table S2a Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]					
	Fast titration		Standard titration		Total	
Any adverse events	19	(51.4)	18	(48.7)	37	(100.0)
Serious adverse events						
[redacted]						
[redacted]						
Discontinuations of study treatment due to adverse events	0	(0.0)	1	(100.0)	1	(100.0)
Other significant adverse events	0		0		0	
	Total number of adverse events					
Adverse events	63	(52.5)	57	(47.5)	120	(100.0)
Serious adverse events	0	(0.0)	1	(100.0)	1	(100.0)
Other significant adverse events	0		0		0	

[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 S2b (Week 1) Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a] (week 1)					
	Fast titration		Standard titration		Total	
Any adverse events	15	(46.9)	17	(53.1)	32	(100.0)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a] (week 1)					
	Fast titration		Standard titration		Total	
Serious adverse events						
[redacted]						
Discontinuations of study treatment due to adverse events	0	(0.0)	1	(100.0)	1	(100.0)
Other significant adverse events	0		0		0	
	Total number of adverse events					
Adverse events	31	(46.3)	36	(53.7)	67	(100.0)
Serious adverse events	0	(0.0)	1	(100.0)	1	(100.0)
Other significant adverse events	0		0		0	

[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 S3 **Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)**

Adverse event (preferred term)	Number (%) of subjects who had an adverse event					
	Fast titration (n=25)		Standard titration (n=24)		Total (n=49)	
Somnolence	6	(24.0)	4	(16.7)	10	(20.4)
Constipation	5	(20.0)	3	(12.5)	8	(16.3)
Dizziness	4	(16.0)	3	(12.5)	7	(14.3)
Headache	3	(12.0)	2	(8.33)	5	(10.20)
Dry mouth	2	(8.0)	2	(8.33)	4	(8.16)
Cough	2	(8.0)	1	(4.17)	3	(6.12)
Dyspepsia	1	(4.0)	2	(8.33)	3	(6.12)
Malaise	1	(4.0)	2	(8.33)	3	(6.12)
Pharyngolaryngeal pain	1	(4.0)	2	(8.33)	3	(6.12)
Toothache	3	(12.0)	.	.	3	(6.12)
Asthenia	1	(4.0)	1	(4.17)	2	(4.08)
Chest pain	1	(4.0)	1	(4.17)	2	(4.08)
Diarrhoea	.	.	2	(8.33)	2	(4.08)
Haematocrit abnormal	2	(8.0)	.	.	2	(4.08)
Hypotension	.	.	2	(8.33)	2	(4.08)
Inflammation	1	(4.0)	1	(4.17)	2	(4.08)
Pain in extremity	1	(4.0)	1	(4.17)	2	(4.08)
Pyrexia	.	.	2	(8.33)	2	(4.08)
Sedation	2	(8.0)	.	.	2	(4.08)
Vomiting	1	(4.0)	1	(4.17)	2	(4.08)
White blood cell count increased	1	(4.0)	1	(4.17)	2	(4.08)

[a] Events with a total frequency of ≥4% across all treatment groups are included in this table.

Table S4 Efficacy results

Change from baseline in PANNS (visit 2 to visit 10)		**Treatment group**					
		Fast titration (n=19)		**Standard titration (n=22)**		**Total (n=41)**	
Total	Mean (SD)	-28.47	(22.36)	-27.86	(22.78)	-28.15	(22.31)
Positive subscale	*Mean (SD)*	*-11.68*	*(8.52)*	*-11.95*	*(9.62)*	*-11.83*	*(9.01)*
Negative subscale	*Mean (SD)*	*-1.74*	*(3.84)*	*-2.09*	*(3.15)*	*-1.93*	*(3.45)*
General psychopathology	*Mean (SD)*	*-15.05*	*(12.59)*	*-13.82*	*(11.89)*	*-14.39*	*(12.08)*
		Fast titration (n=18)		**Standard titration (n=22)**		**Total (n=40)**	
Supplementary items	Mean (SD)	-5.22	(4.67)	-3.64	(4.07)	-4.35	(4.37)
Change from baseline in YMRS (visit 2 to visit 10)		**Treatment group**					
		Fast titration (n=19)		**Standard titration (n=22)**		**Total (n=41)**	
YMRS change	Mean (SD)	-21.05	(15.51)	-20.18	(14.00)	-20.59	(14.54)
Change from baseline in CGI Improvement (visit 2 to visit 10)		**Treatment group**					
		Fast titration (n=18)		**Standard titration (n=19)**		**Total (n=37)**	
Patients with "much" or "very much improved" in CGI Global Improvement at visit	N (%)	13 (72.22)		14 (73.68)		27 (72.97)	
		1 missing data		3 missing data			

Conclusion(s)

[redacted]

Date of the report

2 January 2007