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Clinical Study Report

Drug substance:	Quetiapine
Document No.:	CNS.000-105-629
Edition No.:	1.0
Study code:	DC-990-0165
Date:	30 November 2006

A Canadian, Multicentre, Double-Blind, Randomized, Parallel-Group Study of the Safety, Tolerability, and Efficacy of Treatment with Higher Doses of Quetiapine Fumarate (Seroquel®) greater than 800 mg/day in Schizophrenic or Schizoaffective Subjects

Study dates:	First subject enrolled: 01 October 2003 Last subject enrolled: 07 July 2005
Phase of development:	IIIb
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Sponsor's Responsible Medical Officer:	Dr. Martin Brecher Executive Director

This study was performed in compliance with Good Clinical Practice.

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Drug product:	Seroquel®	**SYNOPSIS**	
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Study centre(s)

This study was conducted at 21 centres in Canada. Subjects were enrolled at 19 centres across Canada.

Publications

None at the time of writing this report.

Study dates		Phase of development
First subject enrolled	01 October 2003	Therapeutic confirmatory (III)
Last subject completed	28 September 2005	

Objectives

Primary Objective

The primary object of this study is:
To assess and compare the parkinsonism side effect profile [extra-pyramidal symptoms (EPS)] of schizophrenic or schizoaffective subjects non- or partially responsive to 800mg/day of quetiapine treated with either 800mg/day or >800mg/day of quetiapine.

Secondary objectives

The secondary efficacy objectives of this study are:

To assess and compare the tolerability and safety (via open questioning for adverse event, weight, body mass index (BMI), vital signs, electrocardiogram (ECG), laboratory values including metabolic measures) of schizophrenic or schizoaffective subjects non- or partially responsive to 800 mg/day of quetiapine treated with either 800 mg/day or >800 mg/day of quetiapine.

To get an indication if treatment with high doses of quetiapine (>800 mg/day) is superior to treatment with 800 mg/day of quetiapine in schizophrenic or schizoaffective patients, non- or partially responsive to 800 mg/day of quetiapine.

To assess and compare the level of social and occupational functioning of schizophrenic or schizoaffective subjects non- or partially responsive to 800 mg/day of quetiapine treated with either 800 mg/day or >800 mg/day of quetiapine.

Study design

This was a Canadian, multi-centre, randomized, double-blind, parallel-group study of the safety, tolerability and efficacy of treatment with higher doses of quetiapine fumarate (Seroquel®) greater than 800 mg/day in schizophrenic or schizoaffective subjects for an eight- week period.

Target subject population and sample size

Male and female schizophrenic or schizoaffective subjects, non- or partially responsive to treatment with 800 mg/day of quetiapine, who required treatment with >800 mg/day of quetiapine. Subjects may be either inpatients or outpatients.
It was estimated that 298 enrolled subjects with would be required to achieve 120 evaluable subjects. Assuming a one-side test, a type-one error of 0.05 and a prior 16% EPS response for both groups as measure in the Simpson-Angus Scale, 120 subjects in total are required. Using a 2:1 allocation ratio, 80 randomized patients will be assigned to the high dose strategy and 40 to the low dose. The statistical power of the study gained under these conditions is 0.8 for a non-inferiority trial in the number of EP events. In this context non-inferiority refers to a lack of excess of adverse events. Under these conditions we have a 0.8 power of detecting a lack of excess adverse events (EPS) and a 5.47 PANSS units of difference between the treatment groups.

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

After meeting the entry criteria, subjects had their previous antipsychotic medication tapered off (during the first 7days), and began taking quetiapine orally, starting at 100mg/day until a dose of 800mg/day (400 mg bid) is obtained. Quetiapine was administered twice daily to subjects (bid), with the exception of the first 100 mg dose on Day 1, which was taken as a single dose in the evening. The study medication of all subjects was titrated according to the schedule recommended below but can be slowed if the subject displays intolerance to the study medication. Subjects were to be on monotherapy by Day 14 at the latest.
During the double-blind study period, a 2:1 allocation ratio to quetiapine >800 mg/day (up to 1200 mg/day) and 800 mg/day were used in order to maximize the number of

subjects in the high dose group. Medications for the 800 mg/day group will include placebo tablets to maintain the blind between both treatment groups.
AstraZeneca supplied study medication as follows (Tablet strength, formulation):

0 Quetiapine 100 mg (Formulation F012689; Batch #22075D04 and #11269K03)

1 Quetiapine 200 mg (Formulation F12690; Batch 22368F04, and #11461C03)

2 Placebo 200 mg (Formulation F12638; Batch #22086H04 and #11272F03)

Duration of treatment

Patients were given randomized study treatment for a period of 8 weeks preceded by a 4-week open-label phase. Subjects were taped off over a period of one-week.
This was a thirteen-week, double blind, parallel group, multi-centre study including a 7-day screen phase, 4-week open label phase (to identify non- or partial responders to quetiapine 800 mg/day), and an 8-week double-blind phase. The double-blinded phase included a 2:1 allocation ratio (>800 mg/day: 800mg/day) treatment.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics
All efficacy variables were secondary variables, as the primary variable in this study is a measure of safety.

3 Primary variable: Not applicable

4 To get an indication if treatment with high doses of quetiapine (>800 mg/day) is superior to treatment with 800 mg/day of quetiapine in schizophrenic or schizoaffective patients, non- or partially responsive to 800 mg/day of quetiapine.

5 To assess and compare the level of social and occupational functioning of schizophrenic or schizoaffective subjects non- or partially responsive to 800 mg/day of quetiapine treated with either 800 mg/day or >800 mg/day of quetiapine.

6 No pharmacokinetics variables were assessed.

Safety

7 Primary Variable: The comparison between treatment groups of the proportion of subject (%) experiencing emergent or a worsening of EPS defined as an increase in the total Simpson-Angus Scale (SAS) (>0) from baseline Day 29 to Day 85 or last observation carried forward (LOCF).

8 Safety evaluation as determined by adverse events, weight, physical examination, BMI, vital signs, ECG and laboratory values including metabolic measures.

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Statistical methods

The intention to treat (ITT) approach was used for both the safety/tolerability and the efficacy analysis of the study; when referring to a subject set, the names "Full Analysis" and "Safety" were used interchangeably in this report. Differences in the proportion of subjects that experienced increase in their EPS symptoms after baseline (Day 29) were calculated in addition to analysis of covariance with centre, and severity at baseline as covariate. The per protocol (PP) analysis excluded those subjects classified as protocol violators, prior to declaring the database locked. The statistical analysis of the primary variable, change in SAS total score from baseline to final visit (SAS difference <=0 and SAS difference >0) was performed using a non-parametric analysis of co-variance via Cochran-Mantel-Haenszel and confidence intervals (CI) for the difference in the response proportion between treatments.

Missing values will be replaced to assess the robustness of the results. To this end, the last observation carried forward (LOCF) was used.

Subject population

Table S1 Subject population and disposition

		Quetiapine 800mg		Quetiapine >800mg		Not Randomised	
Population							
N randomised (N planned)		43	(50)	88	(100)	34	(148)
Demographic characteristics							
Sex (n and % of subjects)	Male	32	74.4	58	65.9	26	76.5
	Female	11	25.6	30	34.1	8	23.5
Age (years)	Mean (SD)	37.9	(10.9)	40.6	(12.5)	35.4	(11.7)
	Range	20 to 60		19 to 62		19 to 56	
Race (n and % of subjects)	Caucasian	37	86.0	80	90.9	30	88.2
	Black	3	7.0	5	5.7	3	8.8
	Oriental	1	2.3	2	2.3	0	0
	Other	2	4.7	1	1.1	1	2.9
Baseline characteristics							
Weight (kg)	Mean (SD)	81.7	(16.3)	83.7	(18.7)	86.5	(22.2)
	Range	50 to 127		47 to 150		58 to 125	
Height (cm)	Mean (SD)	170.2	(11.6)	171.4	(10.5)	172.8	(11.6)
	Range	143 to193		143 to197		150 to195	
Body Mass Index (kg/m²)	Mean (SD)	28.4	(6.4)	28.5	(6.1)	29.0	(7.3)
	Median	27.2		28.1		28.9	
	Range	16.7 to 47.9		18.1 to 50.1		17.9 to 51.0	

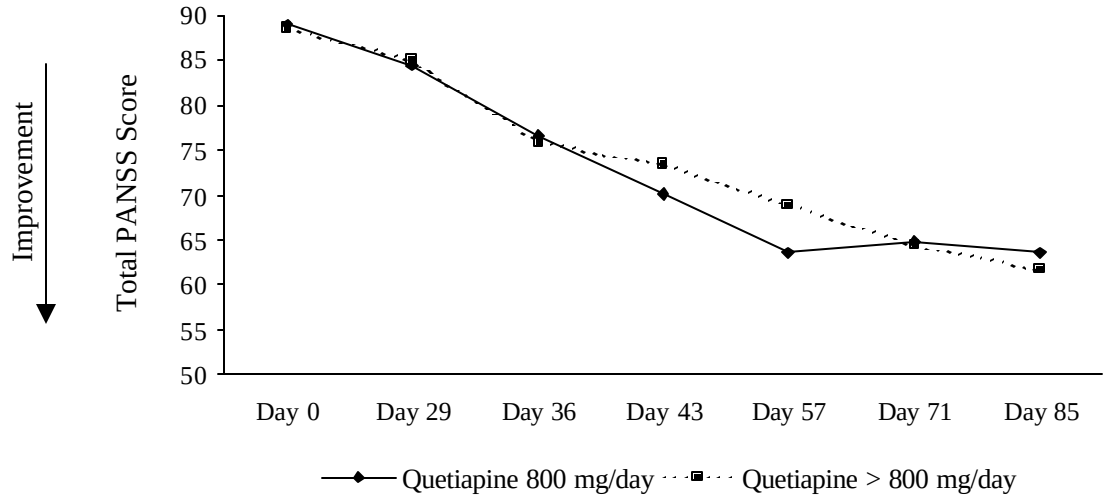
		Quetiapine 800mg		Quetiapine >800mg		Not Randomised	
Pulse (beats/min) Supine	Mean (SD)	77.7	(12.7)	78.5	(10.6)	81.1	(11.9)
	Range	44-100		59-106		60-105	
Systolic BP (mmHg) Supine	Mean (SD)	119.9	(12.5)	121.2	(16.6)	121.5	(16.0)
	Range	96-147		96-200		100-150	
Diastolic BP (mmHg) Supine	Mean (SD)	76.3	(10.5)	75.5	(12.2)	75.7	(11.8)
	Range	50-103		55-135		60-104	
Pulse (beats/min) Standing	Mean (SD)	88.4	(12.3)	86.1	(10.8)	88.1	(13.4)
	Range	68-113		60-120		60-122	
Systolic BP (mmHg) Standing	Mean (SD)	115.8	(13.6)	115.0	(15.2)	117.1	(13.8)
	Range	90-144		86-200		90-145	
Diastolic BP (mmHg) Standing	Mean (SD)	79.1	(11.0)	76.4	(11.4)	74.9	(10.5)
	Range	60-105		50-130		60-101	
Days hospitalized before enrolment[a]	N	7		20		11	
	Mean (SD)	35.6	(42.0)	29.9	(24.2)	38.4	(45.6)
	Median	16.0		29.5		22.0	
	Range	2 to 110		0 to 100		2 to 164	
Disposition							
N (%) of subjects who	Completed	35	(81.4)	68	(77.3)	0	(0)
	Discontinued	8	(18.6)	20	(22.7)	34	(100)
N analysed for safety/efficacy (FAS)[b]		43		88		0	
N analysed for efficacy (PP)		31		57		0	

[a] For patients hospitalized before enrolment.
[b] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
FAS=Full-Analysis Set; N=Number; PP=Per-protocol

Efficacy and pharmacokinetic results

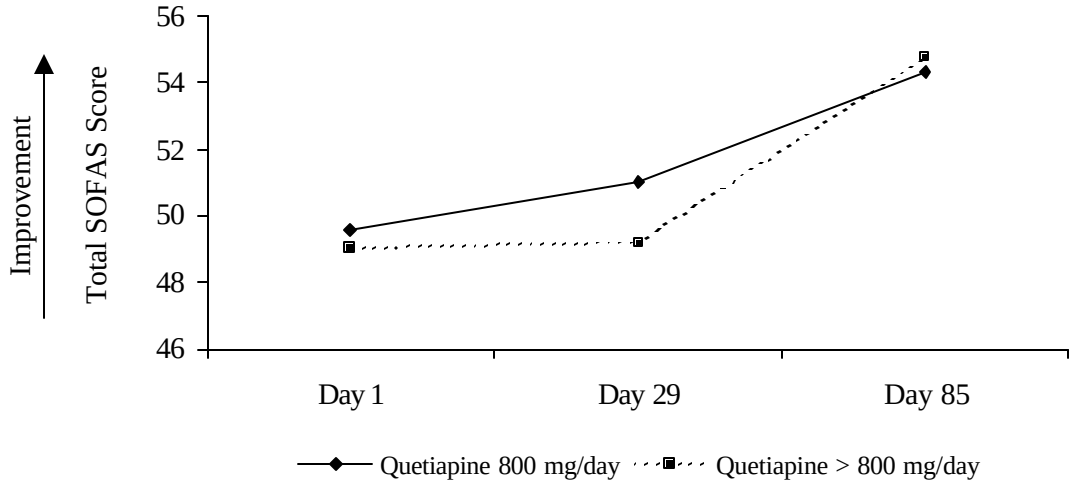
There was no statistical difference observed between treatment groups, based on the mean change in Total PANSS scores from baseline to end of treatment (Figure 1).

Figure 1 Mean Total PANSS Score by treatment, Seroquel 800mg and Seroquel >800mg (Observed cases, Full-Analysis set)*



For social and occupational functioning (measured using SOFAS), there was no statistical difference observed between treatment groups, based on the mean change in total SOFAS scores from baseline to end of treatment).

Figure 2 Mean Total SOFAS Score by treatment, Seroquel 800mg and Seroquel >800mg (LOCF, Full-Analysis set)*



Safety results

A difference of 3.1% (95% CI: -7.8% to +14.0%, p-value= 0.7553), in the percent of patients experiencing an increase in the number of EPS, was observed between both treatments, quetiapine >800mg and quetiapine 800mg, measured with the Simpson Angus Scale (SAS) from baseline to the end of treatment for the FAS group. Since the upper end of the confidence interval is lower than the proposed limit of superiority (16%), no significant increase in the number of EPS was observed in the >800mg quetiapine group.

There was no statistical difference observed between treatment groups for EPS related symptoms, based on the mean total SAS scores. In terms of SAS measure of safety and tolerability, both treatment regimes were well tolerated and safe.

Figure 3 **Mean Total SAS scores by treatment: Seroquel 800mg and Seroquel >800mg (Observed cases, Full Analysis set)***

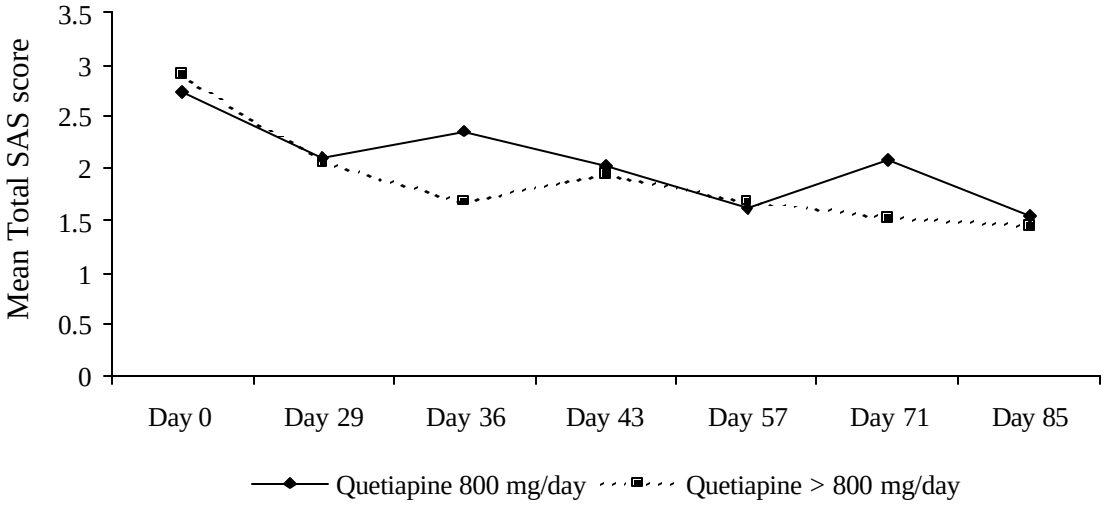


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Table S2 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (FAS)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]		
	Quetiapine 800mg	**Quetiapine >800mg**	**Not Randomised**
Any adverse events	34 (79.1%)	75 (85.2%)	27 (79.4%)
Serious adverse events	1 (2.3%)	3 (3.4%)	3 (8.8%)
Serious adverse events leading to death	0	0	1 (2.9%)
Serious adverse events not leading to death	1 (2.3%)	3 (3.4%)	2 (5.9%)
Discontinuations of study treatment due to adverse events	2 (4.7%)	6 (6.8%)	10 (29.4%)
Other significant adverse events (OAEs)[b]	8 (18.6%)	11(12.5%)	4 (11.8%)
	Total number of adverse events		
Adverse events	140	374	95
Serious adverse events	1	3	3
Other significant adverse events (OAEs)[b]	8	16	6

[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.

[b] OAEs are AEs associated with EPS, QT Prolongation, Diabetes Mellitus, Suicidality, Neutropenia and agranulocytosis. All SAEs and AEs leading to discontinuation are excluded. Cut off date for open label phase and blinded phase is the first dose date of randomised medication. If AEs start in the open label phase and continued, they are associated with treatments received in the open label phase.

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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 (FAS)**

Adverse event (preferred term)	Number (%) of subjects who had an adverse event		
	Quetiapine 800mg	Quetiapine >800mg	Not Randomised
Dizziness	7 (16.3%)	13 (14.8%)	0 (0.0%)
Headache	4 (9.3%)	11 (12.5%)	0 (0.0%)
Fatigue	3 (7.0%)	7 (8.0%)	0 (0.0%)
Somnolence	2 (4.7%)	8 (9.1%)	0 (0.0%)
Anxiety	1 (2.3%)	5 (5.7%)	0 (0.0%)
Dyskinesia	3 (7.0%)	1 (1.1%)	0 (0.0%)

[a] Events with a total frequency of ≥4% across all treatment groups are included in this table. A data cut off of 5% was used.