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Clinical Study Report

Drug substance:	Quetiapine SR
Edition No.:	1
Study code:	D1444C00147
Date:	29 January 2007

A 12-week International, Multicenter, Open Label, Non-comparative Study to Evaluate the Feasibility of Switching any Antipsychotic Treatment to Sustained-release quetiapine Fumarate (SEROQUEL®) in Patients with Schizophrenia

Study dates:	First patient enrolled: 3 November 2004 Last patient enrolled: 13 February 2006 Last patient completed: 16 May 2006
Phase of development:	Therapeutic confirmatory (III)
International Co-ordinating Investigator:	No International Co-ordinating Investigator was appointed

This study was performed in compliance with Good Clinical Practice.

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Drug product:	Seroquel SR	**SYNOPSIS**	
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A 12-week International, Multicenter, Open Label, Non-comparative Study to Evaluate the Feasibility of Switching any Antipsychotic Treatment to Sustained-release quetiapine Fumarate (SEROQUEL®) in Patients with Schizophrenia

International co-ordinating investigator

No international co-ordinating investigator was appointed

Study centres

This study was conducted in Australia (4 centres), Canada (9 centres), Finland (3 centres), Germany (9 centres), Hungary (9 centres), Malaysia (7 centres), South Africa (6 centres), Bulgaria (3 centres), Estonia (3 centres), Latvia (4 centres) and US (12 centres).

Publications

Not published

Study dates		**Phase of development**
First patient enrolled	3 November 2004	Therapeutic confirmatory (III)
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Objectives

Primary objective

To document the clinical benefit of quetiapine SR after switching from other ongoing antipsychotic treatment, regardless of the reason for the switch.

Secondary objective

To document improved efficacy and safety/tolerability after switching to quetiapine SR from other ongoing antipsychotic treatment, regardless of the reason for switch.

Study design

This 12-week, international multicenter, open label, non-comparative study evaluated the clinical benefit of switching to a flexible dose of quetiapine SR from any ongoing antipsychotic treatment in patients with schizophrenia.

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Target patient population and sample size

Male and female in- or outpatients between the age of ≥18 and ≤65 years with DSM-IV diagnostic criteria of schizophrenia, who in their own or in the Investigators' opinion considered their ongoing antipsychotic treatment inadequate because of inadequate efficacy or tolerability.
The null hypothesis was that the proportion of patients with an improved clinical benefit was 50% or less. The sample size calculation is based on the sub group of completers. Given a true proportion of 58%, a sample size of 348 had 85% power to detect that the proportion was greater than 50% with a one-sided significance level of 0.025. To account for withdrawals, a total of 500 patients were to be recruited.

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

The investigational product was quetiapine fumarate tablet SR administered once daily. The treatment with the investigational product started (Day 1) with a 4-day cross-titration phase where ongoing antipsychotic medication was phased out and quetiapine SR was phased in. Quetiapine SR 300 mg/day was given Day 1 and 600 mg/day was given at Day 2. At Day 3 either the 600 mg dose was maintained or the titration continued to the maximum dose 800 mg/day or if the 600 mg dose was not tolerated, the dose was decreased to 400 mg/day. For the remaining period of the 12-week treatment a flexible dosing between 400 mg and 800 mg/day was applied with minimum dose adjustments of 200 mg/day.

Cross-titration/dosing schedule (total daily dose)

	Day 1	**Day 2**	**Day 3**	**Day 4-84**
Other antipsychotic treatment	75%[1]	50%[1]	25%[1]	0%
quetiapine SR	300 mg	600 mg	400, 600 or 800 mg	400 - 800 mg

1 Target remaining dose

The following batches of quetiapine were used:

Tablet	**Formulation number**	**Batch number**
quetiapine SR tablet 200 mg	F12840	9057K, 21041B04, 22319A04, 31742A05
quetiapine SR tablet 300 mg	F12527	9049K, 21042J04

The patients were instructed to take the investigational product once daily, in the evening No comparator was used.

Duration of treatment

The total treatment period was 12 weeks including the 4-day cross-titration period.

Criteria for evaluation (main variables)

Efficacy

- Primary outcome variable: The proportion of patients who at Week 12 had an improved clinical benefit based on assessment of clinical efficacy in combination with assessment of tolerability.

  Clinical benefit was assessed with the Clinical Global Impression-Clinical Benefit (CGI-CB) score, according to a classification based on the principles outlined in the CGI efficacy index. Improvement in clinical benefit was defined as a decrease from baseline in CGI-CB.

- Secondary outcome variables:

  - Change from baseline to Week 12 in CGI-CB score
  - Change from baseline to Week 12 in Positive and Negative Syndrome Scale (PANSS) total score
  - Clinical Global Impression-Improvement (CGI-I) value at Week 12
  - Personal Evaluation of Transitions in Treatment (PETiT) total score, as assessed by change from baseline to Week 12

- Additional secondary outcome variables:

  - PANSS subscale scores (positive-, negative- and general psychopathology scores)
  - Clinical Global Impression-Severity of illness (CGI-S) score

Safety and Tolerability

The secondary objectives were addressed by the following safety/ tolerability variables as well as by the secondary outcome variables shown above.

- Change from baseline to Week 12 in Simpson and Angus (SAS) total score
- Change from baseline to Week 12 in the last item of the Barnes Akathisia Rating Scale (BARS)

Additional secondary outcome variables:

- Reports of adverse events
- Clinically significant changes in clinical chemistry, haematology, ECG and vital signs
- Change in body weight

- The proportion of patients using anticholinergic medication

Genetic analysis

Consent for genetic research was obtained and documented through a form separate from that used for the main study. This form specifically stated that sampling was optional and not a requirement for study participation. The purpose was to enable future analyses aimed at identifying genes that influence susceptibility to schizophrenia, or that impact the efficacy, tolerability, or disposition of quetiapine. The specific analyses to be performed are not yet identified. The DNA samples will be stored for a maximum of 15 years from completion of the clinical study; they will then be destroyed. The results of the DNA analysis are not reported in this Clinical Study Report.

Statistical methods

The primary variable was the proportion of patients achieving an improvement in CGI-CB at Week 12, where improvement was defined as a decrease from baseline in CGI-CB. The statistical method for the primary analysis was a test of difference of that proportion according to a 50% threshold. The null hypothesis was that 50% of patients or less achieved an improvement in CGI-CB. A two-sided 95% confidence interval was calculated for this proportion. If the lower limit of this confidence interval was greater than 50%, then the null hypothesis was rejected and the switching of treatment was considered successful.
The confidence interval for the proportion achieving an improvement in CGI-CB was computed using the asymptotic Normal approximation to the binomial distribution, without continuity correction.
The intention to treat population (ITT) was the population for the primary analysis. Missing values for the primary analysis were handled using the last observation carried forward (LOCF) approach.
To support the primary analysis, the same analysis was performed without LOCF on the set of completers, and with LOCF on the per-protocol population.
As additional support for the primary analysis, further secondary analyses were performed on the intention to treat population, testing for a CGI-I score of <4 as well as favourable change from baseline in

- CGI-CB
- SAS total score
- BARS global score
- PANSS total score
- PETiT total score

Tests and multiplicity

The primary analysis and the secondary analyses were performed with an approach that combines a fixed sequence and Bonferroni-Holm correction, as follows. The

fixed sequence allows considering a global risk error rate of 2.5% for the primary analysis and
the secondary analyses, as the statistical significance of the secondary analyses (using Bonferroni-Holm method) will be studied only if the primary analysis is significant (hierarchical procedure). The Bonferroni-Holm method then allows splitting the 2.5% risk error rate between all the comparisons of the secondary analyses, thus maintaining a global risk error rate of 2.5% for these analyses. The Bonferroni-Holm correction was applied to the six secondary endpoints by comparing nominal p-values to thresholds as illustrated in Figure 1, section 4.1, in the SAP; a statistically significant result for any endpoint of the secondary analyses was only claimed if statistically significant result could be claimed for the primary analysis. This ensured an overall significance level of 2.5% for the primary analysis and its supportive analysis with these secondary outcomes.

Patient population

Demographics and baseline characteristics for the group of all patients switching to quetiapine SR and for the subgroups of patients switching due to insufficient efficacy and insufficient tolerability, respectively, are shown in Table S1.

Table S1 Patient population and disposition (safety/ITT population)

	All patients N=477	Insufficient efficacy N=315	Insufficient tolerability N=162
Demographic characteristics			
Sex, n (%)			
Male	306 (64.2)	208 (66.0)	98 (60.5)
Female	171 (35.8)	107 (34.0)	64 (39.5)
Age (years) [a]			
Mean (SD)	37.9 (11.3)	37.6 (11.3)	38.6 (11.5)
Min to Max	18 to 65	18 to 65	19 to 63
Race/ethnicity, n (%)			
Caucasian	297 (62.3)	186 (59.0)	111 (68.5)
Black	76 (15.9)	53 (16.8)	23 (14.2)
Oriental	87 (18.2)	62 (19.7)	25 (15.4)
Other	17 (3.6)	14 (4.4)	3 (1.9)
Baseline characteristics			
DSM-IV diagnosis, schizophrenic subtype n (%)			
Disorganized	37 (7.8)	28 (8.9)	9 (5.6)
Catatonic	4 (0.8)	3 (1.0)	1 (0.6)
Paranoid	374 (78.4)	249 (79.0)	125 (77.2)
Undifferentiated	62 (13.0)	35 (11.1)	27 (16.7)
CGI-CB score at switch n (%)			
Number of patients with non-missing observation	476	314	162

	All patients N=477	Insufficient efficacy N=315	Insufficient tolerability N=162
Mean (SD)	6.8 (2.37)	6.9 (2.38)	6.6 (2.34)
CGI-S score at switch, mean (SD)	3.8 (0.87)	3.9 (0.80)	3.5 (0.93)
PANSS total score at switch, mean (SD)	73.8 (18.34)	76.9 (17.75)	67.7 (18.01)
Population			
Disposition (switched patients): n			
Eligible for enrolment (Visit 1)	533	357	176
Excluded from safety/ITT population	56	42	14
Did not take study medication	56	42	14
Safety/ITT population	477	315	162
Excluded from PP population [b]	205	139	66
PP efficacy population	388	257	131
Completers subgroup	368	240	128

n Number of patients
[a] At enrollment
[b] Out of the 205 patients excluded from the PP population (from the 533 patients eligible for enrolment) , 145 were excluded for the entire study and 60 were excluded during the study. The last valid assessments for these 60 patients were included in the LOCF analyses.
Note: Percentages are based on the number of patients with non-missing observation. For DSM-IV diagnosis, CGI-S score and PANSS total score at switch, this data is the same as for the group of All Patients and the subgroups.

533 patients were eligible for enrolment. 56 of these discontinued before switching to quetiapine.
477 patients were included in the Safety/ITT efficacy analysis set. 107 (22.4%) of these discontinued during treatment; hence 370 completed the study period. 368 of them had both a baseline assessment for CGI-CB (non missing exam assessed before or the day of the first treatment intake of IP) and a Week 12 assessment (non missing exam performed from 71 days to 91 days after the first treatment intake of IP). These 368 patients were included in the Completers subgroup. 388 patients were included in the PP analysis set.
Of the 477 patients who switched to quetiapine SR, 306 were men (64.2%) and 171 were women (35.8%). The patient ages at enrolment ranged from 18 to 65 years, with an overall mean of 37.9 years. Caucasians (62.3%) made up the largest part of the population, followed by Orientals (18.2%) and Blacks (15.9%).
More patients were recruited to the insufficient efficacy subgroup (357) than to the insufficient tolerability subgroup (176). The subgroups were generally well balanced with respect to demographic and baseline characteristics.

Efficacy results

A summary of the efficacy outcome variables for the group of all patients switching to quetiapine SR and for for the subgroups of patients switching due to insufficient efficacy and insufficient tolerability, respectively, is shown in Table S2.

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Table S2 Efficacy results at Week 12. All patients and for patients switching due to insufficient efficacy and tolerability, respectively (LOCF, safety/ITT population)

	All patients N= 477	Insufficient efficacy N= 315	Insufficient tolerability N= 162
Primary variable			
Number of patients with a non-missing observation	470	311	159
Patients (n, %) who at Week 12 had an improved clinical benefit[a]	295 (62.8)	186 (59.8)	109 (68.6)
95% CI	58.4, 67.1		
p-value [b]	<.0001		
Secondary variables			
Number of patients with a non-missing observation	470	311	159
Change from baseline in CGI-CB score (SD)	-2.1 (3.62)	-2.1 (3.64)	-2.2 (3.61)
LS mean change (95% CI) [b]	-1.9 (-2.32, -1.38)		
Number of patients with a change value	471	312	159
CGI-I value	2.80 (1.485)	2.70 (1.476)	3.00 (1.488)
LS mean change (95% CI) [b]	2.88 (2.67, 3.08)		
Change from baseline in PANSS total score (SD)	-13.6 (19.23)	-15.6 (19.42)	-9.7 (18.29)
LS mean change (95% CI) [b]	-12.3 (-14.95, -9.58)		
Number of patients with a change value	428	286	142
Change from baseline in PETiT total score (SD)	3.2 (9.47)	2.9 (9.53)	3.7 (9.34)
LS mean change (95% CI) [b]	3.0 (1.94, 4.01)		
Additional secondary variables			
Number of patients with a change value	471	312	159
Mean change from baseline in PANSS positive sychopathology subscale score (SD)	-3.2 (5.59)	-3.9 (5.67)	-1.8 (5.18)
Mean change from baseline in PANSS negative psychopathology subscale score (SD)	-3.8 (5.62)	-4.1 (5.78)	-3.2 (5.24)
Mean change from baseline in PANSS general psychopathology subscale score (SD)	-6.7 (9.97)	-7.6 (9.95)	-4.7 (9.75)
Mean change from baseline in CGI-S score (SD)	-0.7 (1.1)	-0.8 (1.1)	-0.4 (1.1)

[a] Improved clinical benefit was based on assessment of clinical efficacy in combination with assessment of tolerability using the CGI-CB score, according to a classification based on the principles outlined in CGI item 3.

Improvement in clinical benefit was defined as a decrease from baseline in CGI-CB. Improvement was defined as a rating of 'much improved', 'improved' and 'minimally improved' on the CGI Global Improvement scale.

[b] Adjusted Mean (LS mean), Standard Error, 95%CI and one-sided p-value (for the one-sided test of the null hypothesis that the change from baseline is less than or equal to 0) are from a generalised linear model with baseline value (fixed effect) and centre (random effect) as covariates.

The results of the study demonstrated that 295 patients (62.8%) experienced improved clinical benefit after 12-weeks of treatment (95% CI 58.4, 67.1), regardless of the reason for switch (ie insufficient efficacy or insufficient tolerability). This was a statistically significant proportion, as determined by the fixed-sequence analysis.

These results were supported by the following secondary variables: change in CGI-CB score, CGI-I value and change in PANSS total score. The results showed a -1.9 LS mean change (95% CI -2.32, -1.38) in CGI-CB, that is to say a clinically significant mean improvement of approximately two steps in the CGI-CB scale. They also showed a clinically significant LS mean CGI-I score of 2.88 (95% CI 2.67, 3.08), and a clinically significant LS mean change in PANSS of -12.3 (95% CI 14.95, 9.58). The results for all three variables demonstrated statistically significant improvement, as determined by the Bonferroni-Holm method.

The efficacy results were also supported by the improvement shown in Patient Reported Outcomes, as tested by the change from baseline in PETiT score. The LS mean change in score to week 12 was 3.0 (SE 0.52; 95% CI 1.94, 4.01). This was a statistically significant change, as determined by the Bonferroni-Holm method.

The following additional variables supported the secondary efficacy analyses: CGI-S and PANSS subscale scores (positive-, negative- and general psychopathology scores). The results for CGI-S showed a -0.7 (SD 1.1) mean change. The results for PANSS showed: a mean change of -3.2 (SD 5.59) mean change for positive psychopathology, a -3.8 (SD 5.62) mean change for negative psychopathology and a -6.7 (SD 9.97) mean change for general psychopathology. As the two most common reasons for switching due to insufficient efficacy were positive and negative symptoms, the improvements in PANSS-P and PANSS-N are noteworthy.

Safety results

The number (%) of patients in the group of patients and subgroups of patients switching to quetiapine SR due to insufficient efficacy and insufficient tolerability, respectively, who had at least 1 adverse event in any category is summarized in Table S3.

Table S3 Various categories of adverse events. All patients and patients switching due to insufficient efficacy and tolerability, respectively (safety/ITT population)

	All patients N=477	Insufficient efficacy N=315	Insufficient tolerability N=162
	n (%)	n (%)	n (%)
Adverse events	338 (70.9)	216 (68.6)	122 (75.3)
Serious adverse events	21 (4.4)	14 (4.4)	7 (4.3)
Serious adverse events leading to death	2 (0.4)	2 (0.6)	0

	All patients N=477	Insufficient efficacy N=315	Insufficient tolerability N=162
	n (%)	n (%)	n (%)
Serious adverse events not leading to death	19 (4.0)	12 (3.8)	7 (4.3)
Drug-related adverse events [a]	255 (53.5)	160 (50.8)	95 (58.6)
Adverse events leading to discontinuation	38 (8.0)	22 (7.0)	16 (9.9)
Other significant adverse events	0	0	0
Total number of adverse events			
Adverse events	922	530	392
Serious adverse events	26	17	9
Drug-related adverse events [a]	538	306	232
Other significant adverse events	0	0	0

a As judged by the investigator.
N Number of patients in group. n Number of patients. Percentages are based on the total number of patient per group.
Note: Patients with multiple events in the same category are counted only once in that category but for total number of AEs.

There were 922 adverse events reported during the study, with a higher proportion being reported by the insufficient efficacy subgroup. 388 patients (70.9%) reported at least one AE in any category. 255 (53.5%) experienced at least one AE that the investigator deemed drug related; however only 38 (8.0%) patients experienced an AE that led to discontinuation. 12 (4.4%) patients reported serious adverse events, and 2 others (0.4%) experienced an SAE that led to death, both of which were considered to be unrelated to treatment by the investigators. There were few DAEs and SAEs during the first week of treatment. Overall, the results were in line with the general AE profile of quetiapine. The incidence of the most common adverse events, summarised over the group of all patients switching to quetiapine SR and the subgroups of patients switching due to insufficient efficacy and insufficient tolerability, respectively, is shown in Table S4.

Table S4 Most common adverse events by preferred term in all patients and patients switching due to insufficient efficacy and tolerability, respectively (safety/ITT population)

	All patients N= 477	Insufficient efficacy N= 315	Insufficient tolerability N= 162
MedDRA Preferred term [a]	N (%)	N (%)	n (%)
SOMNOLENCE	85 (17.8)	58 (18.4)	27 (16.7)
SEDATION	72 (15.1)	37 (11.7)	35 (21.6)
DIZZINESS	67 (14.0)	34 (10.8)	33 (20.4)
DRY MOUTH	67 (14.0)	41 (13.0)	26 (16.0)

	All patients N= 477	Insufficient efficacy N= 315	Insufficient tolerability N= 162
CONSTIPATION	39 (8.2)	23 (7.3)	16 (9.9)
HEADACHE	27 (5.7)	11 (3.5)	16 (9.9)
INSOMNIA	24 (5.0)	15 (4.8)	9 (5.6)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
N Number of patients in treatment group. n Number of patients. Percentages are based on the total number of patient per group.
Note: Common adverse event: adverse events occurring at an incidence of ≥ 5% in any group.
Note: Sorted by descending frequency all patients.

The most common adverse events per preferred term were somnolence (17.8%) and sedation (15.1%), followed by dizziness (14.0%) and dry mouth (14.0%).
The incidence of adverse events association with EPS was low (8.0%). The most common AEs were: Tremor (13 patients, 2.7%), Akasthisa (9 patients, 1.9%), Extrapyrimidal disorder (7 patients, 1.5%) and Tardive dyskinesia (3 patients, 0.6%). This supports the results for SAS total score and BARS global score, both of which showed that most patients experienced improvement or no change for EPS symptoms during treatment. The LS mean changes for SAS and BARS were -2.04 (95% CI -2.28, -1.80) and -0.36 (95% CI -0.42, -0.30) respectively and were determined to be statistically significant by the Bonferroni-Holm method. Overall, these results concur with the declining number of patients using of anticholinergic medication during the study: from 20.8% to 9.1%.
The results for hematology and clinical chemistry (including glucose regulation, evaluation of neutropenia, thyroid function and lipids), ECG and vitals signs were in line with the general safety profile of quetiapine SR. Clinically important treatment emergent vital signs were infrequent, and the results show that the observed changes in orthostatitic and supine vital signs were wel tolerated, as shown by the low rate of adverse events and discontinuations related to vital signs There were no AEs associated with QT prolongation, no AEs associated with diabetes mellitus and no cases of agranulocytosis during the study. All of the patients experiencing clinically significant neutrofils values (≤1.5) normalized within 30 days. Overall, the results were in line with the general safety profile of quetiapine.