Drug product:	Quetiapine fumarate	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate		
Edition No.:	1.0		
Study code:	D1449L00004		
Date:	06 November 2008		

SCORE

An open, randomised, parallel, three treatment groups, multicentre, phase IV study - in real life - to compare the change in social outcome of quetiapine fumarate (Seroquel®) combined with Cognitive Remediation Therapy to conventional treatment in patients

Study centre(s)

This study was conducted in Sweden with 15 centres.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	29 August, 2005	Therapeutic use (IV)
Last patient completed	11 December, 2007	

Objectives

Primary:

The primary objective of this study was to compare efficacy of quetiapine fumarate (hereafter called quetiapine) combined with Cognitive Remediation Therapy (CRT) to conventional

treatment by evaluating change in social outcome, from baseline (visit 1) to the end of CRT (visit 3), in patients with schizophrenia, assessed by Strauss-Carpenter scale.

In this study conventional treatment was defined as antipsychotic medication according to ATC code N05A (with the exception of quetiapine and clozapine) not listed under prohibited medications (Table 3) i.e. chlorpromazine, levomepromazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, haloperidol, melperone, ziprasidone, flupenthixol, chlorprothixene, zuclopenthixol, olanzapine, lithium, risperidone, and aripiprazole.

Secondary:

The secondary objectives of this study were:

1. to compare efficacy of quetiapine combined with CRT to conventional treatment by evaluating change in social outcome in patients with schizophrenia assessed by Strauss-Carpenter scale, from baseline to last visit (visit 4).

The following objectives were analysed by comparing the change from baseline to end of CRT and from baseline to last visit:

2. to compare change in patient's overall clinical status when using quetiapine combined with CRT to conventional treatment assessed by Positive and Negative Syndrome Scale (PANSS).

3. to compare change in Quality of Life of quetiapine combined with CRT to conventional treatment assessed by the Short-form 36-health survey (SF-36) and Drug Attitude Inventory (DAI-10).

4. to compare change in cognition when using quetiapine combined with CRT to conventional treatment assessed by Wechsler Adult Intelligence Scale – Third Edition (WAIS-III), Wisconsin Card Sorting Test (WCST), Tower of London, Controlled Word Association Test, Auditory Verbal Learning Test (AVLT), Benton Visual Retention Test (Benton), Complex Figure Test (CFT) and Motor Speed and Perceptual functioning, hereafter mentioned as Cognitive Battery of Tests.

5. to compare the safety parameter of quetiapine combined with CRT to conventional treatment by evaluating
   - the Simpson-Angus Scale.
   - the Barnes Akathisia Rating Scale (BARS).
   - vital signs including clinical chemistry, only change from baseline to the last visit.
   - weight and body mass index (BMI), only change from baseline to the last visit.

The following objectives were analysed by comparing the change from baseline to visit 2.

6. to compare quetiapine to conventional treatment assessed by the change in PANSS, SF-36, DAI-10, Simpson-Angus Scale and BARS.

Tertiary:

The tertiary objectives of this study were to evaluate change in social outcome, change in patient's overall clinical status, change in Quality of Life, change in cognition and change in safety parameter by comparing all three treatments from baseline to the end of CRT and from baseline to the last visit.

Study design

This was a 50-week, open, multicentre, randomised, parallel study with three treatment groups. Patients with a clinical diagnosis of schizophrenia or schizoaffective disorder were randomised to either an individualised clinically effective dose of quetiapine combined with CRT or continued conventional treatment or continued conventional treatment combined with CRT.

The aim was to evaluate the efficacy of quetiapine combined with CRT compared to conventional treatment.

As a feauture of the study design the patients entering the quetiapine+CRT group had to switch treatment from the medication they have been stabilised on to quetiapine, applying a titration schedule. All other patients should continue the treatment that they were adjusted to. For the two treatment groups with conventional treatment there was no restricted or prohibited antipsychotic medication with the exception for clozapine and quetiapine. Dose and compound could be changed during the study in accordance of the investigator´s judgment of the patient´s medical needs.

Target patient population and sample size

Male or female patients, 18 to 64 years, with a documented clinical diagnosis of schizophrenia or schizoaffective disorder for at least 2 years, as defined by Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria. Patients were to be in stable condition and in an out-patient setting treated with antipsychotic agent(s).

The number of patients to be evaluated in the study should be at least 51 patients in the three treatments groups having fulfilled the Strauss-Carpenter scale from baseline to the end of the CRT giving the specified power. During the study it was observed that the discontinuation rate was higher in one of the treatment groups. To keep the desired power of the study it was necessary to continue the recruitment until 80 patients were randomised.

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

Patients randomised to treatment with quetiapine were switched from conventional antipsychotics. Quetiapine was administered twice daily and the target dose was 500-750 mg/day. Titration was at the clinicians discretion based on their clinical judgement of efficacy and tolerance on an individual patient basis.

Patients randomised to conventional treatment or conventional treatment with CRT continued with their medication as usual with no restrictions other than usage of quetiapine and clozapine was not allowed.

Duration of treatment

The treatment with quetiapine started (Day 1) with a cross-titration period where ongoing oral antipsychotic medication was phased out and quetiapine was phased in. For a brief period, patients took two medications; the duration of this cross-taper has varied according to individual circumstances. Quetiapine should preferably have been titrated to 600 mg/day within 5-7 days. The 10-week titration and stabilisation period was followed by a 40-week treatment period. During this period dosage could be adjusted for therapeutic efficacy and/or tolerability at every visit or at extra visits when needed throughout the study. The treatment phase with quetiapine has lasted 50 weeks in total.

Patients randomised to conventional treatment continued with their own antipsychotic medication from study start (Day 1) until the end of the study and the treatment phase lasted for 50 weeks.

Criteria for evaluation (main variables)

To evaluate the efficacy of quetiapine combined with CRT compared to conventional treatment, following scales have been used:

The Strauss Carpenter (Strauss J.S. et al 1972) is a clear scale measures the following items outcome: time in hospital, employment, social contacts and psychotic symptoms. PANSS is a 30-item scale measuring schizophrenic symptomatology, where each symptom is rated on a severity of symptoms ranging from 1-7.

A number of tests investigating the cognition and defined as Cognitive Battery of Tests.

Instruments for evaluation of Quality of Life , SF36 and DAI10 (Drug Attitude Inventory), a self-report inventory that focuses on the subjective effect of antipsychotic medications in patients with schizophrenia

Instruments for evaluation of extrapyramidala symptoms: The Barnes Akathisia Rating Scale (BARS) that measures akathisia and the Simpson-Angus Scale (SAS) that measures parkinsonian symptoms.

Efficacy

Primary variable: Social outcome measured by Strauss-Carpenter scale, change from baseline to end of CRT.

Secondary variables: Change in Strauss-Carpenter scale from baseline to last visit. Change in PANSS total score from baseline to visit 2, from baseline to end of CRT and from baseline to last visit. Change in PANSS positive, negative and general psychopathology subscales from

baseline to visit 2, from baseline to end of CRT and from baseline to last visit. Change in the Cognitive Battery of Tests from baseline to end of CRT and from baseline to last visit.

Tertiary variables: Change in Strauss-Carpenter scale, PANSS total score, PANSS positive, negative and general psychopathology subscales and the Cognitive Battery of Tests from baseline to end of CRT and from baseline to last visit.

Patient reported outcomes (PROs)

Change in SF-36 and DAI-10 from baseline to visit 2, from baseline to end of CRT and from baseline to last visit.

Safety

Changes in Simpson-Angus scale and Barnes Akathisia Rating scale from baseline to visit 2, from baseline to end of CRT and from baseline to last visit.

Changes in vital signs including clinical chemistry, weight and body mass index (BMI) from baseline to last visit.

Incidence rate of Serious Adverse Event and Discontinuation due to Adverse Event.

Statistical methods

The efficacy analysis was done for the PP population and the safety analysis for the safety population. The primary variable was also analysed for the ITT population from baseline to visit 3, and this analysis was a robustness analysis and conclusions were drawn from the PP population. The primary and secondary variables were tested by an analysis of covariance model with treatment and centre as factors and baseline value as covariate. Nominal p-values were calculated through out the study.

Patient population

The randomised study population comprised 80 patients enrolled from 15 centers. Of the 80 patients 28 were randomised to quetiapine combined with CRT, 24 to conventional treatment and 28 to conventional treatment combined with CRT.

Of the 80 patients assigned to treatment and included in the safety analysis none patients were excluded from the ITT population. Two PP population was established. In total 66 patients were included in the PP1 analysis and 61 in the PP2 analysis. The PP1 population was used after 25 weeks and the PP2 population was used after 50 weeks.

The efficacy analysis has been done for the PP1 population and was selected as the primary analysis set due to the requirement of the CRT training, so consequently the demographic- and baseline disease characteristics were accounted for the PP1 population.

Approximately 74% of patients completed the study, with higher rates of completion in the two groups with conventional treatment. Discontinuations due to adverse event were observed in 12 patients in the quetiapine+CRT group.

All patients were clinically stable, at least during the 4 weeks prior to entering the study in accordance with inclusion criteria no 4. It is of general medical knowledge that switching stabilised patients who have responded to treatment from one medication to another might cause prematurely discontinuation. In clinical practice switching of antipsychotics is recommended mainly due to lack of efficacy or if tolerability problems occurs. However, the discontinuation rate in the quetiapine+CRT group was considered consistent with what has been described in the literature in this type of patients (Kemmler G. et al 2005).

In the two groups who continued with their pre-study treatment, there was a low discontinuation rate during the study and no patient discontinued due to adverse event. This remarkable low rate of discontinuation is interpreted as a consequence of that only patients tolerating and demonstrating clinical response and stabilisation on previous medication were allowed to be randomised, and they were then kept on the same treatment during the randomised part of the study in these two treatment groups.

Another important confounder is that 15 of 48 patients who continued with the same treatment were actually treated with depot antipsychotic injections during the study, which might have had improved adherence in these groups. It should also be remembered that this was an open label study. Both the investigator and the patient were aware of potential the changes from the previous treatment to quetiapine. This should be taken in consideration when evaluating the difference in discontinuation rate.

The treatment groups were well balanced in demographic and baseline characteristics; there were slightly more female patients in the conventional+CRT group.

Table S1 Patient disposition

	Quetiapine + CRT (N=28)	**Conventional treatment (N=24)**	**Conventional treatment + CRT (N=28)**	**Total (N=80)**
Number of patients enrolled				85
Number of patients randomised	28	24	28	80
Number of patients in Full Analysis Set (ITT)	28	24	28	80
Number of patients in Per Protocol Analysis (PP1)	18	23	25	66
Number of patients in Per Protocol Analysis (PP2)	15	21	25	61
Number (%) of patients who discontinued during the study (ITT)	15 (53.6%)	3 (12.5%)	3 (10.7%)	21 (26.3%)

Table S1 Patient disposition

	Quetiapine + CRT (N=28)	Conventional treatment (N=24)	Conventional treatment + CRT (N=28)	Total (N=80)
Reasons for discontinuation (ITT) : n (%)				
Severe non-compliance to CSP	1 (3.6%)	0 (0%)	0 (0%)	1 (1.3%)
Adverse event	12 (42.9%)	0 (0%)	0 (0%)	12 (15%)
Patient not willing to continue study	2 (7.1%)	1 (4.2%)	2 (7.1%)	5 (6.3%)
Patient lost to follow-up	0 (0%)	1 (4.2%)	1 (3.6%)	2 (2.5%)
Other reason	0 (0%)	1 (4.2%)	0 (0%)	1 (1.3%)
Number (%) of patients who completed the study (ITT)	13 (46.4%)	21 (87.5%)	25 (89.3%)	59 (73.8%)

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Table S2 Demographic and baseline characteristics, ITT

	Quetiapine + CRT (N=28)	Conventional treatment (N=24)	Conventional treatment + CRT (N=28)	Total (N=80)
Sex (n and % of patients)				
Male	20 (71.4%)	16 (66.7%)	15 (53.6%)	51 (63.8%)
Female	8 (28.6%)	8 (33.3%)	13 (46.4%)	29 (36.3%)
Age (years)				
Mean (SD)	44.4 (9.7)	45.1 (8.6)	39.7 (7.9)	42.9 (9.0)
Range	25 , 63	21 , 54	23 , 52	21 , 63
Race (n and % of patients)				
Caucasian	28 (100%)	22 (91.7%)	27 (96.4%)	77 (96.3%)
Black	0 (0%)	1 (4.2%)	1 (3.6%)	2 (2.5%)
Oriental	0 (0%)	1 (4.2%)	0 (0%)	1 (1.3%)
Weight (kg)				
Mean (SD)	89.7 (13.9)	91.4 (17.1)	85.7 (19.4)	88.8 (16.9)
Range	65 , 127	64 , 127	50 , 138	50 , 138
Height (cm)				
Mean (SD)	173.9 (9.4)	174.5 (11.2)	173.5 (10.2)	173.9 (10.1)
Range	150 , 192	151 , 189	149 , 190	149 , 192
BMI				
Mean (SD)	29.90 (5.64)	30.10 (5.35)	28.16 (4.20)	29.33 (5.09)
Range	21.0 , 44.1	21.8 , 44.1	19.5 , 38.2	19.5 , 44.1

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Efficacy results

Analysis of the primary variable, the change in social outcome assessed by Strauss Carpenter scale, from baseline to the end of CRT (visit 3) showed no statistically significant differences in quetiapine combined with CRT compared to conventional treatment. The statistical null hypothesis for the study that the treatments are similar can not be rejected.

The secondary objective to compare the overall clinical status measured by PANSS showed a significant advantage for quetiapine combined with CRT versus the conventional treatment in PANSS total, PANSS negative and PANSS General psychpathology subscales.

The overall result of the Cognitive Battery of Tests showed that quetiapine combined with CRT compared with conventional treatment was significant better on a large number of scales, especially WAIS III verbal IQ, verbal comprehension, working memory and that many scales had large improvements versus baseline for quetiapine combined with CRT.

The secondary objective to compare the change in Quality of Life of quetiapine combined with CRT to conventional treatment measured by SF-36 and DAI-10 measuring the patient´s attitude towards their medication, showed no significant differences between the treatments and compared to baseline.

Safety results

The study treatments were well tolerated and no unexpected safety findings were identified in this study. Only SAE and DAE were collected.

Six (6) patients in the group with quetiapine+CRT experienced serious adverse events compared to 4 in conventional treatment and 2 in conventional+CRT.

No death was reported in the study.

The mean value for the laboratory data at baseline and through the study were comparable between the three treatment groups.

The mean changes in pulse, blood pressure were small and comparable between treatment groups. Changes in physical findings were minor. The body weight and BMI increased in the both groups with conventional treatment and was constant in quetiapine+CRT, but there were no statistically significant differences.

Mean SAS and BARS total score at baseline shows a low incidence of EPS symptoms. Both scales shows a minor tendency of improvement for all three treatments from baseline to end of study but no differences between the groups.

In this study 12 patients were discontinued due to an adverse event, all in the quetiapine+CRT group. The majority of them had AE terms reported indicating worsening of the disease, rather than tolerability or safety concerns. Only 4 of these 12 patients were treated within the targeted dose range of 500-750 mg/day, as stated in the study protocol, at the time of onset of

the adverse event that later lead to discontinuation. Five of these patients were therefore considered to have been treated with subtherapeutic doses (300-400mg/day) while 3 had a too high dose (800-1000mg/day). Six of the 12 patients who discontinued their quetiapine treatment did that during the 10 weeks between visit 1 and visit 2, before the CRT treatment started.

Table S3 Various categories of adverse events (Safety analysis set)

	Quetiapine + CRT (N=28)	Conventional treatment (N=24)	Conventional treatment + CRT (N=28)	Total (N=80)
Patient with SAEs	6 (21.4%)	4 (16.7%)	2 (7.1%)	12 (15%)
Patient with SAEs leading to death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Patient with SAEs not leading to death	6 (21.4%)	4 (16.7%)	2 (7.1%)	12 (15%)
Total number of SAEs	10	4	2	16
Patient with DAEs	12 (42.9%)	0 (0%)	0 (0%)	12 (15%)

Patients with multiple events in the same category are counted only once in that category.
Patients with events in more than one category are counted once in each of those categories.
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Table S4 Number (%) of patients who had at least one SAE by preferred term (Safety analysis set)

	Quetiapine + CRT (N=28)	Conventional treatment (N=24)	Conventional treatment + CRT (N=28)	Total (N=80)
Psychotic disorder	4 (14.3%)	1 (4.2%)	1 (3.6%)	6 (7.5%)
Agitation	1 (3.6%)	0 (0%)	0 (0%)	1 (1.3%)
Anxiety	1 (3.6%)	0 (0%)	0 (0%)	1 (1.3%)
Delusion	1 (3.6%)	0 (0%)	0 (0%)	1 (1.3%)
Depression	0 (0%)	0 (0%)	1 (3.6%)	1 (1.3%)
Pyothorax	0 (0%)	1 (4.2%)	0 (0%)	1 (1.3%)
Schizophrenia	1 (3.6%)	0 (0%)	0 (0%)	1 (1.3%)
Poisoning	0 (0%)	1 (4.2%)	0 (0%)	1 (1.3%)
Social problem	0 (0%)	1 (4.2%)	0 (0%)	1 (1.3%)

Number (%) of patients who had at least one SAE for a preferred term, sorted by decreasing order of frequency as summarised over all treatment groups
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