Drug product:	Seroquel	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate		
Study code:	D1449C00009		
Date:	01 November 2008		

An open-label, non-comparative, multi-centre, phase II prospective trial to assess the efficacy of Quetiapine fumarate augmentation of selective serotonin reuptake inhibitors (SSRIs) or selective noradrenalin reuptake inhibitors (SNRIs) in SNRI-or SSRI-resistant major depressive disorder

Study centre(s)

A total of 5 centres in Belgium participated in this study.

Study dates		**Phase of development**
First patient enrolled	1 March 2006	Therapeutic exploratory (II)
Last patient completed	23-November-2007	

Objectives

The primary objective was to assess the efficacy of Quetiapine fumarate augmentation on the overall depression status of patients with major depressive disorder who didn't respond to at least one acute treatment with a SSRI or SNRI.

Study design

This was a 4-week, open-label, non-comparative, multi centre, phase II prospective study. Approximately 40 patients were planned to be enrolled over 10 months in order to reach a total of 30 evaluable patients. The treatment phase lasted for 4 weeks.

The primary objective was to assess the efficacy of Quetiapine fumarate augmentation on the overall depression status of patients with major depressive disorder who didn't respond to at least one acute treatment with a SSRI or SNRI

Non-responders were defined as having a MADRS score ≥ 25 after this(those) initial treatment(s).

Included patients were treated during 4 weeks with Quetiapine fumarate (Quetiapine titration to target dose of 300 mg).

Benzodiazepines (BZD), used at low to moderate doses as hypnotics or sedatives during the initial treatment, were permitted during the augmentation treatment with Quetiapine fumarate on condition that the dose didn't changed.

Target patient population and sample size

Male and female patients, aged between 18 and 65 with a major depressive disorder not responding to at least one acute treatment with a SSRI or SNRI and naïve to any atypical antipsychotic was considered for entry into the study.

Investigator(s) had to keep a record of patients who were considered for enrolment but were never enrolled e.g., subject screening log. This information was necessary to establish that the patient population was selected without bias.

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

The investigational product used in this trial was Quetiapine fumarate (Seroquel®). The investigational product was manufactured, labelled and supplied to the investigator by AstraZeneca. The investigational product was supplied as tablets of 100 mg and 200 mg for oral use. The Quetiapine fumarate 100 mg were yellow round tablets and the Quetiapine fumarate 200 mg white round tablets. Commercial packs were used containing 60 tablets of Quetiapine fumarate 100 mg or 200 mg. The tablets were packed in white PVC/aluminium foil blisters of 10 tablets each.

Commercial packs of Quetiapine fumarate 100 and 200 mg were delivered to the investigators who delivered 1 pack of each to each participating patient to last throughout the 4-week-treatment period. Patients were provided with Pilomats® to be able to divide the tablets if needed.

Details of investigational product and any other study treatments

Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number[a]
100 mg PO	AstraZeneca	624 S 310 F3	05A01 and O6E03
200 mg PO		624 S 311 F3	05A03 and 06J01

Duration of treatment

The treatment period lasted for 4 weeks.

Criteria for evaluation (main variables)

Efficacy

Primary variable

- MADRS

Secondary variables

- Number and type of AEs
- BPRS
- SDS
- CGI
- UKU-SERS

Statistical methods

This pilot study was exploratory and was not powered to address any pre-defined hypothesis. Formal statistical testing was thus an exception, and focus was instead on descriptive statistics and estimation if appropriate.

All data collected in the study were appropriately summarized using tabulations, graphs and summary statistics (including 95% confidence intervals for means and frequencies)

Patient population

Table S1 Patient population and disposition

Population			
N (N planned)		39	(30)
Demographic characteristics			
Sex (n and % of patients)	Male	14	(36.0%)
	Female	25	(64.0%)
Age (years)	Mean	39.5	
	Range	21 to 63	
Race (n and % of patients)	Caucasian	38	(97%)
	Black	1	(03%)
	Oriental	0	
	Other	0	

Baseline characteristics

History of first know depressed episode	7.6 years
History of most recent episode over past year	23.4 weeks
Total number of depressed episodes over life	2.1
MADRS total score	35.2
CGI severity of illness	5
BPRS total score	45.6

Efficacy results

Mean score reduction at the end of the study from baseline in the MADRS score was 16.9 (12.8 – 21.0). Test of wilcoxon gives a $p<0.0001$.

Response as defined as a reduction in MADRS total score greater or equal than 50 % was observed in 45.9% of the 37 patients completing at least 2 weeks of the study.

37.8% of the 37 patients completing at least 2 weeks of the study were considered in remission e.g. MADRS total score ≤ 12 at visit 5 (using last valid value for patients discontinuing study before visit 5).

Mean score reduction at the end of the study from baseline in the CGI score was 1.94 (1.52 – 2.37).

Mean score reduction at the end of the study from baseline in the BPRS score was10.3 (6.7 – 13.6).

Mean score reduction at the end of the study from baseline in the SDS score was 8.5 (5.6 – 11.5).

All secondary variables described above gave statistical significance with a wilcoxon test.

All total score decreased significantly over time during the study (Friedman test P-value < 0.0001).

Tables below give the global assessment of the interference by existing side effects with the patient's daily performance as assessed by the patient and by the doctor.

Table S2 UKU-side effect global assessment of the interference with the patient's daily performance

	Assessed by Patient	Doctor
No side effects	11 (34.4%)	12 (38.7%)
Mild Side effects that do not interfere with the patients performance	18 (56.3%)	15 (48.4%)
Side effects that interfere moderately with the patients performance	3 (9.4%)	4 (12.9%)

Dose reduction was applied for 34.3% of patients.

Safety results

No serious adverse events were reported. Three patients discontinued treatment due to an AE.

Table S3 Adverse events which led to discontinuation of treatment (safety analysis set)

Adverse event (preferred term)	n
Sedation	1
Orthostatic Diziness	1
Somnolence	1