AstraZeneca

Drug product:	Seroquel	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate		
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Quetiapine Augmentation In Treatment-Resistant Depression – An Open Pilot Study

Chief investigator

[redacted]

Study centre(s)

This study was conducted at 2 research sites in Manchester, United Kingdom. It was planned to recruit between 30 and 40 patients.

Publications

There were no publications based on this study prior to the date of the report.

Study dates		**Phase of development**
First patient enrolled	31 January 2006	Therapeutic confirmatory (IIIb)
Last patient completed	25 July 2007	

Objectives

The overall objectives of this study were to determine the efficacy, safety and tolerability of add-on quetiapine in patients with depression who had failed to respond to an adequate trial of 2 antidepressants and were currently taking a monoamine reuptake inhibitor [selective serotonin reuptake inhibitor (SSRI), noradrenaline reuptake inhibitor (NARI), or serotonin and noradrenaline reuptake inhibitor (SNRI)].

The primary objective of this study was to determine the efficacy of quetiapine in the treatment of depression at 8 weeks and was assessed by calculation of the proportion of patients responding by week 8, derived from the change in Montgomery Asberg Depression Rating Scale (MADRS) score from baseline to week 8.

Response was defined as a reduction of ≥50% in MADRS score at assessment.

Secondary objectives of the study were:

1. To assess the change in MADRS score

2. To assess the proportion of patients achieving remission, defined as MADRS score ≤12

3. To obtain preliminary data on the speed of onset of antidepressant action with assessments at weeks 1 and 2

4. To determine the effect of quetiapine on anxiety associated with depression

5. To assess if predefined variables predict response to quetiapine (anxiety, insomnia, depression and treatment resistance)

6. To assess safety and tolerability by measuring frequency and severity of adverse events, random plasma glucose, serum prolactin, routine haematology and biochemistry, vital signs and weight.

Study design

This was an open label, pilot study of the efficacy, safety and tolerability of quetiapine add-on therapy, in patients with treatment-resistant depression.

Target patient population and sample size

Male and female patients aged 18 years and over were recruited from referrals to the Specialist Service for Affective Disorders (SSAD), a tertiary clinic serving Greater Manchester, or were under psychiatric care in Greater Manchester. Patients had current DSM-IV Major Depressive Episode resistant to at least 2 adequate trials of medication and were taking a monoamine reuptake inhibitor (SSRI, NARI or SNRI).

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

Quetiapine tablets, for oral administration, were dose-titrated over a period of 14 days, aiming for a target dose of 150 mg bd by day 14. Titration to the target dose was at the discretion of the investigator based on their clinical judgement of tolerability on an individual patient basis.

Day 1-2: 50 mg nocte

Day 3-4: 50 mg bd

Day 5-7: 50 mg mane, 100 mg nocte

Day 8-9: 100 mg mane, 100 mg nocte

Day 10-11: 100 mg mane, 150 mg nocte

Day 12-14: 150 mg mane, 150 mg nocte

From day 14 onwards, the target dose for all patients was 150 mg bd. However a maximum dose of up to 300 mg bd could be administered at the discretion of the investigator based upon response and tolerability. All tablets used were DHP [redacted]

Duration of treatment

The duration of study treatment was 8 weeks, or 26 weeks in patients showing clinical benefit after 8 weeks of treatment.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable:
  - Number (%) of patients demonstrating a MADRS response (MADRS ≥50% decrease from baseline) at 8 weeks
- Secondary variables:
  - Change in MADRS score from baseline to 1, 2, 4, 8 and 26 weeks
  - Percentage change in MADRS score from baseline to 1, 2, 4, 8 and 26 weeks
  - Number (%) of patients demonstrating a MADRS response (≥50% decrease from baseline) at 1, 2, 4 and 26 weeks
  - Number (%) of patients achieving a MADRS remission (MADRS ≤12) at 1, 2, 4, 8 and 26 weeks
  - Number (%) of patients with Clinical Global Impression-Improvement (CGI-I) rating of 1 + 2 (very much improved + much improved) at 1, 2, 4, 8 and 26 weeks
  - Change in Clinical Global Impression-Severity (CGI-S) from baseline to 1, 2, 4, 8 and 26 weeks
  - Change in anxiety score in Clinical Anxiety Scale (CAS) from baseline to 1, 2, 4, 8 and 26 weeks
  - Change in panic attack score in CAS from baseline to 1, 2, 4, 8 and 26 weeks
  - Change in Global Assessment of Functioning (GAF) from baseline to 1, 4, 8 and 26 weeks

- Predictors of response to quetiapine: anxiety, insomnia, depression and time since onset of most recent depressed episode.

Patient reported outcomes (PROs)

- Secondary variables:
  - Change in weighted score of EuroQol-5D (EQ-5D) quality of life scale from baseline to 8 and 26 weeks
  - Change in visual analogue scale (VAS) score of EQ-5D from baseline to 8 and 26 weeks
  - Change in anxiety [A] subscore in Hospital Anxiety and Depression (HAD) scale from baseline to 1, 2, 4, 8 and 26 weeks
  - Change in depression [D+] subscore in augmented HAD scale (7 standard items + 4 additional questions) from baseline to 1, 2, 4, 8 and 26 weeks
  - Change in mental component score in Short Form 36 (SF-36) patient functioning questionnaire from baseline to 8 and 26 weeks
  - Change in physical component score in SF-36 patient functioning questionnaire from baseline to 8 and 26 weeks.

Safety

- Secondary variables:
  - Frequency and severity of adverse events (AEs) including AEs of specific interest ie, AEs associated with extra pyramidal side effects (EPS), diabetes, neutropenia and agranulocytosis, suicidality, somnolence, nausea and vomiting
  - Haematology and clinical chemistry (including random plasma glucose and serum prolactin) at baseline, 8 and 26 weeks
  - Change in random glucose from baseline to 8 weeks and 26 weeks
  - Number (%) of patients with clinically important laboratory values
  - Vital signs at baseline, 8 and 26 weeks
  - Change in weight from baseline to 8 and 26 weeks, overall and according to the patients' baseline BMI
  - Number (%) of patients with a clinically important change in weight (an increase or decrease of ≥7% from baseline) at 8 and 26 weeks.

Statistical methods

The main data analyses were based on an intention to treat (ITT) population, which included all patients who took at least one dose of investigational product and had at least 1 assessment of efficacy after enrolment. A last-observation carried forward (LOCF) approach was applied to all efficacy analyses, but a completer analysis was also performed on the primary variable. For discrete outcomes, the relative proportions of patients with outcomes at analysis point have been summarised, together with 95% confidence intervals. For continuous measures, the changes over time were analysed by a paired t-test. Logistic regression analysis was used to analyse predictors of response to quetiapine.

Patient population

The patient population and disposition are shown in Table S1. A total of 24 patients were enrolled into the study and entered the acute 8-week treatment phase to receive add-on treatment with quetiapine. Eighteen patients completed the treatment phase. Eleven of the 18 patients who completed the treatment phase showed clinical benefit at the end of the 8 weeks and entered the extension phase. All 11 patients completed the 26-week extension phase.

Table S1 Patient population and disposition

		Number(%) of patients	
Population			
Number enrolled		24	
Number entered in treatment phase		24	(100)
Disposition			
Number (%) of patients who	discontinued treatment phase	6	(25.0)
	completed treatment phase	18	(75.0)
	entered extension phase	11	(45.8)
	discontinued extension phase	0	
	completed extension phase	11	(45.8)
Analysis sets			
Number (%) of patients:	analysed for safety [a]	24	(100)
	analysed for efficacy (Intention to treat, ITT)	24	(100)
	analysed for efficacy (clinical benefit)	11	(45.8)

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing

The patient demographic and baseline characteristics are summarised in Table S2. The 24 patients (9 males and 15 females) had a mean age of 46 years (range 25 to 62 years). The patients were experiencing residual depressive symptoms (mean MADRS score of 28.1, range

20 to 38) and their baseline CGI-S score was 4.3 (moderately ill). Twenty-two of the 24 patients were treated with a SSRI, NARI or SNRI and 2 patients were treated with a tricyclic antidepressant.

Table S2 Demographic and baseline characteristics

		ITT analysis set (n=24)	
Demographic characteristics			
Sex (number and % of patients)	Male	[redacted]	[redacted]
	Female	[redacted]	[redacted]
Age (years)	Mean (SD)	46.3	(11.0)
	Range	25 to 62	
Race (number and % of patients)	Caucasian	22	(91.7%)
	[redacted]	[redacted]	[redacted]
Weight (kg) [a]	Mean (SD)	82.5	(18.2)
	Range	43 to 121	
Baseline disease characteristics			
Time since onset of most recent depressed episode (months) [a]	Mean (SD)	22.3	(29.2)
Time since first known depressed episode (years)	Mean (SD)	13.4	(10.0)
MADRS	Mean (SD)	28.1	(5.7)
CGI-S	Mean (SD)	4.3	(0.8)
Antidepressant treatment (number and % of patients)			
Treated with SSRI, NARI or SSRI		22	(91.7%)
Treated with other monoamine reuptake inhibitor [b]		2	(8.3%)

[a] N=23
[b] Tricyclic antidepressant

Efficacy and patient reported outcome (PRO) results - Treatment Phase

The efficacy and patient reported outcome results for the treatment phase at 8 weeks are summarised in Table S3 and Table S4.

Seven (29%) patients showed a MADRS response at 8 weeks (ie, had at least a 50% improvement from baseline in MADRS total score), which was the primary variable (Table S3). Four (17%) patients achieved remission at 8 weeks (ie, MADRS total score ≤12) and 13 (54%) patients had a CGI-I response of very much improved or much improved.

Table S3 Number (%) patients with MADRS response, MADRS remission and CGI-I rating at 8 weeks, ITT analysis set

Outcome variable	Number (%) of patients	95% CI
MADRS response [a]	7 (29.2)	(11.0, 47.4)
MADRS remission [b]	4 (16.7)	(1.8, 31.6)
CGI-I rating [c]	13 (54.2)	(34.2, 74.1)

[a] MADRS response = proportion of patients with ≥50% reduction from baseline in MADRS total score.
[b] MADRS remission = proportion of patients with a MADRS total score ≤12.
[c] CGI-I: Clinical Global Impression-Improvement rating of very much / much improved

The percentage improvement of 32% (9.0 in absolute score) in MADRS score from baseline to 8 weeks was statistically significant (p<0.0001). Statistically significant improvements from baseline were also observed in CGI-S, CAS (anxiety and panic attack scores), GAF, HAD anxiety and depression [D+] scores, and EQ-5D weighted and visual analogue scores after 8 weeks of treatment. Numerical improvements in SF-36 mental and physical component scores were shown after 8 weeks treatment.

Table S4 Analyses of change in efficacy and PRO variables from baseline to 8 weeks, ITT analysis set

Outcome variable	Baseline Mean (SD)	Change from baseline to 8 weeks Mean (SD)	95% CI of change	p-value
Efficacy				
MADRS total score (absolute)	28.1 (5.7)	-9.0 (6.9)	(-11.9, -6.1)	<0.0001
MADRS total score (percentage)	28.1 (5.7)	-32.0 (22.5)	(-41.5, -22.5)	<0.0001
CGI-S score	4.3 (0.8)	-0.7 (0.9)	(-1.1, -0.3)	0.0017
CAS anxiety score	10.0 (3.0)	-2.7 (2.8)	(-3.9, -1.5)	0.0001
CAS panic attack score	1.4 (0.8)	-0.7 (1.0)	(-1.1, -0.2)	0.0036
GAF score	52.1 (6.2)	8.2 (8.2)	(4.7, 11.7)	0.0001
Patient reported outcomes				
EQ-5D (weighted score)	0.27 (0.30)	0.18 (0.27)	(0.05, 0.31)	0.0080
EQ-5D (VAS)	35.5 (20.4)	14.4 (15.2)	(7.1, 21.8)	0.0006
HAD anxiety [A] subscore	14.3 (4.3)	-2.9 (3.8)	(-4.5, -1.2)	0.0013
HAD depression [D+] subscore	23.3 (5.4)	-6.0 (7.0)	(-9.0, -3.0)	0.0005
SF-36 mental functioning score	22.6 (11.1)	4.2 (13.4)	(-2.1, 10.5)	0.1758
SF-36 physical functioning score	37.3 (14.9)	1.3 (9.4)	(-3.1, 5.7)	0.5575

CAS: Clinical Anxiety scale, CGI-S: Clinical Global Impression-Severity, EQ-5D EuroQol-5D: a European Quality of Life Health Questionnaire, GAF: Global assessment of functioning, HAD: Hospital anxiety and depression rating scale, ITT: Intention-to-treat, LOCF: Last observation carried forward, MADRS: Montgomery Asberg Depression Rating Scale, SF-36: Short form 36.

A reduction in depressive symptoms was evident after 1 to 2 weeks of add-on treatment with quetiapine. Statistically significant improvements in MADRS, CAS (anxiety and panic attack scores), GAF and HAD depression [D+] score were first observed after just 1 week of treatment, and in CGI-S and HAD anxiety score after 2 weeks treatment.

Efficacy and patient reported outcome (PRO) results - Extension Phase

The proportion of patients with a MADRS response, MADRS remission and CGI- I rating of much improved or very much improved at 26 weeks is presented in Table S5, with the 8 week data for the clinical benefit analysis set.

After 26 weeks of treatment, 4 (36.4%) of the 11 patients showed a MADRS response and 5 (45.5%) achieved remission (ie, MADRS total score ≤12). Eight (73%) patients had a CGI-I rating of very much improved or much improved at the end of the extension phase.

Table S5 Number (%) patients with MADRS response, MADRS remission and CGI-I rating at 8 and 26 weeks, Clinical benefit analysis set

	8 weeks (n=11)		26 weeks (n=11)	
Outcome variable	**Number (%) of patients**	**95% CI**	**Number (%) of patients**	**95% CI**
MADRS response [a]	5 (45.5%)	(16.0, 74.9)	4 (36.4%)	(7.9, 64.8)
MADRS remission [b]	3 (27.3%)	(1.0, 53.6)	5 (45.5%)	(16.0, 74.9)
CGI-I[c]	11 (100.0%)	(100.0, 100.0)	8 (72.7%)	(46.4, 99.0)

[a] MADRS response = proportion of patients with ≥50% reduction from baseline in MADRS total score.
[b] MADRS remission = proportion of patients with a MADRS total score ≤12.
[c] CGI-I: Clinical Global Impression-Improvement rating of very much / much improved

Statistically significant improvements from baseline were observed in MADRS score, CGI-S, CAS (anxiety and panic attack scores), GAF, HAD anxiety and depression [D+] scores, EQ-5D weighted and visual analogue scores, and SF-36 mental component scores after 26 weeks of treatment (Table S6).

Table S6 Analyses of change in efficacy and PRO variables from baseline to 26 weeks (LOCF, Clinical benefit analysis set)

Outcome variable	Baseline Mean (SD)	Change from baseline to 26 weeks Mean (SD)	95% CI	p-value
Efficacy				
MADRS total score (absolute)	27.5 (5.2)	-11.7 (5.3)	(-15.3, -8.1)	<0.0001
MADRS total score (percentage)	27.5 (5.2)	-42.4 (15.1)	(-52.5, -32.2)	<0.0001
CGI-S score	4.3 (0.6)	-1.2 (0.8)	(-1.7, -0.7)	0.0004
CAS anxiety score	10.4 (2.6)	-3.5 (3.7)	(-6.0, -1.0)	0.0117
CAS panic attack score	1.5 (0.5)	-1.3 (0.5)	(-1.6, -1.0)	<0.0001
GAF score	52.1 (6.4)	14.2 (5.9)	(10.2, 18.1)	<0.0001
Patient reported outcomes				
EQ-5D (weighted score)	0.19 (0.26)	0.34 (0.31)	(0.13, 0.54)	0.0045
EQ-5D (VAS)	33.7 (14.4)	19.5 (23.8)	(3.6, 35.5)	0.0215
HAD anxiety [A] subscore	15.9 (3.2)	-3.9 (2.7)	(-5.7, -2.1)	0.0007
HAD depression [D+] subscore	24.2 (3.7)	-8.8 (5.4)	(-12.5, -5.2)	0.0003
SF-36 mental functioning score	23.8 (10.9)	11.2 (10.6)	(3.0, 19.4)	0.0135
SF-36 physical functioning score	37.2 (16.6)	-1.2(10.6)	(-9.3, 7.0)	0.7496

CAS: Clinical Anxiety scale, CGI-S: Clinical Global Impression-Severity, EQ-5D EuroQol-5D: a European Quality of Life Health Questionnaire, GAF: Global assessment of functioning, HAD: Hospital anxiety and depression rating scale, ITT: Intention-to-treat, LOCF: Last observation carried forward, MADRS: Montgomery Asberg Depression Rating Scale, SF-36: Short form 36.

Safety results

The mean daily dose of quetiapine taken was 245.1 mg during the 8-week treatment phase (range 71 to 343 mg) and 346 mg (range 300 to 421 mg) during the 18-week extension phase. A summary of AEs in each category is shown in Table S7.

Quetiapine in addition to a SSRI, NARI or SNRI was generally well tolerated. There were no deaths during the study and the incidences of non-fatal SAEs (12.5%, 3/24 patients) and discontinuations due to AE were low (8.3%, 2/24 patients). Three patients each experienced a SAE during the study; [redacted] All were considered by the investigator to be unrelated to study drug treatment.

Drug-related AEs were common (87.5%, 21/24 patients). Sedation, dry mouth, dizziness and abnormal dreams were the most commonly reported preferred terms assessed as possibly related to quetiapine treatment. Most adverse events were of mild to moderate intensity.

Table S7 Number (%) of patients who had an adverse event in any category, safety analysis set

Category of adverse event	Number (%) patients who had an adverse event in each category [a] n=24
Any Adverse Event	23 (95.8)
Serious adverse events:	
Serious adverse events leading to death	0
Serious adverse events not leading to death	3 (12.5)
Discontinuation of study treatment due to adverse events	2 (8.3)
Causally related AEs	21 (87.5)
Causally related SAEs	0

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Adverse events associated with nervous system disorders, gastrointestinal disorders and psychiatric disorders predominated, with sedation, dry mouth, dizziness, headache and abnormal dreams the most commonly reported AEs (Table S8).

Table S8 Number (%) of patients with the most commonly reported treatment emergent adverse events, safety analysis set

Preferred Term	Number (%) of patients (N=24)
Sedation	13 (54.2)
Dry mouth	9 (37.5)
Dizziness	7 (29.2)
Headache	6 (25.0)
Abnormal dreams	5 (20.8)
Constipation	3 (12.5)
Dyspepsia	3 (12.5)
Hypotension	3 (12.5)
Orthostatic hypotension	3 (12.5)

[a] Most common adverse events with occurrence of 10% or more are given. Events are sorted by decreasing order of frequency.

The incidence of AEs potentially related to EPS was low (12.5%, 3/24 patients), and all AEs were mild in intensity. The incidence of AEs potentially related to somnolence was relatively high (58%, 14/24), but the AEs were mainly mild in intensity. Sedation of mild intensity and somnolence of severe intensity led to the discontinuation of study treatment for one patient.

Minor increases in mean ALT and random glucose concentrations were observed. One patient had a clinically important abnormal value of raised neutrophils and 2 patients had a clinically important abnormal random glucose. Median sitting pulse was higher at 8 weeks (78 bpm) and 26 weeks (86 bpm) than at baseline (72 bpm). There were no clinically important orthostatic changes in systolic or diastolic blood pressure. There were mean weight gains of 2.4 kg from baseline to 8 weeks and 4.5 kg from baseline to 26 weeks.

Conclusion(s)

- [redacted]

[redacted]

[redacted]

The conclusions related to the patient reported outcome variables assessed in this study are as follows:

- [redacted]

[redacted]

[redacted]

Date of the report

6 February 2008