AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Quetiapine XR
Study Code	D1443L00044
Edition Number	1
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A randomised, 6-week, multicentre, open-label, rater-blinded parallel group study comparing Quetiapine extended release monotherapy and augmentation with Lithium augmentation in patients with Treatment Resistant Depression

Study dates: First patient enrolled: 6 November 2008
Last patient completed: 17 August 2009

Phase of development: Therapeutic confirmatory IIIb

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centre(s)

The study was conducted in 12 countries in Europe. In the study 777 patients were enrolled and 688 ramdomized at 107 sites.

Publications

Montgomery et al., 2010

Stuart Montgomery, Liliana Dell'Osso, Siegfried Kasper, William Pitchot, Eva Dencker-Vansvik, Jürgen Köhler, Leif Jörgensen, Michael Bauer. Quetiapine XR or lithium combination with antidepressants in treatment-resistant depression.
Presented at the 18th European Congress of Psychiatry, Munich, Germany, 27 February-2 March, 2010.

Bauer et al., 2010

Michael Bauer, Liliana Dell'Osso, Siegfried Kasper, William Pitchot, Eva Dencker-Vansvik, Jürgen Köhler, Leif Jörgensen, Stuart Montgomery. Quetiapine XR monotherapy, quetiapine XR + ongoing antidepressants and lithium + ongoing antidepressants in patients with treatment-resistant major depressive disorder**.**
Presented at the XXVII Annual Meeting of the International College of Neuropsychopharmacology (CINP), Hong. Kong, 6-10 June, 2010.

Objectives

The primary objective of the study was to evaluate the efficacy of quetiapine XR monotherapy and add-on quetiapine XR treatment versus add-on lithium in patients with TRD.

As an independent objective, the primary objective was evaluated in two subgroups of patients: (1) patients resistant to one previous antidepressant therapy and (2) patients resistant to two previous antidepressant therapies.

The efficacy variable was the change in depressive symptoms between randomisation and week 6 as measured by the MADRS.

The secondary objective of the study was to compare the efficacy of the three different treatment regimens as assessed by the changes from randomisation (visit 2) to week 6 (end of study) in the variables below. These analyses were also performed in the subgroup of patients with 1 and 2 previous antidepressant treatment failures. Additionally the time to onset of therapeutic effect was evaluated by assessing efficacy data after four days of treatment (Day 4) and after one week of treatment (Day 8).

1. MADRS: proportion of patients with remission at end of study (week 6), i.e., MADRS ≤ 10 (in addition, cut-off scores of ≤ 8 and ≤ 12 were also analysed)

2. Response rate, where response was defined as the proportion of patients with $\geq 50\%$ reduction in the MADRS total score at end of study (Visit 6, week 6) compared to randomisation (Visit 2)

3. Clinical Global Impression improvement item 2 (CGI-I) responder, i.e., proportion of patients who improved "very much" or "much" at week 6

4. Change in CGI severity of illness item 1 (CGI-S) from randomisation to end of study as well as values at week 6 and frequency distribution of categories in CGI items 2 and 3

5. Change in the Beck Depression Inventory (BDI) (self-rating) from randomisation to end of study

6. Change in Pain (visual analogue scale, VAS – self-rating) from randomisation to end of study

7. Change in Anxiety (VAS and State-Trait anxiety inventory (STAI)- self-rating) from randomisation to end of study

8. Change in Sleep Quality (Pittsburgh Sleep Quality Index (PSQI) and MADRS item 4) from randomisation to end of study

9. Change in MADRS total score from randomisation to Day 4 and Day 8

10. Change in the BDI (self-rating) from randomisation to Day 4 and Day 8

11. Change in quality of life (Short-form 36 Health Survey, SF-36 – self-rating) from randomisation to end of study on each of the 8 sub-scores and the two component scales

12. Change in health-related quality of life (EuroQoL Health Utility Index, EQ-5D – self-rating) from randomisation to end of study on each of the 5 preference domains and on the VAS

13. Change in work productivity and activity impairment (WPAI:GH) from randomisation to end of study

14. Safety and tolerability as assessed by incidence of adverse events (AE) and notable abnormal laboratory test results as well as frequency distribution of the CGI tolerability item 4

Study design

This study was a randomised, multinational, mullticentre, rater-blinded parallel study comparing the efficacy, tolerability and safety of the three different treatment regimens in MDD patients and with inadequate responses to antidepressant treatment.

Target patient population and sample size

Male or female patients, 18 to 65 years old, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of MDD, Single Episode (296.2x) or MDD, Recurrent (296.3x) as confirmed by the Mini-International Neuropsychiatric Interview (MINI).

Patients should have been on treatment with one or two treatments of the current depressive episode for at least 28 days. The current episode should be at least 42 days but not more than 18 months.

In addition, patients had to have a MADRS total score ≥25 at both enrollment and randomization.

It was planned to randomly assign 600 patients to obtain a total of 576 evaluable patients

(192 per treatment group). The study was designed to show non-inferiority between quetipiane XR, monotherapy and add-on vs. add-on lithium.

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

The eligible patients were randomly assigned to 1 of the 3 treatment arms: quetiapine XR monotherapy 300 mg/day, add-on quetiapine XR 300 mg/day or add-on lithium 900 mg/day. Tablets used in the study were: 50 mg, 200 mg and 300 mg quetiapine XR tablets and 450 mg lithium tablets. The tablets were administered once daily in the evening.

The following batch numbers were used in the study: quetiapine XR 50 mg B80104B, B80106A; quetiapine XR 200 mg B80102A; quetiapine XR 300 mg B80102A, B80304A and lithium carbonate 450 mg 847293, 896516, 872409.

Duration of treatment

Eligible patients underwent a washout period of up to 14 days for the discontinuation of all prohibited medications. Patients then entered a 6-week treatment period, when they were randomly assigned to blinded treatment in a 1:1:1 ratio quetiapine XR monotherapy, add-on quetiapine XR or add-on lithium. All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3 and up-titrated to 300 mg on Day 5. The titration period could be prolonged maximum 3 days, i.e., all patients should be on 300 mg no later than Day 8. Patients in the add-on lithium group started on 450 mg and was uptitrated to 900 mg on Day 3. The serum concentration of lithium should be between 0.6 and 1.0 mmol/L and this was checked at visit 4, 5 and 6. If the concentration was outside the limits the dose was adjusted.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary variable

Change in depressive symptoms between randomisation and week 6 as measured by MADRS total score (rater blinded). The non-inferiority margin was 3 points on the MADRS scale.

Secondary variables
Remission; MADRS
Response rate; MADRS
Responder; CGI-I item 2
Change CGI-S
Change BDI
Change pain; VAS
Change anxiety; VAS and STAI
Change sleep quality; PSQI and MADRS item 4
Change in depression at Day 4 and Day 8, MADRS
Change in depression at Day 4 and Day 8, BDI
Change quality of life; SF-36
Change quality of life; EQ-5D
Change in WPAI:GH

Criteria for evaluation - safety (main variables)

AEs, lab tests, CGI tolerability item 4, vital signs and physical examination

Statistical methods

To evaluate non-inferiority of quetiapine XR monotherapy and quetiapine XR add-on treatment compared to lithium add-on treatment to SSRIs or venlafaxine, a one-sided 98.75% confidence interval (CI) for the difference between the treatment groups in MADRS total score was used. This corresponds to the upper limit in a 2-sided 97.5% CI. The non-inferiority limit of 3 points on the MADRS scale was defined specifically for this study.

All p-values in the report are nominal p-values, without correction on the p-values for multiplicity. If non-inferiority was established a test for superiority for the comparisons of the quetiapine groups versus adjunct lithium was to be made.

An ANCOVA (Analysis of Covariance) was used to analyse the change from baseline to week 6 (LOCF; Last observation carried forward) in MADRS total score and the secondary variable with a baseline value. The model included treatment, centre and randomisation MADRS total score as explanatory variables where centre was treated as a random effect, treatment group and stratification variable as fixed effects and baseline value as a covariate. The per-protocol (PP) analysis set was used for the primary non-inferiority analysis and the modified intention to treat (MITT) analysis set was used for a robustness analysis as well as for testing whether any of the quetiapine groups were superior to add-on lithium treatment and for evaluation of secondary efficacy variables. Subgroup analyses were done for patients with treatment failures to 1 or 2 previous antidepressant treatments during the current episode.

Subject population

Analysis sets and patient baseline characteristics are presented in Table S 1and Table S 2.

Table S 1 Analysis set

	Add-on Quetiapine XR	Quetiapine XR monotherapy	Add-on Lithium
Analysis set			
Randomised	231	228	229
Safety analysis set	231	228	229
MITT analysis set	229	225	221
PP analysis set	183	180	109

The low number of patients in the PP analysis in the add-on lithium group is due to that many patients had lithium serum concentration outside the pre-defined range.

Table S 2 Patient baseline characteristics

	Add-on Quetiapine XR		Quetiapine XR mono		Add-on Lithium	
	MITT (N=229)	**PP (N=183)**	**MITT (N=225)**	**PP (N=180)**	**MITT (N=221)**	**PP (N=109)**
Sex, n(%)						
Male	67 (29)	53 (29)	73 (32)	61 (34)	69 (31)	31 (28)
Female	162 (71)	130 (71)	152 (68)	119 (66)	152 (69)	78 (72)
Age (years)						
Mean (SD)	46.52 (11.18)	45.95 (10.99)	46.92 (10.07)	46.69 (10.11)	47.46 (10.75)	46.68 (10.74)
Range	20.0, 68.4	20.0, 66.1	19.8, 65.2	19.8, 64.8	19.1, 66.8	19.1, 66.8
Race, n (%)						
White	228 (99.6)	182 (99.5)	224 (99.6)	180 (100)	219 (99.1)	108 (99.1)
Asian	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Other	1 (0.4)	1 (0.5)	0 (0)	0 (0)	2 (0.9)	1 (0.9)
DSM-IV diagnosis: n (%)						
296.2x, single episode	36 (15.7)	31 (16.9)	50 (22.2)	43 (23.9)	41 (18.6)	24 (22.0)
296.3x, recurrent	193 (84.3)	152 (83.1)	175 (77.8)	137 (76.1)	180 (81.4)	85 (78.0)

Table S 2 Patient baseline characteristics

	Add-on Quetiapine XR		Quetiapine XR mono		Add-on Lithium	
	MITT (N=229)	PP (N=183)	MITT (N=225)	PP (N=180)	MITT (N=221)	PP (N=109)
Severity of Illness, CGI-S: n (%)						
Unavailable	0 (0)	0 (0)	0 (0)	0 (0)	1 (.45)	0 (0)
Mildly Ill	5 (2.2)	5 (2.7)	1 (.44)	0 (0)	3 (1.4)	0 (0)
Moderately Ill	70 (31)	56 (31)	88 (39)	66 (37)	89 (40)	50 (46)
Markedly Ill	107 (47)	84 (46)	105 (47)	91 (51)	97 (44)	45 (41)
Severely Ill	47 (21)	38 (21)	31 (14)	23 (13)	31 (14)	14 (13)
Total MADRS score (0-60)						
Mean (SD)	33.15 (5.34)	33.62 (5.38)	33.74 (5.60)	33.89 (5.62)	32.91 (5.20)	33.17 (4.93)

Summary of efficacy results

Non-inferiority to lithium add-on to SSRIs or venlafaxine in the PP analysis sets was concluded for both quetiapine XR monotherapy and quetiapine XR add-on treatment since the 97.5% CIs for the difference between the quetiapine XR groups vs Lithium was entirely below the pre-defined non-inferiority limit of 3 points on MADRS total score. At the end of treatment, a mean reduction in MADRS total score was observed to be approximately 17 points in the PP analysis set and 15 points in the MITT analysis set in all treatments groups, numerically a little bit better in the quetiapine XR groups.

Although the power of the study to demonstrate non-inferiority of the quetiapine groups versus lithium add-on treatment to SSRI or venlafaxine was based on the total number of patients, subgroup analyses were done for patients with treatment failures to 1 or 2 previous antidepressant treatments during the current episode. These analyses showed that the criterion for non-inferiority was fulfilled for quetiapine add-on treatment in patients with both 1 and 2 treatment failures, and for quetiapine monotherapy in patients with 2 treatment failures.

Since non-inferiority was shown for quetiapine XR monotherapy or quetiapine XR add-on treatment vs. lithium add-on to to SSRIs or venlafaxine in the PP analysis sets, tests for superiority were performed on MITT analysis sets. Neither quetiapine XR monotherapy nor quetiapine XR add-on was superior to lithium add-on in reducing MADRS total score from randomisation to Week 6.

A total of 50.7% of the MITT patients in the quetiapine XR monotherapy group, 52.4% in the quetiapine XR add-on group and 46.2% in the lithium add-on group showed a MADRS response of ≥50% reduction from randomisation. Remission defined as a MADRS total score ≤10 at Week 6 was reached in similar proportions of patients in the MITT analysis sets in all treatment groups.

Clinical Global Impression (CGI) item 3 is a benefit:risk index based on an integrated evaluation of therapeutic effect and adverse events. This assessment was not rater-blinded. Marked or moderate improvement together with no adverse events or adverse events not significantly interfering with patient's functioning, could be considered as a beneficial treatment outcome. 59.2% of the patients in the quetiapine XR monotherapy group, 63.3% in the quetiapine XR add-on group and 57.2% in the lithium add-on group had this beneficial treatment outcome.

The secondary objevtive to measure reduction in LS mean MADRS total score was significantly higher with both quetiapine XR monotherapy and add-on quetiapine XR compared to add-on lithium at Day 4 and Day 8. Sleep, measured by PSQI and MADRS item 4, was significantly improved in the quetiapine XR groups compared to the add-on lithium group. The other secondary variables in MITT analysis set supported the primary objective and showed no differences from add-on lithium that reinforced the finding of a clinically relevant, positive, therapeutic effect of quetiapine XR in the treatment of TRD (MADRS response at Week 6, MADRS remission at Week 6, CGI, BDI, change in self-rated overall pain using VAS, change in anxiety using VAS or STAI, Change in quality of life with SF-36 and EQ-5D, WPAI:GH).

Summary of safety results

Change from baseline in physical examination, laboratory values and vital signs
The change in vital signs (pulse and blood pressure) is similar in the treatment groups. Increase in pulse somewhat more frequent in the quetiapine XR groups. Quetiapine XR was associated with elevations in lipid parameters. There were no other changes in physical findings, laboratory values or vital signs.

Adverse Events
Quetiapine XR monotherapy and add-on quetiapine XR therapy was generally well-tolerated. The overall incidence of AEs was more frequent in the quetiapine XR groups compared to the add-on lithium group and the most common AEs in the quetiapine XR groups were related to somnolence. Most AEs were of mild or moderate in intensity

Serious Adverse Events
Few patients had a SAE in the study. The incidence was higher in the quetiapine XR groups

AEs leading to discontinuation
The most common non-serious AEs leading to discontinuation from quetiapine XR treatment groups were related to sedation. In the add-on lithium group were vomiting, nausea and diarrohea the most common causes.

Other significant AEs (neutropenia, diabetes mellitus, somnolence, suicidality)
No notable differences in the incidences of AEs of special interest were observed in the three treatment groups. Quetiapine XR was not associated with an increased incidence of AE related to syncope, diabetes mellitus, neutropenia or agranulocytosis.

Change in weight and BMI from randomisation to end-of study
Increase in weight and BMI was slightly more common in the quetiapine XR groups.

Change in waist circumference from randomisation to end-of study
The change in waist circumference was small and similar between the treatment groups.

Proportion of patients with ≥7% increase or decrease in weight from randomisation to end-of study
Weight increase of ≥7% was more common in the quetiapine groups. Higher increase in weight and BMI can be noted in the lower BMI categories

Change in CGI item 4
Side effects measured as change in CGI item 4 was similar in all treatment groups.