| | | | |
|---|---|---|---|
| Drug product: | Seroquel | **SYNOPSIS** | |
| Drug substance(s): | Quetiapine fumarate | | |
| Edition No.: | 1 | | |
| Study code: | D1447C0001 | | |
| Date: | Date 28 September 2007 | | |

# An International, Multi-centre, Double-blind, Randomised, Parallel-group, Placebo-controlled, Phase III study of the Efficacy and Safety of Quetiapine Fumarate (Seroquel™, single oral 300 mg or 600 mg dose) and Lithium as Monotherapy in Adult Patients with Bipolar Depression for 8 weeks and Quetiapine in Continuation Treatment for 26 up to 52 weeks

## Study centres

This study was conducted in a total of 110 centres in Europe (84 centres), Canada (10 centres), and Asia (16 centres).

## Publications

None.

| **Study dates** | | **Phase of development** |
|---|---|---|
| **First patient enrolled** | 31 August 2005 | III |
| **Last patient completed** | 24 May 2007 | |

## Objectives

The **primary objective** of this study was to demonstrate superior efficacy of quetiapine compared with placebo in the **Acute Phase** treatment of patients with bipolar depression by assessment of the change from baseline to Day 57 in the MADRS (Montgomery-Asberg Depression Rating Scale) total score.

The **secondary objectives** relating to the **Acute Phase** of the study were: to demonstrate the efficacy of quetiapine in reducing suicidal ideation and anxiety symptoms in patients with

bipolar depression; to demonstrate that quetiapine is superior to placebo in improving the level of functioning; to evaluate the incidence of withdrawals due to adverse events in patients receiving quetiapine in comparison to placebo; to demonstrate that quetiapine has a comparable incidence of treatment-emergent mania as placebo, to explore the incidence of treatment-emergent suicidal ideation, and to explore the effect of quetiapine in improving cognitive functioning.

The **secondary objectives** relating to the **Continuation Phase** of the study were: to demonstrate the efficacy of quetiapine versus placebo in increasing time to recurrence of a mood event, time to recurrence of a depressed event; and time to recurrence of a manic/hypomanic event; to explore the efficacy of quetiapine in maintaining improvement in anxiety symptoms; to determine whether quetiapine is safe and well tolerated, and to explore the incidence of treatment emergent suicidal ideation.

**Study design**

This was a multi-centre, double-blind, randomised, parallel-group, placebo-controlled, phase III study comparing the efficacy and safety of quetiapine and lithium as monotherapy in acutely ill depressed patients with bipolar I or II disorder, consisting of an 8-week Acute Phase followed by a 26- to 52-week Continuation Phase.

**Target patient population and sample size**

Male or female patients aged 18 to 65 years old with a documented clinical diagnosis of bipolar disorder, most recent episode depressed, meeting the DSM-IV criteria, with or without rapid cycling course. Patients were required to have a Hamilton Rating Scale for Depression (HAM-D; 17-item scale) score of ≥20 and a Young Mania Rating Scale (YMRS) score of ≤12 at enrolment and randomisation. In total, 922 patients were enrolled of which 802 were randomised to obtain 654 evaluable patients. Aiming to detect a 4 units difference in MADRS total score change from baseline Day 57, between each quetiapine dose and placebo, and a pooled standard deviation of 10, the power was 87%. Patients in remission at the end of the Acute Phase (MADRS total score ≤12 and YMRS total score ≤12) were eligible for the Continuation Phase.

**Investigational product and comparators: dosage, mode of administration and batch numbers**

Quetiapine fumarate 25 mg, 100 mg and 200 mg immediate-release tablets (or placebo to match) were administered once a day at bedtime, with dose titration to reach a dose of 300 mg/day by Day 4 in the 300 mg/day treatment group and 600 mg/day by Day 8 in the 600 mg/day group.

Lithium 300 mg capsules (or placebo to match) were to be administered twice daily in the morning and at bedtime.

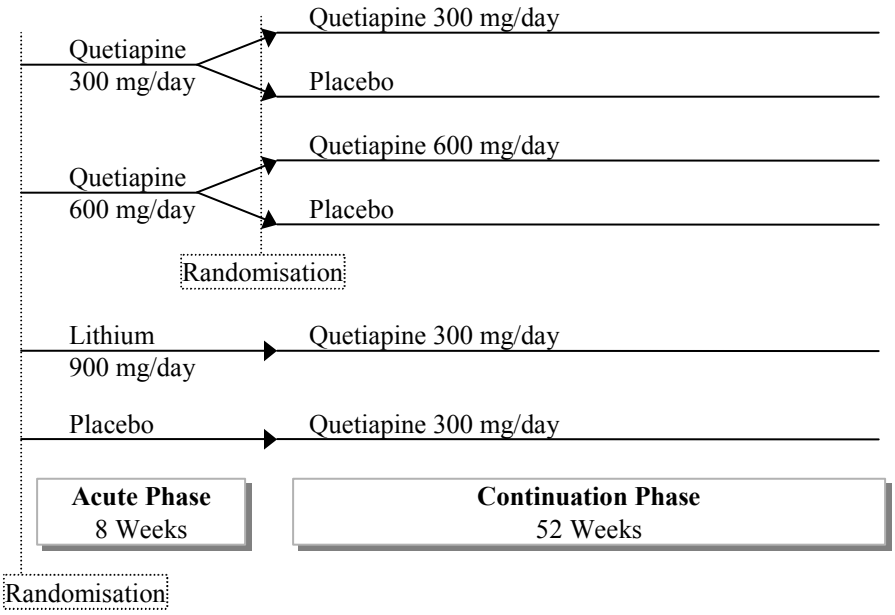
Multiple batches of the investigational products were used for different participating countries. A complete list of batch numbers and formulation numbers used during the Acute and Continuation Phases of the study can be found in Appendix 12.1.6.

**Duration of treatment**

Eligible patients had a washout of all psychotropic medications from 5 to 28 days, depending on the medication they were taking. Patients then entered an 8-week Acute Phase. Eligible patients with a Montgomery Asberg Depression Rating Scale (MADRS) score of ≤12 and a YMRS score of ≤12 after the Acute Phase then entered a Continuation Phase which lasted from 26 up to a maximum of 52 weeks, or until recurrence of a mood event, or discontinuation for any other reason.

The duration of treatment is presented in the Figure S 1, below:

**Figure S 1 Overall Study Flow**




**Criteria for evaluation (main variables)**

The outcome variables in the Acute and Continuation Phases are presented in Table S1.

## Table S1 Outcome variables in the acute and Continuation Phases

**Acute Phase**

Primary efficacy outcome variable

- Change from baseline to Day 57 assessment in the MADRS total score.

Secondary efficacy outcome variables

- MADRS total score response (patients with a ≥50% reduction from baseline in the MADRS total score at Day 57) MADRS total score remission (patients with a MADRS total score ≤12 at Day 57)
- Change from baseline to Day 57 in MADRS Item 10 (suicidal thought), HAM-D total score, HAM-D Item 1 (depressed mood), CGI BP-S total score and HAM-A total score
- Day 57 assessment in CGI BP-C.

Patient reported outcomes

- Change from baseline to Day 57 in MOS-Cog score, in total SDS score and in the number of missed workdays and under-productive workdays reported on the SDS

Safety variables

- Incidence in adverse events
- Percentage of patients with an AE of mania or hypomania, or YMRS score of ≥16 on two consecutive assessments or at final assessment
- Incidence of patients with an AE of suicidality/suicidal ideation/suicide attempts/suicide completion
- Incidence of patients with HAM-D Item 3 score value ≥3
- Change from enrolment or randomisation at Day 1 to subsequent assessments in laboratory values, vital signs, weight, waist circumference, EPS, physical examinations including eye examination and ECG

**Continuation Phase**

Secondary efficacy outcome variables

- Time from Continuation Phase baseline to recurrence of a mood event, a depressed event, or a manic/ hypomanic event
- Change from Continuation Phase baseline to end of treatment in HAM-A total score.

Safety variables

- Incidence in adverse events
- Proportion of patients withdrawing due to AEs
- Incidence of patients with an AE of suicidality/suicidal ideation/suicide attempts/suicide completion. Change from Continuation Phase baseline to subsequent assessments in laboratory values, vital signs, weight, waist circumference, EPS, physical examinations including eye examination and ECG

AE Adverse event; CGI BP-C Clinical Global Impression Bipolar -Change; CGI BP-S Clinical Global Impression Bipolar -Severity; ECG electrocardiogram; EPS extrapyramidal symptoms; HAM-A Hamilton Rating Scale for Anxiety; HAM-D Hamilton Rating Scale for Depression; MADRS Montgomery-Asberg Depression Rating Scale; MOS-Cog Medical Outcomes Study Cognitive Scale; SDS Sheehan Disability Scale; YMRS Young Mania Rating Scale.

## Statistical methods

### Acute Phase

The primary outcome variable, change from baseline to Day 57 in MADRS total score, was analysed using a linear mixed model with fixed effects for treatment and bipolar diagnosis strata (ie bipolar I or bipolar II); baseline MADRS total score was included as a covariate, and country was included as a random effect. The comparison of interest was the difference between quetiapine dose and placebo and adjustments for multiple comparisons used a Hochberg approach.

Secondary analyses in support of the primary analysis utilised the same linear model as in the primary analysis for variables changes, from baseline to Day 57, in HAM-D, HAM-D Item 1, HAM-A, CGI-BP-S, and MADRS items scores and HAM-D in rapid and non-rapid cycles. The variable CGI BP-C was analysed using a similar linear model. In addition, the dichotomous variables responders (≥50% decrease in MADRS total score) and remitters

(MADRS total score ≤12) were analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by bipolar diagnosis.

The data analyses in the Acute Phase were based on the following populations:

- Acute Phase safety population: All randomised patients who took at least one dose of study medication, classified according to the treatment actually received.

- Acute Phase intention to treat (ITT) population: All randomised patients who received at least one dose of study treatment and who had a baseline value and at least one post-randomisation MADRS assessment, classified according to which treatment they were randomised. Data from the ITT population were used for analysis of the efficacy objectives.

- Per-protocol (PP) population: A subset of the ITT population, including patients who completed the study treatment with no major protocol violations or deviations affecting efficacy. Data from this population were used as a consistency check for analysis of the primary objective.

**Continuation Phase**

This study was not planned to be powered to detect treatment differences during the Continuation Phase. A separate analysis, with pooled data from the current study and the similarly designed study D1447C0000134, was planned. However, a Cox proportional hazard analysis was done on the study level to obtain an estimate of treatment difference between the quetiapine and placebo groups with regard to time to first event (mood, depression or mania). Descriptive statistics were provided for time to first event (mood, depression or mania) and HAM-A.

The data analyses in the Continuation Phase were based on the following populations:

- Continuation Phase safety population: All patients randomised to the Continuation Phase who took at least one dose of study medication, classified according to the treatment actually received. Patients going into the Continuation Phase from the lithium and placebo groups were primarily followed for safety and to maintain the blind during the entire duration of the study.

- Continuation Phase ITT population: All patients randomised to the Continuation Phase from quetiapine treatment in the Acute Phase, who took at least one dose of study medication, classified according to the treatment randomised to in the Continuation Phase.

**Patient population**

Baseline patient characteristics and disposition in the Acute Phase are presented in Table S2.

## Table S2 Baseline patient characteristics and disposition – Acute Phase

| | | QTP300 | QTP600 | PLA | LI | Total |
|---|---|---|---|---|---|---|
| **Demographic characteristics (ITT population)** | | | | | | |
| N | | 255 | 263 | 129 | 136 | 783 |
| Sex: n(%) | Male | 109(42.7) | 96(36.5) | 59(45.7) | 55(40.4) | 319(40.7) |
| | Female | 146(57.3) | 167(63.5) | 70(54.3) | 81(59.6) | 464(59.3) |
| Age: (years) [a] | Mean (SE) | 42.3(0.73) | 42.8(0.70) | 41.5(1.12) | 41.4(1.01) | 42.2(0.42) |
| | Min to max | 18 to 65 | 18 to 65 | 18 to 64 | 18 to 64 | 18 to 65 |
| Race: n(%) | Caucasian | 215(84.3) | 226(85.9) | 110(85.3) | 117(86.0) | 668(85.3) |
| | Black | 1(0.4) | 0 | 0 | 0 | 1(0.1) |
| | Oriental | 38(14.9) | 37(14.1) | 19(14.7) | 19(14.0) | 113(14.4) |
| | Other | 1(0.4) | 0 | 0 | 0 | 1(0.1) |
| Weight (kg) | Mean (SE) | 75.8(0.96) | 74.4(1.02) | 76.0(1.26) | 77.0(1.49) | 75.5(0.57) |
| | Min to max | 44 to 129 | 40 to 138 | 44 to 144 | 45 to 145 | 40 to 145 |
| **Baseline disease characteristics (ITT population)** | | | | | | |
| N | | 255 | 263 | 129 | 136 | 783 |
| DSM-IV diagnosis: n(%) | | | | | | |
| Bipolar I disorder | | 160(62.7) | 162(61.6) | 78(60.5) | 87(64.0) | 487(62.2) |
| Bipolar II disorder | | 95(37.3) | 101(38.4) | 51(39.5) | 49(36.0) | 296(37.8) |
| Mood episodes over past year: n(%) | | | | | | |
| <4 | | 239(93.7) | 247(93.9) | 124(96.1) | 128(94.1) | 738(94.3) |
| ≥4 [b] | | 16(6.3) | 16(6.1) | 5(3.9) | 8(5.9) | 45(5.7) |
| MADRS: mean (SE) | | 28.1(0.39) | 28.3(0.40) | 28.5(0.54) | 28.3(0.48) | 28.3(0.22) |
| HAM-D: mean (SE) | | 24.2(0.22) | 24.3(0.21) | 24.4(0.28) | 24.1(0.28) | 24.2(0.12) |
| HAM-A: mean (SE) | | 18.3(0.40) | 18.2(0.37) | 18.3(0.51) | 18.0(0.47) | 18.2(0.21) |
| YMRS: mean (SE) | | 3.1(0.12) | 3.3(0.12) | 3.3(0.19) | 3.4(0.19) | 3.2(0.07) |
| **Patient disposition** | | | | | | |
| Randomised to Acute Phase | | 265 | 268 | 133 | 136 | 802 |
| Randomised but received no dose | | 5 | 1 | 2 | 0 | 8 |
| Acute Phase safety population | | 260 | 267 | 131 | 136 | 794 |
| Acute Phase ITT population | | 255 | 263 | 129 | 136 | 783 |
| PP population | | 241 | 250 | 126 | 87 | 704 |

[a] At enrolment.
[b] With rapid cycling course.

CGI BP-S Clinical Global Impression Bipolar –Severity. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. ITT Intention-to-treat. LI Lithium. MADRS Montgomery-Asberg Depression Rating Scale. N Number of patients in treatment group. n Number of patients, PLA Placebo. PP Per-protocol. QTP Quetiapine. SE Standard error.YMRS Young Mania Rating Scale.

Note: Percentages are calculated as n/N*100.

In general the study populations in both the Acute Phase and the Continuation Phase were considered representative of a patient population with bipolar I and bipolar II disorder, and the treatment groups in both treatment phases were generally well balanced in demographic and baseline disease characteristics. The characteristics of the patients who entered the Continuation Phase were generally similar to those of the patients who had entered the Acute Phase.

The 783 patients in the ITT population with either bipolar I disorder or bipolar II disorder exhibiting moderate to severe depression who participated in this study provided an adequate number to meet the design requirements for statistical power in the Acute Phase of the study.

After the completion of the Acute Phase, 467 patients in remission (MADRS total score ≤12, YMRS total score ≤12) were randomized to the Continuation Phase of the study. The patients who had been taking quetiapine during the Acute Phase were randomised to either quetiapine or placebo treatment during the Continuation Phase: 80 patients to quetiapine 300 mg/day, 83 patients to quetiapine 600 mg/day, and 165 patients were randomized to placebo. Patients treated with placebo or lithium during the Acute Phase were allocated to treatment with quetiapine 300 mg in a blinded manner to preserve the overall treatment blind. At entry to the Continuation Phase the mean baseline MADRS and YMRS total scores were 7.1 and 1.3 respectively.

**Efficacy results (Acute Phase)**

The key efficacy results for the Acute Phase are presented in Table S3.

**Table S3 Efficacy results at Day 57 (LOCF, ITT population)**

| Outcome variable | QTP300 N=255 | QTP600 N=263 | PLA N=129 | LI N=136 |
| --- | --- | --- | --- | --- |
| MADRS total score, LS mean change from baseline | -15.36[d] | -16.10[d] | -11.81 | -13.60 |
| MADRS response[a] | 68.6%[e] | 69.6%[f] | 55.8% | 62.5% |
| MADRS remission[b] | 69.8%[f] | 70.3%[f] | 55.0% | 62.5% |
| MADRS item 10, (suicidal thoughts), LS mean change from baseline | -0.59 | -0.64[e] | -0.43 | -0.49 |
| HAM-D total score, LS mean change from baseline | -13.98[d] | -14.17[d] | -10.72 | -12.36 |
| HAM-D item 1 score, LS mean change from baseline | -1.52[e] | -1.62[f] | -1.26 | -1.36 |
| HAM-A total score, LS mean change from baseline | -9.14[d] | -9.29[d] | -6.55 | -7.72 |
| CGI-BP-S score, LS mean change from baseline | -1.51[f] | -1.57[f] | -1.14 | -1.40 |
| CGI-BP-C response | 64.7%[f] | 61.6%[e] | 48.1% | 51.1% |

**Table S3 Efficacy results at Day 57 (LOCF, ITT population)**

| Outcome variable | QTP300 N=255 | QTP600 N=263 | PLA N=129 | LI N=136 |
|---|---|---|---|---|
| SDS total score, LS mean change from baseline | -6.90[e] | -7.54[f] | -5.33 | -7.00 |
| MOS-Cog total score, LS mean change from baseline | 5.67 | 6.34[e] | 4.64 | 5.98 |

[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-BP-C response: Much Improved or Very Much Improved.
[d] p<0.001 comparison with placebo.
[e] p<0.05 comparison with placebo.
[f] p<0.01 comparison with placebo.
CGI-BP-C Clinical Global Impression-Bipolar-Change. CGI-BP-S Clinical Global Impression-Bipolar-Severity. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. ITT Intention-to-treat. LI Lithium. LOCF Last observation carried forward. MADRS Montgomery-Asberg Depression Rating Scale. MOS-Cog Medical Outcomes Study Cognitive scale. SDS Sheehan disability scale. N number of patients in treatment group. LS Least square. PLA Placebo. QTP Quetiapine.
Note: For the analyses of MADRS change from baseline, p-values were adjusted using the Hochberg procedure.
Study: D1447C0001A Source document: S_ALL_ANCOVA_LOCF_ITT.SAS. Generated: 15:17:50 06Sep2007 DB version prod: 13

Quetiapine 300 mg and 600 mg were both superior to placebo in improving MADRS total score at Day 57. The quetiapine groups were superior to the placebo group from Day 8 and throughout the Acute Phase. There was a numerically greater improvement in MADRS total score in lithium patients than in placebo patients at Day 57, although the difference did not reach statistical significance. Quetiapine 600 mg was superior to lithium at Day 57 in improving MADRS total score.

Quetiapine 300 mg and 600 mg were both superior to placebo in all secondary variables at the end of the 8-week Acute Phase, except for quetiapine 300 mg in MADRS item 10 and Mos-Cog. In HAM-D, HAM-A and in the CGI-BP-Change overall bipolar illness response quetiapine 300 mg and 600 mg were superior to placebo at Day 8 and throughout the Acute Phase. Quetiapine 300 mg and 600 mg were superior to lithium in reducing HAM-D and HAM-A total score at Day 57.

Lithium-treated patients had numerically greater improvements in all variables compared with placebo-treated patients, although none of the differences between lithium and placebo was statistically significant.

Quetiapine 300 mg and 600 mg were superior to placebo in improving the level of social functioning (SDS) and quetiapine 600 mg was superior in improving cognitive functioning (MOS-Cog) at the end of the 8-week Acute Phase (Day 57).

**Efficacy results (Continuation Phase)**

Throughout the Continuation Phase 46 (28.2%) patients in the quetiapine group and 68 (41.2%) patients in the placebo group experienced a mood event. The time to when 10% of patients experienced recurrence of a mood event was 89 days in the quetiapine treated patients and 30 days in the placebo treated patients. The Cox-proportional hazard analysis

demonstrated that quetiapine significantly increased the time to recurrence of a mood event (estimated hazard ratio 0.56, 95% CI 0.39 to 0.82) and a depressed event (estimated hazard ratio 0.48, 95% CI 0.29 to 0.77) compared to placebo, showing maintenance of quetiapine treatment effect during the Continuation Phase. The number of manic events were low during the Continuation Phase. The analysis of the time to first manic event was in favour of quetiapine although not statistically significant.

### Safety results

Quetiapine treatment was safe and generally well-tolerated during both acute and long term treatment.

### Safety during Acute Phase treatment

A summary of AEs in each category during the Acute Phase is presented in Table S4.

**Table S4 Patients who had an adverse event in any category – Acute Phase (safety population)**

| Category of adverse event | QTP300 N=260 n (%) | QTP600 N=267 n (%) | PLA N=131 n (%) | LI N=136 n (%) |
|---|---|---|---|---|
| Any adverse event | 142 (54.6) | 173 (64.8) | 63 (48.1) | 79 (58.1) |
| Serious adverse event | 10 (3.8) | 7 (2.6) | 3 (2.3) | 3 (2.2) |
| Serious adverse event leading to death | 0 | 0 | 0 | 0 |
| Serious adverse event not leading to death | 10 (3.8) | 7 (2.6) | 3 (2.3) | 3 (2.2) |
| Drug-related adverse event[a] | 117 (45.0) | 128 (47.9) | 37 (28.2) | 55 (40.4) |
| Adverse event leading to discontinuation | 27 (10.4) | 37 (13.9) | 11 (8.4) | 12 (8.8) |

[a] As judged by the investigator.
LI Lithium N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as (n/N)*100.
Study: D1447C0001A Source document: TA_AE1_CAT_ST.SAS. Generated: 15:52:27 06Sep2007 DB version prod: 13
Table corresponds to Table 11.3.2- 1.

Adverse event rates were higher in all treatment groups compared to placebo, with more AEs observed in the quetiapine 600 mg group than the quetiapine 300 mg and lithium groups. The proportion of patients with SAEs was generally small, but slightly higher in the quetiapine 300 mg dose group (3.8%) than in the other treatment groups (2.2 to 2.6%). In the quetiapine treatment groups higher proportions of patients had adverse events leading to discontinuation than in the lithium and placebo groups.

The most common AEs in the Acute Phase of the study summarized by preferred term are shown in Table S 5.

**Table S 5 Common AEs by preferred term - Acute Phase (safety population)**

| MedDRA preferred term[a] | QTP300 N=260 n (%) | QTP600 N=267 n (%) | PLA N=131 n (%) | LI N=136 n (%) |
|---|---|---|---|---|
| Somnolence | 47 (18.1) | 47 (17.6) | 5 (3.8) | 12 (8.8) |
| Dry mouth | 37 (14.2) | 40 (15.0) | 2 (1.5) | 10 (7.4) |
| Dizziness | 25 (9.6) | 30 (11.2) | 7 (5.3) | 6 (4.4) |
| Headache | 19 (7.3) | 23 (8.6) | 18 (13.7) | 13 (9.6) |
| Sedation | 16 (6.2) | 14 (5.2) | 2 (1.5) | 1 (0.7) |
| Constipation | 12 (4.6) | 21 (7.9) | 3 (2.3) | 4 (2.9) |
| Nausea | 10 (3.8) | 15 (5.6) | 10 (7.6) | 23 (16.9) |
| Diarrhoea | 6 (2.3) | 7 (2.6) | 5 (3.8) | 9 (6.6) |
| Insomnia | 6 (2.3) | 3 (1.1) | 7 (5.3) | 12 (8.8) |
| Tremor | 2 (0.8) | 9 (3.4) | 1 (0.8) | 8 (5.9) |

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
LI Lithium. MedDRA Medical Dictionary for Regulatory Activities. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine.
Note: Common adverse event is defined as an event occurring at an incidence of ≥5% in any treatment group.
Note: Events sorted by decreasing frequency in the QTP300 treatment group.
Note: Percentages are calculated as (n/N)*100.
Study: D1447C0001A Source document: TA_AE_COMMON_BYPT_SAF.SAS. Generated: 15:54:38 06Sep2007 DB version prod: 13
Table corresponds to Table 11.3.2- 8.

The most commonly reported AEs for the quetiapine-treated groups were somnolence, dry mouth, dizziness, sedation and constipation, with similar frequencies in the 300 mg and 600 mg dose groups. Nausea, diarrhea, insomnia and tremor were more common in the lithium treated patients than in patients treated with quetiapine or placebo. Headache was more common in the placebo group (13.7%) than in the active treatment groups (7.3 to 9.6%).

Aggregation of all terms potentially associated with EPS revealed that the incidence in both quetiapine treatment groups was similar but higher than that in the placebo group during Acute Phase treatment. No differences were observed across treatment groups in mean changes in EPS rating scales.

### Safety during Continuation Phase treatment

A summary of AEs in each category during the Continuation Phase is presented in Table S 6 and Table S 7.

**Table S 6 Patients who had an AE (treatment emergent only) in any category – Continuation Phase (safety population)**

| Category of adverse event | QTP300 N=80 n (%) | QTP600 N=84 n (%) | PLA N=165 n (%) | QTP300 (PLA) N=63 n (%) | QTP300 (LI) N=74 n (%) |
|---|---|---|---|---|---|
| Any adverse event | 49 (61.3) | 44 (52.4) | 80 (48.5) | 38 (60.3) | 50 (67.6) |
| Drug-related adverse event[a] | 24 (30.0) | 21 (25.0) | 32 (19.4) | 17 (27.0) | 33 (44.6) |

[a] As judged by the investigator.
LI Lithium. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine.
Note: Treatment within parenthesis is treatment during Acute Phase.
Note: Events first reported or worsened intensity during Continuation Phase.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as (n/N)*100.
Study: D1447C0001B Source document: TB_AE_ALL_BYCAT_SAF.SAS. Generated: 12:23:05 23Aug2007 DB version prod: 12
Table corresponds to Table 11.3.2- 15

In the Continuation Phase, the overall treatment emergent adverse event rate was higher in quetiapine treated patients (ranging from 52.4 to 67.6% in the 4 quetiapine groups) than in the placebo treated patients (48.5%). Among the quetiapine groups, the overall treatment emergent adverse event rate was higher in patients switching from lithium to quetiapine 300 mg (67.6%) than in the other quetiapine 300 mg groups (61.3 and 60.3%) and in the quetiapine 600 mg (52.4%) group.

**Table S 7 Patients who had an AE (ongoing at start of phase or treatment emergent) in any category – Continuation Phase (safety population)**

| Category of adverse event | QTP300 N=80 n (%) | QTP600 N=84 n (%) | PLA N=165 n (%) | QTP300 (PLA) N=63 n (%) | QTP300 (LI) N=74 n (%) |
|---|---|---|---|---|---|
| Serious adverse event | 5 (6.3) | 0 | 10 (6.1) | 2 (3.2) | 0 |
| Serious adverse event leading to death | 0 | 0 | 1 (0.6) | 0 | 0 |
| Serious adverse event not leading to death | 5 (6.3) | 0 | 9 (5.5) | 2 (3.2) | 0 |
| Adverse event leading to discontinuation | 6 (7.5) | 2 (2.4) | 12 (7.3) | 4 (6.3) | 7 (9.5) |

[a] As judged by the investigator.
LI Lithium. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine.
Note: Treatment within parenthesis is treatment during Acute Phase.
Note: Events first reported or worsened intensity during continuation phase.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as n/N*100.
Study: D1447C0001B Source document: TB_AE_ALL_BYCAT_ONGC_SAF.SAS. Generated: 12:25:43 23Aug2007 DB version prod: 12
Table corresponds to Table 11.3.2- 31

One patient had a myocardial infarction and died during placebo treatment in the Continuation Phase.

SAEs were most frequent in the quetiapine 300 mg group (6.3%) and the placebo group (6.1%). No SAEs were reported in the quetiapine 600 mg group or in patients switching from lithium to quetiapine 300 mg. The frequency of AEs leading to discontinuation were lower in the quetiapine 600 mg group (2.4%) than in the other groups (quetiapine 300 mg groups 6.3 % to 9.5% and the placebo group 7.3%).

The most common AEs in the Continuation Phase of the study summarized by preferred term are shown in Table S 8.

**Table S 8 Common AEs (treatment emergent only) by preferred term – Continuation Phase (safety population)**

| MedDRA preferred term[a] | QTP300 N=80 n (%) | QTP600 N=84 n (%) | PLA N=165 n (%) | QTP300 (PLA) N=63 n (%) | QTP300 (LI) N=74 n (%) |
|---|---|---|---|---|---|
| Headache | 11 (13.8) | 13 (15.5) | 16 (9.7) | 6 (9.5) | 9 (12.2) |
| Nasopharyngitis | 10 (12.5) | 2 (2.4) | 11 (6.7) | 5 (7.9) | 2 (2.7) |
| Diarrhoea | 6 (7.5) | 1 (1.2) | 3 (1.8) | 0 | 2 (2.7) |
| Somnolence | 5 (6.3) | 3 (3.6) | 5 (3.0) | 5 (7.9) | 14 (18.9) |
| Weight increased | 4 (5.0) | 3 (3.6) | 2 (1.2) | 1 (1.6) | 7 (9.5) |
| Dizziness | 3 (3.8) | 4 (4.8) | 6 (3.6) | 4 (6.3) | 5 (6.8) |
| Dry mouth | 3 (3.8) | 5 (6.0) | 0 | 2 (3.2) | 5 (6.8) |
| Insomnia | 3 (3.8) | 0 | 14 (8.5) | 3 (4.8) | 3 (4.1) |
| Nausea | 3 (3.8) | 2 (2.4) | 9 (5.5) | 2 (3.2) | 4 (5.4) |
| Abdominal pain | 0 | 1 (1.2) | 0 | 4 (6.3) | 2 (2.7) |

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
LI Lithium. MedDRA Medical Dictionary for Regulatory Activities. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine.
Note: Treatment within parenthesis is treatment during Acute Phase.
Note: Events first reported or worsened intensity during continuation phase.
Note: Events sorted by decreasing frequency in the quetiapine 300 mg group.
Note: Common adverse event is defined as an event occurring at an incidence of ≥5% in any treatment group.
Note: Percentages are calculated as (n/N)*100.
Study: D1447C0001B Source document: TB_AE_COMMON_BYPT_SAF.SAS. Generated: 15:36:18 06Sep2007 DB version prod: 12
Table corresponds to Table 11.3.2- 21.

In the Continuation Phase, the pattern of common treatment emergent AEs was generally in-line with the results for the Acute Phase. Adverse events of increased weight were recorded more frequently in the quetiapine treatment groups than in the placebo group.

Throughout the study, the quetiapine groups showed a mean weight gain (ranging from 0.4 to 1.3 kg) compared to placebo (-0.4 kg). Consistent with this, a greater proportion of quetiapine than placebo patients had a ≥7% weight gain of at end of treatment (12.0 to 15.4% in the quetiapine groups compared to 2.9% in the placebo group).

There was a larger proportion of patients in the all active treatment groups than in the placebo group meeting the criteria for a treatment-emergent aggregate of ≥3 metabolic syndrome risk factors in both treatment phases.