Drug product:	Seroquel	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate		
Edition No.:	1		
Study code:	D1447C00134		
Date:	05 October 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 Paroxetine as Monotherapy in Adult Patients with Bipolar Depression for 8 weeks and Quetiapine in Continuation Treatment for 26 up to 52 weeks

Study centre(s)

This study was conducted in a total of 83 centers in the USA (33 centers), EU member states (10 centers), Turkey (4 centers), Central and South America (24) South Africa (7 centers), and Australia (5 centers).

Publications

None.

Study dates		**Phase of development**
First patient enrolled	20 May 2005	III
Last patient completed	31 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 and the overall quality of life; 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 effects of quetiapine on sexual function in comparison to placebo.

The **secondary objectives** relating to the **Continuation Phase** (maintenance of effect period) 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 and in the overall quality of life; 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 paroxetine as monotherapy in acutely ill patients with Bipolar disorder for 8 weeks and of quetiapine for 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 Acute Phase randomisation. Patients with a score of >12 on the MADRS or >12 on the YMRS at Day 57 of the Acute Phase were excluded from the Continuation Phase.

In total, 1076 patients were enrolled and 740 patients were randomly assigned to the Acute Phase. 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. [redacted]

Due to a lower-than-expected rate of mood events during the Continuation Phase, the recruitment period was extended by 2 months, and the originally planned number of patients in the Acute Phase was increased by approximately 10%.

Investigational product and comparator(s): 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.

Paroxetine 20 mg, encapsulated in 10 mg and 20 mg tablets (or encapsulated placebo to match), was to be administered once a day at bedtime.

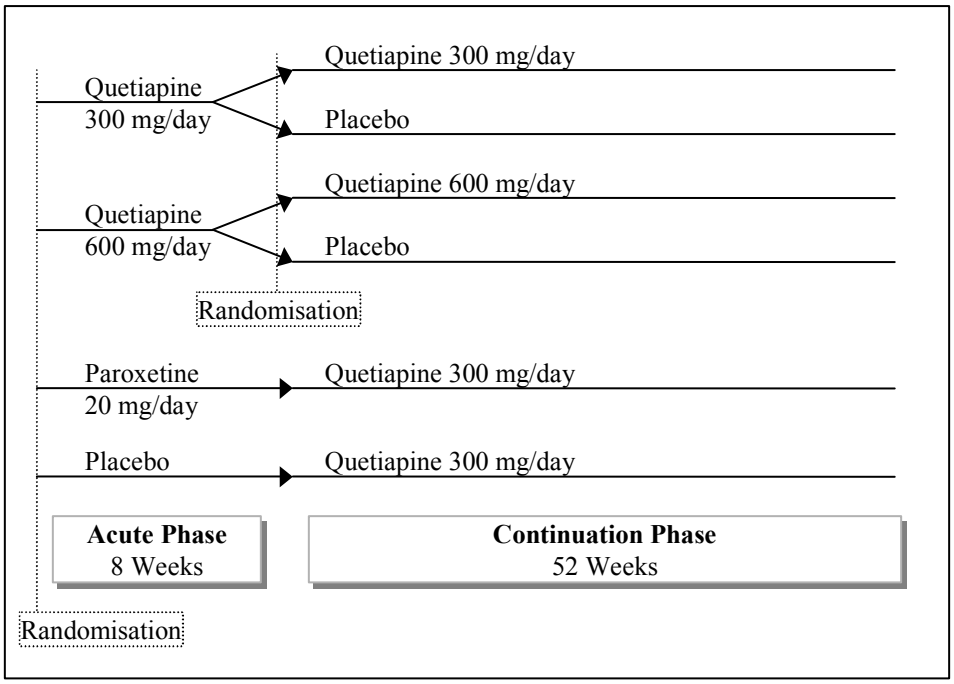
Multiple batches of the investigational products were used for different participating countries. [redacted]

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 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 total SDS score, the number of missed workdays and under-productive workdays reported on the SDS and change from baseline to Day 57 and to each assessment in Q-LES-Q total score

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.

Patient reported outcomes

- Change from Continuation Phase baseline to end of treatment in Q-LES-Q 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 Week 8 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; SDS Sheehan Disability Scale; Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire; 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 each 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 and CGI-BP-S. The variable CGI BP-C was analysed using a similar linear model. In addition, the dichotomous variables responders (50% decrease in MADRS total score),

remitters (MADRS total score ≤12) and CGI-BP-C response (CGI-BP-C overall illness score ≤2) 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-baseline 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 designed to be powered to detect treatment differences during the Continuation Phase. To draw conclusions on the efficacy results for the Continuation Phase, the data from the current study will be pooled, in a separate analysis presented outside this report, with data from a similarly designed study (D1447C00001). 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 mood event (depression or mania). Descriptive statistics were provided for mood event, depressed event, manic event, HAM-A, and Q-LES-Q.

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 paroxetine 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	PAR	Total
Baseline demographics (ITT population)						
N		229	232	121	118	700
Sex: n(%)	Male	88 (38.4)	91 (39.2)	40 (33.1)	43 (36.4)	262 (37.4)
	Female	141 (61.6)	141 (60.8)	81 (66.9)	75 (63.6)	438 (62.6)
Age (years)	Mean (SE)	38.4 (0.73)	38.5 (0.74)	38.7 (1.10)	39.3 (1.05)	38.6 (0.43)
	Min to max	18 to 65	18 to 63	18 to 65	19 to 62	18 to 65
Race: n(%)	Caucasian	134 (58.5)	132 (56.9)	72 (59.5)	72 (61.0)	410 (58.6)
	Black	63 (27.5)	66 (28.4)	25 (20.7)	29 (24.6)	183 (26.1)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Other	30 (13.1)	34 (14.7)	23 (19.0)	15 (12.7)	102 (14.6)
Weight[a]	Mean (SE)	82.4 (1.43)	82.7 (1.31)	80.2 (1.94)	84.3 (2.31)	82.4 (0.82)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline disease characteristics (ITT population)						
N		229	232	121	118	700
DSM-IV diagnosis: n(%)						
Bipolar I disorder		148 (64.6)	150 (64.7)	76 (62.8)	74 (62.7)	448 (64.0)
Bipolar II disorder		81 (35.4)	82 (35.3)	45 (37.2)	44 (37.3)	252 (36.0)
Mood episodes over past year: n(%)						
<4		183 (79.9)	197 (84.9)	97 (80.2)	94 (79.7)	571 (81.6)
≥4[b]		46 (20.1)	35 (15.1)	24 (19.8)	24 (20.3)	129 (18.4)
MADRS: mean (SE)		27.1 (0.49)	26.5 (0.51)	27.2 (0.71)	27.3 (0.64)	26.9 (0.28)
HAM-D: mean (SE)		24.2 (0.24)	24.2 (0.23)	24.2 (0.30)	24.1 (0.30)	24.2 (0.13)
HAM-A: mean (SE)		18.6 (0.41)	18.5 (0.38)	18.6 (0.60)	18.8 (0.54)	18.6 (0.23)
YMRS: mean (SE)		5.5 (0.19)	5.9 (0.21)	5.9 (0.30)	5.5 (0.29)	5.7 (0.12)
Patient disposition						
Randomized to Acute Phase		245	247	126	122	740
Randomized but received no dose		2	3	2	1	8
Acute Phase safety population		243	244	124	121	732
Acute Phase ITT population		229	232	121	118	700
PP population		211	216	118	112	657

[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. MADRS Montgomery-Asberg Depression Rating Scale. N Number of patients in treatment group. n Number of patients. PAR Paroxetine. PLA Placebo. PP Per-protocol. QTP Quetiapine. SE Standard error.YMRS Young Mania Rating Scale.
Note: Percentages are calculated as n/N*100.
Table derived from: Table 11.1.3- 1, Table 11.1.3- 4 and Table 11.1.2- 1

In general the Acute Phase population was considered representative of a patient population with Bipolar I and Bipolar II disorder, and the treatment groups were generally well balanced in demographic and baseline disease characteristics.

The total number of patients in the Acute Phase ITT population with either Bipolar I disorder or Bipolar II disorder exhibiting moderate to severe depression provided an adequate number to meet the design requirements for statistical power in the phase.

The characteristics of the patients who entered the Continuation Phase were generally similar to the patients who entered the Acute Phase, and the treatment groups were generally well balanced in demographic and baseline disease characteristics.

Of the 471 patients who completed the Acute Phase, 373 were eligible for randomisation to the Continuation Phase. Of the eligible quetiapine patients, approximately half were randomised to placebo and half to continue at the same dose, thereby providing 61 patients treated with quetiapine 300 mg, 66 patients treated with quetiapine 600 mg and 130 patients treated with placebo to the Continuation Phase. In order to preserve blinding, the eligible 76 placebo patients and 76 paroxetine patients were switched to quetiapine 300 mg for the Continuation Phase; these patients were included in the safety population but not the ITT population. Baseline mean MADRS scores for the ITT Continuation Phase population were 5.9, 6.1 and 6.1 in the quetiapine 300 mg, quetiapine 600 mg and placebo groups 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=229	QTP600 N=232	PLA N=121	PAR N=118
MADRS total score, LS mean change from baseline	-16.19[d]	-16.31[d]	-12.60	-13.76
MADRS response[a]	66.8%[e]	67.2%[f]	52.9%	55.1%
MADRS remission[b]	64.6%	68.5%[e]	55.4%	56.8%
MADRS item 10, (suicidal thoughts), LS mean change from baseline	-0.71	-0.76[e]	-0.52	-0.55
HAM-D total score, LS mean change from baseline	-14.68[d]	-15.09[d]	-11.42	-12.53
HAM-D item 1 score, LS mean change from baseline	-1.66[f]	-1.67[f]	-1.33	-1.51
HAM-A total score, LS mean change from baseline	-10.61[d]	-10.19[d]	-7.32	-9.15[e]
CGI-BP-S score, LS mean change from baseline	-1.67[e]	-1.65[e]	-1.33	-1.44
CGI-BP-C response [c]	53.3%[e]	53.4%[e]	40.5%	49.2%

Outcome variable	QTP300 N=229	QTP600 N=232	PLA N=121	PAR N=118
Q-LES-Q total score, LS mean change from baseline	8.75	8.96	7.28	7.96
SDS total score, LS mean change from baseline	-6.97	-6.66	-6.00	-6.04

[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. LOCF Last observation carried forward. MADRS Montgomery-Asberg Depression Rating Scale. Q-LES-Q Quality of life and enjoyment satisfaction questionnaire. SDS Sheehan disability scale. N number of patients in treatment group. LS Least square. PAR Paroxetine. PLA Placebo. QTP Quetiapine.
Note: For the analyses of MADRS change from baseline, p-values were adjusted using the Hochberg procedure.

Quetiapine treatment showed superiority to placebo in the change from baseline to Day 57 in MADRS total score for both the 300 mg and 600 mg groups.

Acute treatment with both quetiapine 300 mg and 600 mg was superior to placebo at Day 57 in rates of patients experiencing MADRS response and in the reduction of HAM-D total score, HAM-D item 1 (depressed mood) score and CGI-BP-S score. Superiority was shown in MADRS remission by quetiapine 600 mg, with a numerical advantage shown by quetiapine 300 mg. Acute treatment with quetiapine was superior to placebo at Day 57 in the reduction of HAM-D item 10 (suicidal thoughts) score and HAM-A total score; numerical advantages over placebo were shown by quetiapine-treament in SDS total score and Q-LES-Q total score.

Paroxetine treatment generally showed numerically greater improvements than placebo in these outcome variables at Day 57, although the differences were generally not statistically significant. The difference was statistically significant for HAM-A total score.

Quetiapine treatment showed numerically greater improvements than paroxetine in each of these outcome variables at Day 57, with superiority shown for both 300 mg and 600 mg in MADRS total score, MADRS response, HAM-D total score and CGI-BP-S score; quetiapine 600 mg also showed superiority to paroxetine in MADRS remission.

Efficacy results (Continuation Phase)

Treatment with quetiapine during the Continuation Phase (maximum 52 weeks) indicated maintenance of effect.

Fewer patients in the quetiapine groups experienced mood events than those treated with placebo: 25 (19.7%) vs 52 (40.3%). Patients treated with quetiapine experienced a 10% recurrence rate at 56 days, compared to 17 days among placebo treated patients. The Cox-proportional hazard analyses demonstrated that quetiapine was superior to placebo in increasing the time to recurrence of a mood event (hazard ratio = 0.43; 95% CI=0.27, 0.69).

Fewer patients in the quetiapine groups experienced depressed events than those treated with placebo: 17 (13.4%) vs 42 (32.6%). Patients treated with quetiapine treatment showed a 10% recurrence rate at 124 days, compared to 28 days for those treated with placebo. The Cox-proportional hazard analyses demonstrated that quetiapine was superior to placebo in increasing the time to recurrence of a depressed event (hazard ratio = 0.36; 95% CI=0.21, 0.63).

Few patients experienced a manic event during Continuation Phase. The incidence was lower in the quetiapine groups than those treated with placebo: 8 (6.3%) vs 10 (7.8%); however the difference was not statistically significant. (hazard ratio = 0.75; 95% CI=0.30, 1.90).

Safety results (Acute Phase)

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

Table S4 Patients who had an AE in any category - Acute Phase (safety population)

Category of adverse event	QTP300 N=243 n (%)	QTP600 N=244 n (%)	PLA N=124 n (%)	PAR N=121 n (%)
Any adverse event	160 (65.8)	171 (70.1)	78 (62.9)	84 (69.4)
Serious adverse event	1 (0.4)	9 (3.7)	4 (3.2)	9 (7.4)
Serious adverse event leading to death	0	0	0	0
Serious adverse event not leading to death	1 (0.4)	9 (3.7)	4 (3.2)	9 (7.4)
Drug-related adverse event[a]	118 (48.6)	141 (57.8)	45 (36.3)	51 (42.1)
Adverse event leading to discontinuation	22 (9.1)	30 (12.3)	10 (8.1)	16 (13.2)

[a] As judged by the investigator.
N Number of patients in treatment group. n Number of patients. PAR Paroxetine. 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.

[redacted]

There were no deaths among the randomised patients during the Acute Phase. [redacted]

One (1) patient (0.4%) in the quetiapine 300 mg group experienced an SAE [redacted]. In the quetiapine 600 mg group, there were reported 3 SAEs (1.2%) of depression. [redacted]

The most common AEs in the Acute Phase of the study summarized by preferred term are shown in Table S5.

Table S5 Common (≥5%) adverse events by preferred term – Acute Phase (safety population)

MedDRA preferred term[a]	QTP300 N=243 n (%)	QTP600 N=244 n (%)	PLA N=124 n (%)	PAR N=121 n (%)
Dry mouth	53(21.8)	63(25.8)	7(5.6)	12(9.9)
Somnolence	46(18.9)	43(17.6)	10(8.1)	7(5.8)
Sedation	31(12.8)	39(16.0)	6(4.8)	10(8.3)
Dizziness	28(11.5)	34(13.9)	7(5.6)	8(6.6)
Headache	24(9.9)	24(9.8)	16(12.9)	19(15.7)
Fatigue	16(6.6)	19(7.8)	4(3.2)	4(3.3)
Constipation	14(5.8)	22(9.0)	2(1.6)	6(5.0)
Nausea	14(5.8)	22(9.0)	7(5.6)	15(12.4)
Dyspepsia	8(3.3)	14(5.7)	3(2.4)	2(1.7)
Increased appetite	8(3.3)	13(5.3)	3(2.4)	3(2.5)
Insomnia	5(2.1)	5(2.0)	13(10.5)	16(13.2)
Diarrhoea	4(1.6)	7(2.9)	5(4.0)	8(6.6)
Decreased appetite	2(0.8)	2(0.8)	0	6(5.0)
Anxiety	1(0.4)	6(2.5)	7(5.6)	6(5.0)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
MedDRA Medical Dictionary for Regulatory Activities. N Number of patients in treatment group. n Number of patients. PAR Paroxetine. 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.

[redacted]

The most commonly reported AE for the quetiapine-treated groups were dry mouth, sedation, dizziness and headache, with similar frequencies in the 300 mg and 600 mg dose groups. Heachache, nausea, insomnia, diarrhoea and decreased appetite were more common in the paroxetine treated patients than in patients treated with quetiapine or placebo. Anxiety was more common in the placebo group than in the active treatment groups.

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 results (Continuation Phase)

A summary of treatment emergent AEs and drug-related AEs during the Continuation Phase is presented in Table S6.

Table S6 Patients who had an AE (treatment emergent only) in any category – Continuation Phase (safety population)

Category of adverse event	QTP300 N=61 n (%)	QTP600 N=66 n (%)	PLA N=129 n (%)	QTP300 (PLA) N=60 n (%)	QTP300 (PAR) N=50 n (%)
Any adverse event	34 (55.7)	36 (54.5)	69 (53.5)	33 (55.0)	29 (58.0)
Drug-related adverse event[a]	10 (16.4)	18 (27.3)	24 (18.6)	23 (38.3)	21 (42.0)

[a] As judged by the investigator.
N Number of patients in treatment group. n Number of patients. PAR Paroxetine. PLA Placebo. QTP Quetiapine.
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.
Note: Treatment within parenthesis is treatment during Acute Phase
[redacted]

The overall treatment emergent adverse event rate during the Continuation Phase was higher in quetiapine treated patients (54.5 to 58.0%) than in the placebo treated patients (53.5%). Among the quetiapine groups, the overall treatment emergent adverse event rate was higher in patients switching from paroxetine to quetiapine 300 mg (58.0%) than in the other quetiapine groups.

A summary of ongoing or treatment emergent SAEs and AEs leading to discontinuation during the Continuation Phase is presented in Table S7

Table S7 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=61 n (%)	QTP600 N=66 n (%)	PLA N=129 n (%)	QTP300 (PLA) N=60 n (%)	QTP300 (PAR) N=50 n (%)
Serious adverse event	2 (3.3)	1 (1.5)	6 (4.7)	1 (1.7)	1 (2.0)
[redacted]					
Adverse event leading to discontinuation	5 (8.2)	7 (10.6)	9 (7.0)	6 (10.0)	4 (8.0)

[a] As judged by the investigator.
N Number of patients in treatment group. n Number of patients. PAR Paroxetine. PLA Placebo. QTP Quetiapine.
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.

Note: Treatment within parenthesis is treatment during Acute Phase

[redacted]

Serious Adverse Events were lower among patients treated with quetiapine than those treated placebo. Adverse Events leading to discontinuation were higher among patients treated with quetiapine and most common in the quetiapine 600 mg group.

[redacted]

Overall, the AE profile in the Continuation Phase was consistent with the findings in the Acute Phase.

The most common treatment emergent AEs in the Continuation Phase of the study summarized by preferred term are shown in Table S8

Table S8 Common AEs (treatment emergent only) by preferred term – Continuation Phase (safety population)

MedDRA preferred term[a]	QTP300 N=61 n (%)	QTP600 N=66 n (%)	PLA N=129 n (%)	QTP300 (PLA) N=60 n (%)	QTP300 (PAR) N=50 n (%)
Headache	8(13.1)	4(6.1)	12(9.3)	5(8.3)	5(10.0)
Nausea	7(11.5)	1(1.5)	2(1.6)	3(5.0)	1(2.0)
Abdominal pain upper	4(6.6)	1(1.5)	3(2.3)	0	1(2.0)
Nasopharyngitis	4(6.6)	2(3.0)	5(3.9)	4(6.7)	2(4.0)
Vomiting	4(6.6)	0	2(1.6)	1(1.7)	0
Dizziness	3(4.9)	2(3.0)	3(2.3)	11(18.3)	6(12.0)
Fatigue	3(4.9)	1(1.5)	2(1.6)	1(1.7)	3(6.0)
Insomnia	3(4.9)	3(4.5)	20(15.5)	2(3.3)	1(2.0)
Sedation	3(4.9)	2(3.0)	0	8(13.3)	5(10.0)
Dry mouth	2(3.3)	4(6.1)	4(3.1)	6(10.0)	10(20.0)
Hypertension	2(3.3)	0	0	3(5.0)	1(2.0)
Upper respiratory tract infection	2(3.3)	2(3.0)	2(1.6)	1(1.7)	3(6.0)
Back pain	1(1.6)	4(6.1)	2(1.6)	2(3.3)	0
Sinusitis	1(1.6)	0	1(0.8)	4(6.7)	0
Somnolence	1(1.6)	4(6.1)	6(4.7)	7(11.7)	6(12.0)
Cough	0	0	1(0.8)	0	3(6.0)
Dyspepsia	0	0	2(1.6)	3(5.0)	3(6.0)
Irritability	0	0	2(1.6)	0	3(6.0)
Restlessness	0	2(3.0)	1(0.8)	3(5.0)	0

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.

MedDRA Medical Dictionary for Regulatory Activities. N Number of patients in treatment group. n Number of patients. PAR Paroxetine. PLA Placebo. QTP Quetiapine.

Note: Events first reported or worsened in 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.
Note: Treatment within parenthesis is treatment during Acute Phase

[redacted]

In the Continuation Phase, the pattern of common, treatment emergent AEs was generally in-line with the patten shown during the Acute Phase. Nausea was reported most often by patients treated with quetiapine 300 mg (11.5% vs 1.5% to 5% in the other treatment groups), and insomnia was reported most often by patients treated with placebo (15.5% vs 2.0% to 4.9% in the other treatment groups). Patients switched from placebo and paroxetine showed the greatest incidences of somnolence, sedation, dry mouth and dizziness.