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Clinical Study Report

Drug substance:	Quetiapine SR
Study code:	D1444C00004
Date:	23 September 2006

A 1-year, International, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Phase III Study to Evaluate Prevention of Relapse in Patients in Stable Condition with Chronic Schizophrenia Receiving Either Sustained-release Quetiapine Fumarate (SEROQUEL) or Placebo

Study dates: First patient enrolled: 15 March 2005
Last patient completed: 6 April 2006

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice.

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Drug product:	Seroquel SR	**SYNOPSIS**	
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A 1-year, International, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Phase III Study to Evaluate Prevention of Relapse in Patients in Stable Condition with Chronic Schizophrenia Receiving Either Sustained-release Quetiapine Fumarate (SEROQUEL) or Placebo

Study centers

327 patients had been enrolled when the study was stopped after a pre-planned interim analysis after 45 relapses. 26 centers in Europe and India participated. Enrollment was competitive between countries and centers, and was stopped was stopped after 45 relapses.

Publications

Not published

Study dates		**Phase of development**
First patient enrolled	15 March 2005	Therapeutic confirmatory (III)
Last patient completed	6 April 2006	

Objectives

Primary objective

The primary objective in this study was to demonstrate superior efficacy of quetiapine fumarate sustained-release (Seroquel SR, hereafter called quetiapine SR) to placebo by evaluating relapse prevention in longer-term use in patients with schizophrenia as measured by the time to first psychiatric relapse up to one year (time to relapse was assessed using randomization and time to first instance of the first psychiatric relapse).

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Secondary objectives

Secondary objectives of the study were:

1. To demonstrate superiority of quetiapine SR to placebo by evaluating the risk of relapse (defined as proportion of relapses per treatment group) in long-term use in patients with schizophrenia by evaluating the 6-month relapse rate.

2. To document that quetiapine SR was superior to placebo in treating positive and negative symptoms by evaluating the Positive and Negative Syndrome Scale (PANSS) total score and PANSS sub scores

3. To document continuing stability of negative symptoms with quetiapine SR by evaluating the change in PANSS-Negative score (PANSS-N) from baseline to last visit before relapse, but not including relapse visit.

4. To document that the effect of quetiapine SR on global clinical status was superior to placebo by measuring the Clinical Global Impression-Severity of Illness (CGI-S) as change from baseline to last visit and to measure the proportion of patients with a CGI-S score of ≤4 at last visit

5. To document that the effect of quetiapine SR on global clinical status was superior to placebo by measuring the Clinical Global Impression-Improvement (CGI-I) at last visit.

6. To show that quetiapine SR was safe and well tolerated in long-term use

Study design

This multi-center, randomized, double-blind, parallel group, placebo-controlled study evaluated the efficacy and safety of quetiapine SR compared to placebo in long-term use (up to one-year), by examining relapse in patient's psychiatric conditions.
An optional part of the study included the collection of a blood sample for future genetic research. The sampling was optional on both patient, center and country level.
Stabilization period: Prior to randomization, a 16-week stabilization period ensured that the patients were clinically stable and receiving a stable dose of quetiapine.
Patients were judged clinically stable when they met the following criteria:

- 0 CGI-S score ≤4 and a PANSS score ≤60 at enrollment and baseline (randomization visit) with no change ≥10 points in PANSS total score from enrollment to baseline visit or from enrollment to the visit 8 weeks before randomization

- 1 received a stable dose of quetiapine SR in the dose range 400 to 800 mg/day (patients enrolled in the stabilization period were already receiving a stable dose of an antipsychotic medication and were judged clinically stable by the principal investigator at each site)

Randomized period: The double-blind portion of the study started at randomization. The patients were assigned to treatment e with either quetiapine SR or placebo. The patients were planned to be treated for one year or until relapse.
A pre-planned interim analysis was conducted by a Data and Safety Monitoring Board (DSMB) after 45 observed relapses. Another interim analysis was planned to be done after 60 relapses and the final analysis after 90 relapses. The study was terminated at the recommendation of the DSMB after the interim analysis of 45 relapses since the difference between quetiapine SR and placebo reached statistical significance in the primary outcome variable.

Target patient population and sample size

Male and female patients between the ages of 18 and 65 years, who fulfilled the criteria of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (American Psychiatric Association 1994) for at least 2 years and who were stable in their condition after switch to a stable dose of quetiapine SR.

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

The product used was quetiapine fumarate sustained-release (SR) 50 and 200 mg tablets. The investigational product was administered orally once daily in the evening.
Treatment with the investigational product started with a 4-day cross-titration phase where ongoing antipsychotic medication was phased out and quetiapine SR was phased in. Quetiapine SR 300 mg/day was given at Day 1 and 600 mg/day was given at Day 2. At Day 3, either the 600 mg dose was maintained or the titration continued to the maximum dose 800 mg/day. If the 600 mg dose was not tolerated, the dose was decreased to 400 mg/day at Day 3. For the remaining period of the 16-week stabilization period a flexible dosing between 400 mg and 800 mg/day was applied with minimum dose adjustments of 200 mg/day.
After the stabilization period the patients were randomized. Following randomization, a cross-titration of 4 days started. The open-label quetiapine SR used during the stabilization period was replaced with blinded quetiapine SR (or placebo) over 4 days. Open-label quetiapine SR was decreased by 25% each day and blinded quetiapine SR (or placebo) were increased by 25% each day. The cross-titration was followed by a treatment period planned to be oneyear (ie, randomized period) during which dosing was flexible by doses of 200 mg, ie, the dose could be 400, 600 or 800 mg/day. Dosage could be adjusted for therapeutic efficacy and/or tolerability reasons within the allowed dosing range at every visit or at extra visits throughout the study.
Placebo tablets had the same appearance, smell and taste as the quetiapine SR tablets to ensure the blinding of the study. Placebo was administered orally once daily in the evening.
The batch numbers for quetiapine SR used during the open label stabilization period were 22597I04, 23557G04 and LJ4707 for 50 mg, and 22319A04, 22321J04, LA4601, 31534I05, LA4602 and 22366A04 for 200 mg. During the randomized period batch numbers 22597I04, 23557G04 and LJ4707 were used for 50 mg and 22319A04, 22321J04, LA4601, 31534I05, LA4602 and 22366A04 were used for 200 mg. The batch

numbers for placebo 50 mg were 85068K01, 32202B05 and 22947I04 and for placebo 200 mg 21157H04 and 22948F04.

Duration of treatment

All patients were treated with quetiapine SR for 16 weeks during the stabilization period. The placebo controlled randomized period was to be one year or until relapse for each patient or until the study was terminated**.** As the study was terminated after a positive interim analysis the mean duration of the double-blind, randomized treatment period with quetiapine SR was 4 months (120 days) and the maximum period was 9 months (270 days). During the whole study, including both stabilization and randomization period, 63 patients were treated with quetiapine SR for more than 6 months.

Criteria for evaluation (main variables)

Efficacy

- Primary outcome variable: Time to relapse in long-term treatment in patients with schizophrenia.

The primary endpoint was deterioration in the patient's condition or insufficient clinical effect despite dose adjustments according to at least one of the following definitions of relapse: hospitalization due to worsening of the schizophrenia, an increase in PANSS score of 30% from baseline, a rating of "much worse" or "very much worse" (score 6 or 7) on the CGI-I scale or need for any other antipsychotic medication to treat psychosis.

- Secondary variables: The relapse rate at 6 months, PANSS total score, PANSS subscale (PANSS-P, -N and –G) score change from baseline to last visit prior to relapse, CGI-S change from baseline to last visit, proportion of patients with CGI-S ≤4 at last visit, proportion of patients with CGI-I ≤4 at last visit and CGI-I score at last visit

Safety

The safety assessments included: AEs during the randomization period, laboratory measurements (hematology, clinical chemistry and urinalysis), electrocardiogram (ECG), vital signs (blood pressure and pulse rate), weight, waist circumference, Simpson Angus Scale (SAS) Simpson 1970, Barnes Akathisia Rating Scale (BARS) Barnes 1989 use of anticholinergic medication, and data for other specific safety areas (extrapyramidal symptom (EPS) events, diabetes mellitus, QT prolongation, neutropenia/agranulocytosis, metabolic risk factors, suicidality, and weight changes).

Statistical methods

Three analysis sets were used for efficacy analyses; the interim ITT population that included all ITT patients and all assessments available at the time of the interim analysis (apart from two patients with randomization date before date of last visit in the data in the interim analysis), the total ITT population that included all ITT patients including visits occurring after the interim analysis as well as the additional patients that entered between interim analysis and stop of study, and the PP population.
The primary endpoint was time to schizophrenic relapse in the interim intention to treat (interim ITT) population. The main analysis of time to schizophrenic relapse was a Cox

proportional hazards model to estimate the hazard ratio of relapse rate between treatment groups, with a 95% confidence interval. A 2-sided score test of the null hypothesis that the hazard ratio was equal to unity was performed. The time to event was censored when a patient was discontinued for other reasons than relapse or completed the study. The time of censoring was the date of the patient's final assessment. The primary analysis was repeated for the total ITT population and for the PP population as a consistency check.

One secondary endpoint was the risk of relapse at 6 months in each treatment. The proportion of patients having a schizophrenic relapse at 6 months in each treatment was estimated from the same Cox model that was used in the primary analysis, where one minus the estimation of the survivor function at 6 months provided the estimation for this proportion and the t-test was used to test the difference between treatment groups. The secondary endpoints PANSS total score and subscale scores were all analyzed using a mixed effect repeated measurement analysis of all post-baseline measurements from randomization up to, but not including, the relapse. Score at randomization, treatment and visit were included as fixed effects, and subjects nested within a treatment were treated as a random effect. The secondary endpoint CGI-S change from baseline to last visit was analyzed descriptively. The proportion of patients with CGI-S =4 at last visit was analyzed using a Cochran-Mantel-Haenszel (CMH) technique. The mean CGI-I score at last visit was analyzed using a t-test. All secondary endpoints were analyzed on the total ITT population.

Descriptive statistics were used for safety and tolerability assessments.

O'Brien-Flemming boundaries (Jennison and Turnbull 2000a, 2000b, 2000c) was used in the interim analysis to ensure an overall significance level of 0.05. As a result of the analysis of the time to relapse after 45 relapses carried out by the DSMD, the study was stopped.

A stepwise sequential procedure was used for the confirmatory part of this study to ensure a multiple level of significance of 0.05. The confirmatory part included the primary analysis, and the analysis of risk of schizophrenic relapse at 6 months, PANSS total score, CGI-S, CGI-I.

Patient population

A total of 327 patients started open label treatment and 197 patients completed the open label stabilization period. 63 patients (19.3% of the enrolled) discontinued during the open label period and 67 ongoing patients (20.5% of the enrolled) were discontinued due to the early study termination. In the interim analysis (covering the first 45 relapses), 171 (52.3% of the enrolled) patients were randomized; 87 received placebo and 84 patients received quetiapine SR.

The randomized safety/total ITT population is summarized in Table S1.

Table S1 Patient population and disposition

	PLA N=103	**QTP SR N=94**
Demographic characteristics (Total ITT)		
Sex: n (%)		
Male	65 (63.1)	57 (60.6)

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Table S1 Patient population and disposition

	PLA N=103	QTP SR N=94
Female	38 (36.9)	37 (39.4)
Age (years)[a]		
Mean (SD)	34.1 (9.8)	36.5 (10.6)
Range	18 to 64	18 to 63
Race/ethnicity: n (%)		
Caucasian	103 (100.0)	94 (100.0)
Black	0	0
Oriental	0	0
Other	0	0
Baseline disease characteristics (Total ITT)		
DSM-IV diagnosis, schizophrenic subtype: n (%)		
Disorganized	4 (3.9)	2 (2.1)
Paranoid	84 (81.6)	81 (86.2)
Residual	3 (2.9)	1 (1.1)
Undifferentiated	12 (11.7)	10 (10.6)
PANSS at randomization[b]		
Mean (SD)	47.4 (7.7)	47.9 (8.1)
CGI severity of illness at randomization[c]		
Mean (SD)	2.7 (0.8)	2.6 (0.7)
Patient populations analyzed:		
N analyzed for safety during stabilization period		327
N analyzed for safety during randomized period	103	94
N analyzed for primary efficacy only (interim ITT population)	87	84
N analyzed for efficacy (total ITT population)	103	94
N analyzed for primary efficacy only (PP population)	81	77

[a] At enrollment.

[b] Inclusion criterion was PANSS score at enrollment and randomization ≤60.

[c] Inclusion criteria was CGI score at enrollment and randomization ≤4.

CGI Clinical Global Impression. DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th edition. N Number of patients in treatment group. n Number of patients. PANSS Positive and Negative Syndrome Scale. PLA Placebo. PP Per protocol. QTP Quetiapine. SR Sustained-release.

The 171 patients in the interim ITT population was used for the primary analysis of efficacy. The 197 patients in total ITT population (presented in Table S1) was used for all other efficacy analyses. The primary analysis of time to relapse was repeated for the total ITT and PP populations for a consistency check.

There were no apparent differences in demography and background variables across the three populations, and the placebo and the quetiapine SR groups were well balanced in

demographic and baseline characteristics. All of the patients in the total ITT population were Caucasian and the majority were men (approximately 62%). The mean age was approximately 35 years (34.1 years in the placebo group and 36.5 years in the quetiapine group). The patients were predominantly diagnosed as paranoid schizophrenics (approximately 84%) with minimal schizophrenic symptoms (mean PANSS total score approximately 48 and mean CGI Severity of Illness approximately 2.7).
The randomized population was similar to the enrolled population with regard to demography and disease characteristics.

Efficacy results

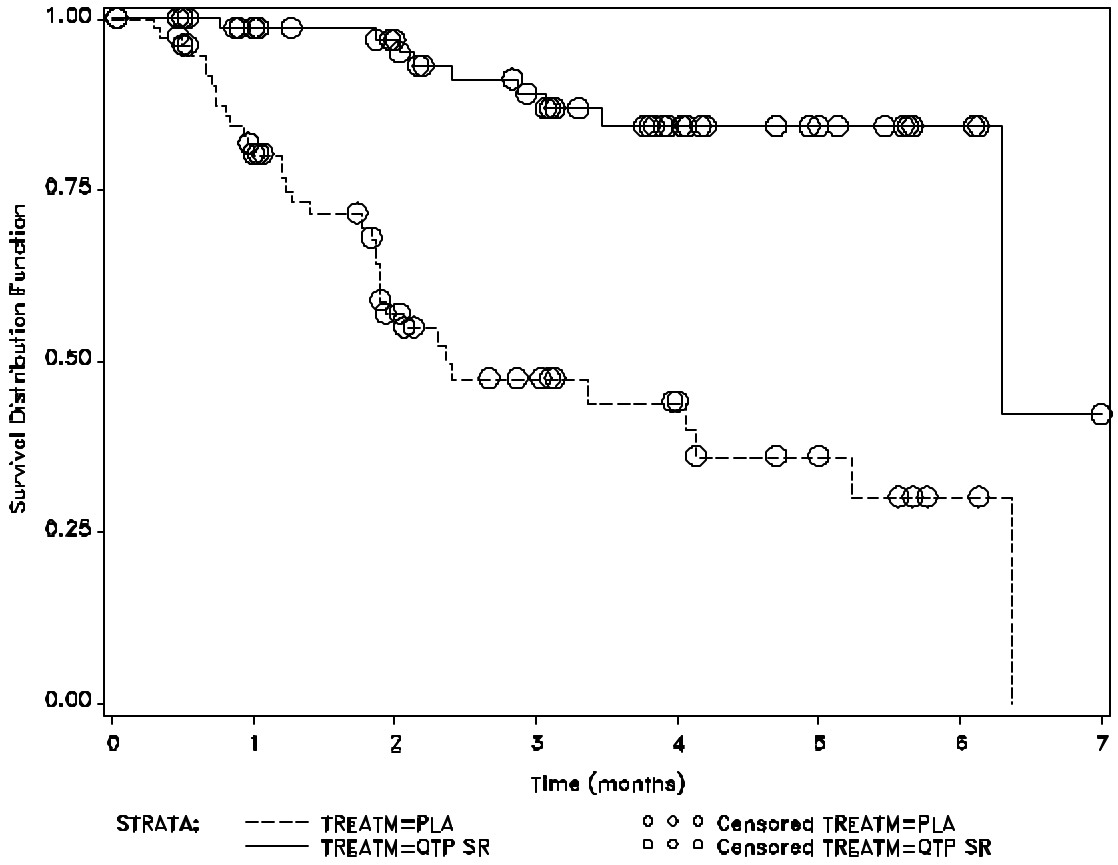
The main efficacy results are summarized in Table S2.

Table S2 Efficacy results, randomized treatment period (ITT population)

Outcome variable		PLA	QTP SR	Hazard ratio / Estimated difference / Odds ratio (95% CI)	p-value
Primary analysis (interim ITT population)	N	87	84		
Time to schizophrenic relapse[a, b]	Number of relapses (%)	36 (41.4)	9 (10.7)	HR[c] : 0.16 (0.08, 0.34)	<.0001[d]
Secondary analyses (total ITT population)	N	103	94		
Time to schizophrenic relapse[b]	Number of relapses (%)	50 (48.5)	11 (11.7)	HR[c] : 0.13 (0.07, 0.26)	<.0001[e]
Risk of schizophrenic relapse at 6 months[a]	Proportion of patients[f] (95% CI)	68.2 (59.2, 77.2)	14.3 (7.2, 21.3)	Diff: -54.0 (-65.4, -42.5)	<.0001[e]
PANSS total score[a]	LS mean[g] (SE)	48.86 (0.51)	47.15 (0.40)	Diff: -1.71 (-2.84, -0.58)	0.0033[e]
PANSS-P subscale score	LS mean[g] (SE)	9.95 (0.20)	9.48 (0.16)	Diff: -0.47 (-0.93, -0.00)	0.0483[e]
PANSS-N subscale score	LS mean[g] (SE)	14.42 (0.25)	13.89 (0.21)	Diff: -0.53 (-1.01, -0.05)	0.0296[e]
PANSS-G subscale score	LS mean[g] (SE)	24.52 (0.31)	23.69 (0.23)	Diff: -0.83 (-1.55, -0.12)	0.0224[e]
CGI-S[a]	Patients with CGI-S ≤4[h] : n (%)	84 (84.0)	87 (93.5)	OR: 2.76 (1.03, 7.40)	0.0375[e]
CGI-I[a]	Mean score at last visit[i] (95% CI)	4.5 (4.2, 4.8)	3.7 (3.4, 4.0)	Diff: -0.83 (-1.24, -0.42)	<.0001[e]

[a] The analysis of this variable was included in the confirmatory part of the study and a stepwise sequential testing procedure was pre specified. The multiple level of significance of 0.05 was ensured for this variable.
[b] Due to the low rate of relapse in the quetiapine SR group it is not possible to calculate a reliable median time to relapse. The number of relapses is presented for information. The p value relates to the analysis of time to schizophrenic relapse.
[c] Hazard ratio estimated by Cox proportional hazards model.
[d] significant at alpha level 0.004455
[e] significant at alpha level 0.05
[f] Cox regression estimate.
[g] estimate of LS mean change during randomized period from a mixed effect repeated measures analysis of all post-baseline measurements from randomization up to, but not including, the relapse.
[h] Proportion of patients with CGI-S≤4 at last assessment (including any relapse)

Figure S1 Time to schizophrenic relapse, Kaplan Meier curves (interim ITT population)



ITT Intention-to-treat. PLA Placebo. QTP Quetiapine. SR Sustained-release.

Note: The drop of the quetiapine SR Kaplan Meier curve at the end of the figure is due to a late relapse of a single patient at a time where only two quetiapine SR patients were at risk. The drop of the placebo Kaplan Meier curve at the end of the figure is due to a late relapse of a single patient at a time where no other placebo patient was at risk. The right hand parts of the Kaplan Meier curves (after 6 months exposure) depend on single events. These parts doesn't give reliable estimates of the percentage of relapse free patients.

The estimated time to relapse in minimally symptomatic patients with stable chronic schizophrenia was significantly longer in the quetiapine SR group compared to the placebo group.

In the interim ITT population, the risk of a relapse was reduced by 84% (HR 0.16, $p<0.0001$) in the patients treated with quetiapine SR compared to patients treated with placebo. The estimated time at which 90% of patients remained relapse free was 2.9 months for the quetiapine SR group, compared to 0.7 months for patients for the placebo group. Fewer patients experienced a relapse in the quetiapine SR group (10.7%) compared to patients in the placebo group (41.4%). Due to the low rate of relapse in the

quetiapine SR group no later time to relapse could be reliably estimated for the interim ITT population.

In the total ITT population, the risk of relapse was similarly reduced by 87% (HR 0.13, $p<0.0001$). The estimated risk of relapse at 6 months was significantly lower in the quetiapine SR group (14.3%) than in the placebo group (68.2%).

In clinically stable schizophrenic patients, there were statistically significant differences in favor of quetiapine SR compared to placebo in PANSS total score, negative symptoms score, positive symptoms score and in general psychopathology score up to the visit prior to a relapse. Maintenance of treatment effect of quetiapine SR was also supported by statistically significant differences between treatment groups in CGI Severity of Illness and CGI Improvement scores at last visit.

Safety results

During the randomized treatment period, the mean mean dose of quetiapine SR was 669 mg/day, and the most frequently used doses were 600 mg/day and 800 mg/day. There was no indication of changes in dosage over time during randomized treatment.

The number (%) of patients who had at least 1 adverse event in any category is summarized in Table S3.

Table S3 Various categories of adverse events (randomized safety population)

	PLA N=103	**QTP SR N=94**
	n (%)	**n (%)**
Adverse events[a]	42 (40.8)	30 (31.9)
Serious adverse events[a]	2 (1.9)	0
Serious adverse events leading to death[a]	1 (1.0)	0
Serious adverse events not leading to death[a]	1 (1.0)	0
Drug-related adverse events[a b]	22 (21.4)	17 (18.1)
Adverse events leading to discontinuation[a]	1 (1.0)	1 (1.1)
Total number of adverse events		
Adverse events	88	62
Serious adverse events	2	0
Drug-related adverse events[b]	40	25

[a] Patients with multiple events in the same category are counted only once in that category.
[b] As judged by the investigator.
N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine. SR Sustained-release.
Note: Events emerging during randomized period.

Overall, quetiapine SR was generally safe and well tolerated in this study. During the open-label treatment period there were no SAEs, and only 4 patients were discontinued due to an adverse event. During the randomized phase, there was one death, a completed suicide in a 25-year-old male after 173 days of placebo treatment. SAEs and discontinuations due to AEs were infrequent in both treatment groups. The incidence of AEs judged by the investigator to be drug-related was not higher in the quetiapine SR

group than in the placebo group. Most AEs in both groups were mild or moderate in intensity. There was no indication of late emergence of adverse events

The most common AEs during the randomized treatment period are summarized in Table S4.

Table S4 Common adverse events emerging after randomization (randomized safety population)

	PLA N=103	QTP SR N=94
MedDRA Preferred term[a]	**n(%)**	**n(%)**
Insomnia	18 (17.5)	8 (8.5)
Headache	5 (4.9)	7 (7.4)

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

MedDRA Medical Dictionary of Regulatory Activities. N Number of patients in treatment group. n Number of patients. PLA Placebo. QTP Quetiapine. SR Sustained-release.

Note: Common adverse event: adverse events occurring at an incidence of ≥5% in any randomized treatment group. Events emerging during randomized period by decreasing frequency in the QTP treatment group.

The most frequent system organ classes represented in the quetiapine SR group were psychiatric disorders, the nervous system, infections and infestations, and the gastrointestinal system. The incidence of AEs were similar in the two treatment groups; placebo 40.8% and quetiapine SR 31.9%. There were no time-dependent changes in adverse events during the randomisation period. Only two separate AE preferred terms occurred at an incidence =5 % during the randomized treatment period. Headache was more common in the quetiapine SR group and insomnia was more than twice as common in the placebo group as in the quetiapine SR group. Other separate adverse event preferred terms that has previously been reported to be relatively common with quetiapine, eg somnolence and dizziness, were infrequently reported as emerging during randomized treatment in this study. Similar low incidences were noted in aggregated analyses of AEs associated with somnolence (1 patient treated with quetiapine SR and 2 patient treated with placebo) and dizziness (2 patients treated with quetiapine SR and 1 patient treated with placebo).

During the randomizatio n period there were 5 patients with either an AE associated with neutropenia or emerging low neutrophil values, 4 in the SR group (E1305001, E1306007, E1208002, and E1206006) and 1 in the placebo group (E1404007). For 3 of the 4 patients on quetiapine SR, the neutrophil count returned to normal while still on treatment. For the 4^{th} patient (E1306007) the neutrophil count had increased somewhat after 11 weeks to 1.59 x 10^9 cells/L when the patient was discontinued due to the termination of the study. The patient in the placebo group had neutrophil counts between 1.60 and 2.78 x 10^9 cells/L until the last visit on Day 36, when the value decreased to 1.45 and the patient was discontinued due to “condition worsened”.

During the stabilization period there were 11 patients that had a low neurophil value (<1.5 x 10^9 cells/L). 4 of them still had low values at the end of the stabilization period, but all returned to above 1.5 during the randomization period when 3 of the patients were in the quetiapine group and one in the placebo group.. No agranulocytosis was reported during any of the 2 treatment periods.

No AEs associated with QT prolongation or diabetes mellitus were registered in the two groups. There were no AEs associated with suicidality in addition to the completed suicide in the placebo group.
Mean and median changes in clinical laboratory variables including glucose and neutrophils during randomized treatment with quetiapine SR were small and similar to those seen with placebo treatment. For glucose similar values were seen for patients with documented fasting. The incidences of patients observed with shifts from normal glucose levels at baseline to high levels at end of treatment was 8.0% in the placebo group and 4.1% in the quetiapine SR group. The mean changes in glucose regulation variables were small during the open label treatment period and not clinically meaningful. Concerning clinically important values at any time, the incidence was higher for high total cholesterol, LDL and triglycerides in the quetiapine SR group than in the placebo group.
A small increase in pulse rate was observed in the quetiapine SR group, in contrast to a similarly small decrease in the placebo group. There was no patient in the quetiapine SR group with potentially clinically important combined pulse and systolic blood pressure values. No increase in mean QTcF was observed in either of the treatment groups at end of the randomized treatment period.
During the randomized treatment period a small increase in mean weight (0.46 kg) and mean circumference (0.49 cm) was observed in the quetiapine SR treatment group while there was a small mean decrease (-0.68 kg and -0.52 cm) in the placebo group.
The incidence of AEs associated with EPS in the quetiapine SR group was low and comparable to placebo. The low and placebo-like incidence of AEs associated with EPS was supported by the mean SAS and BARS scores. Consistent with these findings, anticholinergic use was low throughout the randomized treatment period with no indication of an increased use over time. In an aggregated analyses of AEs associated with EPS (1 patient in each treatment group) the incidence was low with quetiapine SR.
This study also indicates that the quetiapine SR dose escalation scheme used in this study, 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg on Day 3 while tapering down the ongoing antipsychotic in four days was safe and well tolerated.
There was no evidence of marked withdrawal effects in the placebo patients after a rapid withdrawal (4 days) of quetiapine SR at randomization.
Overall, there were no unexpected findings related to safety and tolerability with the use of quetiapine SR in this study.