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Clinical Study Report

Drug Substance:	quetiapine
Edition Number	01
Study Code	D1441C00125
Date	12 June 2006

A 24-Week, International, Multi-centre, Open-label, Flexible-dose, Randomised, Parallel-Group, Phase IV Study to Compare the Effect on Glucose Metabolism of Quetiapine, Olanzapine, and Risperidone in the Treatment of Patients with Schizophrenia

Study dates: First patient enrolled: 29 April 2004
Last patient completed: 24 October 2005

Phase of development: IV

This study was performed in compliance with Good Clinical Practice.

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Drug Product	Seroquel	**SYNOPSIS**	
Drug Substance(s)	quetiapine		
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A 24-Week, International, Multi-centre, Open-label, Flexible-dose, Randomised, Parallel-Group, Phase IV Study to Compare the Effect on Glucose Metabolism of Quetiapine, Olanzapine, and Risperidone in the Treatment of Patients with Schizophrenia

Study centres

The study was conducted in Bulgaria (8 active centres), Czech Republic (8 active centres), Germany (6 active centres), Hungary (7 active centres), Norway (1 active centre), Romania (7 active centres), Slovakia (12 active centres), South Africa (8 active centres), and United Kingdom (1 active centre).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	29 April 2004	Therapeutic use (IV)
Last patient completed	24 October 2005	

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Objectives

Primary objective

To compare the safety/tolerability profile of quetiapine and olanzapine on glucose metabolism in schizophrenic patients by evaluating the change from randomisation at Week 24 in Area Under the Curve (AUC) 0-2h of the plasma glucose values following Oral Glucose Tolerance Test (OGTT).

Secondary objectives

Glucose metabolism, blood lipid levels and weight

- To compare the safety/tolerability profile of quetiapine and risperidone on glucose metabolism in schizophrenic patients by evaluating the change from baseline at Week 24 in AUC 0-2h of the plasma glucose values following OGTT.

- To further compare the safety/tolerability profile of quetiapine, olanzapine and risperidone on glucose metabolism by evaluating change from randomisation at Week 24 in the following: fasting plasma glucose; proportion of patients with hyperglycemia; proportion of patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT); fasting plasma insulin; AUC 0-2h of the plasma values of insulin following OGTT; index of insulin sensitivity (ISI) derived from OGTT; homeostasis model assessment (HOMA); haemoglobin A_{1c} (HbA_{1c}); C-peptide.

- To compare the safety/tolerability profile of quetiapine, olanzapine and risperidone on lipid levels by evaluating change from randomisation at Week 24 in fasting lipid levels: total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL) and triglycerides.

- To compare the safety/tolerability profile of quetiapine, olanzapine and risperidone on weight by evaluation of change from randomisation at Week 24 in weight, body mass index (BMI) and waist circumference.

Other safety and tolerability objectives

- To compare the safety/tolerability profile of quetiapine, olanzapine and risperidone on prolactin level by evaluation of change from randomisation at Week 24.

- To compare the safety/tolerability profile of quetiapine, olanzapine and risperidone on extrapyramidal symptoms (EPS) and other adverse events (AEs)

as measured by: reporting of AEs; changes in electrocardiogram (ECG), blood pressure and pulse rate; change in Simpson-Angus Scale (SAS) total score and Barnes Akathisia Rating Scale (BARS) score from randomisation at Week 24; proportion of patients using anticholinergic medication.

Efficacy objectives

- To document maintained efficacy of quetiapine, olanzapine and risperidone by evaluating clinical symptoms in patients with schizophrenia by assessment of: proportion of patients with a Clinical Global Impression Severity of Illness (CGI-S) score of =3 at Week 24; Clinical Global Impression Global Improvement (CGI-I) score at Week 24; proportion of patients with CGI-I score of "very much improved" or "much improved" at Week 24.

Other objectives

- To compare the patients' well-being, measured by Personal Evaluation of Transitions in Treatment (PETiT) total score, by change from randomisation at Week 12 and Week 24/end of treatment, and by absolute value at Week 12 and Week 24/end of treatment.

- To compare the treatment satisfaction, measured by PETiT subscore, by change from randomisation at Week 12 and Week 24/end of treatment, and by absolute value at Week 12 and Week 24/end of treatment.

- To investigate the attitudes to compliance and non-compliance, measured by the Rating of Medical Influences Scale (ROMI), by change from randomisation at Week 12 and Week 24/end of treatment, and by absolute value at Week 12 and Week 24/end of treatment.

Study design

This was an international, multicentre, randomised, open-label, flexible-dose, comparative, parallel group study evaluating the effect on glucose metabolism of quetiapine, olanzapine and risperidone in schizophrenic patients after 24 weeks of treatment.

Target patient population and sample size

Male and female patients aged 18 to 65 and fulfilling diagnostic criteria of schizophrenia in Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Patients with increased risk of changes in glucose metabolism prior to inclusion due to eg diabetes mellitus or use of concomitant medications affecting glucose metabolism, as well as patients who had previously used atypical antipsychotics, were excluded.

A total of 285 patients (95 per treatment group) with valid AUC (0-2 h) plasma glucose assessments following OGTT at baseline and at Week 24 were required to provide 90% power for a 2-sided test at the 5% alpha level. To compensate for discontinuations, 574 patients were actually enrolled in the study and 510 randomised, of which 168 patients to the quetiapine, 169 to the olanzapine, and 173 to the risperidone treatment group.

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

During the titration period (Day 1-5), quetiapine was gradually increased to a total daily dose of 600 mg/day, olanzapine to 15 mg/day, and risperidone to 6 mg/day. The titration period was followed by the 23-week treatment period, during which dosing was flexible. Dosage could be adjusted for therapeutic efficacy and/or tolerability within the following ranges: quetiapine 400, 600, or 800 mg/day; olanzapine 10, 15, or 20 mg/day; risperidone 4, 6, or 8 mg/day. Quetiapine was administered twice daily, and at least 25% of the dose had to be taken in the morning. Olanzapine was administered once daily, and risperidone once or twice daily according to local prescribing information.
Study treatment was given in tablets of the following doses (manufacturer): quetiapine 100 mg (AstraZeneca), quetiapine 200 mg (AstraZeneca), olanzapine 5 mg (Eli Lilly), olanzapine 10 mg (Eli Lilly), risperidone 2 mg (Janssen-Cilag), and risperidone 4 mg (Janssen-Cilag). For the titration period, blister packages designed and packed for the study were used. For the flexible dose period, quetiapine was packed in bottles. For olanzapine and risperidone, locally available commercial packs of the investigational products in original containers were used for the flexible dose period. Multiple batches were used for the different participating countries. A complete list of batch numbers used during the titration period and flexible dose period can be found in the Clinical Study Report, Table 11.1.4-6 and Table 11.1.4-7, respectively. Batches used per patient are listed in Appendix 12.1.6.

Duration of treatment

Randomisation to study treatments was followed by a 5-day titration period, and thereafter by a 23-week flexible dose period. The complete treatment period was 24 weeks.

Criteria for evaluation (main variables)

Efficacy

- Primary variable – not applicable. See Safety section below for primary variable.

- Secondary variables: CGI-I score at Week 24; the proportion of patients with a CGI-S score = 3 at Week 24; the proportion of patients who have a CGI-I rating of “very much improved” or “much improved” at the final assessment;

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PETiT total score (item 1-30); PETiT perception and satisfaction with current medication score (item 25-30); ROMI total score and change from baseline for compliance and non-compliance; ROMI change from baseline (randomisation visit) at Week 12 and at final visit at Week 24/end of treatment; ROMI absolute value at Week 12 and Week 24/end of treatment.

Safety

- Primary variable: Change from baseline at Week 24 in AUC 0-2h of the plasma glucose values following OGTT (comparison between quetiapine and olanzapine).

- Secondary variables: Change from baseline in AUC 0-2h of the plasma glucose values following OGTT (comparison between quetiapine and risperidone); fasting glucose; fasting insulin; AUC based on plasma insulin values following OGTT; index of insulin sensitivity (ISI); HOMA; proportion of patients with hyperglycemia; proportion of patients with IFG or IGT; HbA_{1c}; C-peptide; weight; BMI; waist circumference; fasting lipid levels (total cholesterol, HDL, LDL, triglycerides); prolactin levels; standing and sitting systolic and diastolic blood pressure and pulse rate; SAS; BARS; proportion of patients using anticholinergic medication; standard safety assessments including AE reports, clinical laboratory data (haematology, hepatic and renal clinical chemistry, urinalysis), vital signs, ECGs, and physical examination.

Statistical methods

The primary analysis was an analysis of covariance (ANCOVA). The dependent variable in the model was the primary outcome variable (change from baseline in AUC plasma glucose value following OGTT at Week 24). Independent variables were baseline BMI group, age group, baseline AUC glucose measurement and treatment. The contrast of primary interest was between the quetiapine-treated group and the olanzapine-treated group. Least square means, 95% confidence interval, and the p-value for the primary contrast were presented.
The secondary analysis was performed mainly by descriptive statistics, frequency tables, and graphs by treatment as appropriate. For the analysis of the outcome variables at Week 24, the primary analysis population (PAP) was used. For the analysis of the development over time in the outcome variables, the intention to treat (ITT) population was used.

Patient population

Patient disposition is shown in Table S1.

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Table S1 Patient disposition, completion or discontinuation (all patients)

	Quetiapine N	Olanzapine N	Risperidone N	Total N
All enrolled patients				574
Non-randomised patients (screen failure)				64
All randomised patients	168	169	173	510
Not treated[a]	0	0	1	1
Received investigational product[b]	169	168	172	509
Discontinued study treatment	59	23	40	122
Completed randomised treatment phase	110	145	133	388

[a] Patients not treated are also included in the Discontinued study treatment group (due to protocol non-compliance).
[b] One patient randomised to the olanzapine group received quetiapine instead.

The main reasons for discontinuation in the quetiapine group were AEs (mainly worsening of schizophrenia), lack of therapeutic response, and withdrawal of consent. In the risperidone group, discontinuations were largely due to AEs related to EPS. For olanzapine, the main discontinuation reason was withdrawal of consent.

Demographic and baseline characteristics of the study population are shown in Table S2. Baseline glucose metabolism and lipid characteristics are summarised in Table S3. Overall, the treatment groups were well balanced with regard to demographic and baseline characteristics.

Table S2 Demographic and baseline characteristics (PAP)

	Quetiapine N=115	Olanzapine N=146	Risperidone N=134	Total N=395
Sex: n (%)				
Male	76 (66.1)	97 (66.4)	87 (64.9)	260 (65.8)
Female	39 (33.9)	49 (33.6)	47 (35.1)	135 (34.2)
Age (years)[a]				
n[b]	115	146	134	395
Mean (SD)	39.4 (11.1)	40.5 (10.4)	38.3 (11.1)	39.5 (10.9)
Median	39.0	41.0	37.0	40.0
Min to max	20 to 63	19 to 65	19 to 62	19 to 65
Age distribution[a] : n (%)				
18 to 50	95 (82.6)	121 (82.9)	110 (82.1)	326 (82.5)
51 to 65	20 (17.4)	25 (17.1)	24 (17.9)	69 (17.5)
Race/ethnicity: n (%)				

Caucasian	104 (90.4)	134 (91.8)	116 (86.6)	354 (89.6)
Black	9 (7.8)	11 (7.5)	15 (11.2)	35 (8.9)
Other[d]	2 (1.7)	1 (0.7)	3 (2.2)	6 (1.5)
Weight (kg)				
n[b]	115	146	134	395
Mean (SD)	73.6 (15.4)	71.9 (14.6)	72.1 (15.8)	72.5 (15.2)
Median	69.5	70.1	69.0	69.5
Min to max	43 to 116	46 to 121	42 to 117	42 to 121
BMI (kg/m^2): n (%)				
<18.5	8 (7.0)	10 (6.8)	9 (6.7)	27 (6.8)
18.5 to <25	54 (47.0)	72 (49.3)	70 (52.2)	196 (49.6)
25 to <30	37 (32.2)	43 (29.5)	35 (26.1)	115 (29.1)
≥ 30	16 (13.9)	21 (14.4)	20 (14.9)	57 (14.4)
Smoking[c]	67 (58.3)	86 (58.9)	86 (64.2)	239 (60.5)

[a] At randomisation.
[b] Number of patients with non-missing values.
[c] Current smoker or any other nicotin use at enrolment.
[d] Other race was mixed race.

Table S3 Baseline metabolism characteristics (PAP)

	Quetiapine N=115		Olanzapine N=146		Risperidone N=134	
	N[a]	Mean (SD)	N[a]	Mean (SD)	N[a]	Mean (SD)
Fasting plasma glucose (mmol/L)	113	5.14 (0.67)	143	5.199 (0.99)	132	5.203 (0.66)
Two-hour glucose (mmol/L)	109	5.934 (1.86)	145	6.163 (2.33)	128	6.266 (2.13)
Haemoglobin A_{1c} (%)	106	5.329 (0.43)	140	5.323 (0.39)	128	5.332 (0.49)
Fasting plasma insulin (µIU/ml) (geometric mean (CV))	82	5.209 (79.9)	117	5.363 (63.7)	113	5.442 (52.5)
AUC of plasma insulin values following OGTT (µIU/ml x h) (geometric mean (CV))	84	80.28 (64.9)	111	71.26 (68.7)	103	67.58 (56.9)
Index of insulin sensitivity (ISI) (geometric mean (CV))	76	108.5 (64.4)	112	118 (69.6)	103	118.3 (64.5)
Homeostastasis model assessment (HOMA) (geometric mean (CV))	82	1.183 (89.8)	117	1.227 (69.7)	112	1.257 (54.7)
C-peptide (pmol/L)	90	747.3 (366)	118	735.3 (300)	110	742.2 (346)

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Table S3 Baseline metabolism characteristics (PAP)

	Quetiapine N=115		Olanzapine N=146		Risperidone N=134	
	N[a]	Mean (SD)	N[a]	Mean (SD)	N[a]	Mean (SD)
Fasting lipids:						
Total cholesterol (mmol/L)	107	4.992 (1.22)	142	4.976 (1.24)	124	5.044 (1.04)
HDL (mmol/L)	89	1.088 (0.29)	116	1.128 (0.29)	106	1.162 (0.36)
LDL (mmol/L)	108	3.053 (0.95)	142	3.157 (1)	125	3.149 (0.84)
Triglycerides (mmol/L)	104	1.877 (1.46)	142	1.65 (0.84)	123	1.741 (1.02)

[a] Number of patients with non-missing values.

Efficacy and pharmacokinetic (not applicable) results

Overall, the vast majority of patients in all treatment groups improved during the study in their symptoms of schizophrenia. The improvement was similar across the treatment groups.

The proportion of patients with CGI-S score =3 at Week 24 in the ITT population was 70.2% in the quetiapine group, 75.7% in the olanzapine group, and 74.3% in the risperidone group. In the PAP, this proportion was 79.6% in the quetiapine group, 77.9% in the olanzapine group, and 82.7 % in the risperidone group. The mean CGI-S scores improved equally in all treatments groups from 4 at randomisation to about 2.9 at Week 24 in the ITT population, and from 4 to 2.7 in the PAP population.

The proportion of patients with CGI-I score of "very much improved" or "much improved" at Week 24 in ITT population was 57.7% for the quetiapine, 63.9% for the olanzapine, and 55.6% for the risperidone treatment group. The mean CGI-I score at Week 24 in the ITT population was 2.3 in the olanzapine group, 2.7 in the quetiapine group and 2.6 in the risperidone group. The mean CGI-I scores showed similar improvement over time for all 3 treatment groups from Week 1 to Week 12 in both PAP and ITT, and at Week 24 in PAP (from about 3.5 at Week 1 to about 2.5 at Week 24).

The patients' well-being, treatment satisfaction, and attitude to compliance and non-compliance as measured by PETiT and ROMI scales were notably improved at Week 24 in the quetiapine, olanzapine and risperidone treatment groups. The benefits were similar across the treatment groups.

Safety results related to glucose metabolism and lipids

Differential effects on glucose excursion after glucose load were seen in the 3 treatment groups after 24 weeks of treatment. With regard to mean change in AUC 0-2h of plasma

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glucose values at Week 24 (primary variable), the comparison between the quetiapine and olanzapine groups showed statistically significant difference (p=0.0480 in the PAP, and p=0.0199 in the PP population) to the advantage of the quetiapine group. The difference between the quetiapine and risperidone groups in mean change in AUC 0-2h of plasma glucose values at Week 24 was numerically to the advantage of the quetiapine group. The results for AUC 0-2h of plasma glucose values in the PAP are presented in Table S4 and Table S5.

Table S4 AUC 0-2h of plasma glucose values following OGTT, change from randomisation (PAP)

		Quetiapine	Olanzapine	Risperidone
AUC plasma glucose value (mmol/L x h)				
n[a]		111	144	130
Randomisation	Mean (SD)	14.16 (3.02)	14.48 (3.83)	14.4 (3.63)
Change at Week 24	LS mean (SE)	0.506 (0.32)	1.218 (0.29)	1.041 (0.3)
	95% CI	(-0.13, 1.139)	(0.638, 1.798)	(0.45, 1.633)

[a] Number of patients with non-missing values at randomisation and Week 24.
Note: Analysis using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.

Table S5 AUC 0-2h of plasma glucose values following OGTT, treatment differences in change from randomisation (PAP)

		Quetiapine - Olanzapine	Quetiapine - Risperidone	Olanzapine - Risperidone
AUC plasma glucose value (mmol/L x h)				
Change at Week 24	LS mean (SE)	-0.71 (0.359)	-0.54 (0.368)	0.177 (0.344)
	95% CI	(-1.42, -0.01)	(-1.26, 0.188)	(-0.5, 0.853)
	p-value[a]	0.0480		

[a] No formal tests of quetiapine vs risperidone or olanzapine vs risperidone were planned for.
Note: Analysis using ANCOVA with baseline value, BMI group, age group and treatment as independent variables.

With regard to mean 2h-glucose value, the quetiapine group showed no change from randomisation at Week 24, while in the olanzapine and risperidone groups an increase from baseline was seen (0.543 and 0.587 mmol/L, respectively). Although no difference was observed at Week 24 between the treatment groups in the proportion of patients with 2h-glucose =11.1 mmol/L (hyperglycemia) or the proportion of patients with IGT, a shift to a higher 2h-glucose category (ie, from normal to impaired/high or from impaired to high) was seen in about twice as many patients in the risperidone group compared to the

quetiapine group, and about 50% more patients in the olanzapine group than in the quetiapine group.

In absence of glucose load, there was no difference between the treatment groups as measured by fasting glucose level, HbA_{1c} level, C-peptide level, or the proportion of patients shifting from normal to abnormal (high or impaired) fasting glucose level at Week 24.

The proportion of patients with hyperglycemia, ie, patients with fasting glucose =7.0 mmol/L or/and with 2-hour glucose =11.1 mmol/L, was small in the PAP at Week 24 (4.3% in the quetiapine group, 6.8% in the olanzapine group, and 6.8% in the risperidone group) and similar to baseline within each treatment group.

The proportion of patients with IFG or IGT in the PAP changed in the quetiapine group from 26.1% at randomisation to 32.2% at Week 24, in the olanzapine group from 19.9% to 29.5%, and in the risperidone group from 32.1% to 40.3%. With regard to 2h-glucose, about twice as many patients shifted at Week 24 to worse category (from normal to impaired/high or from impaired to high) in either the olanzapine or risperidone groups, than in the quetiapine group.

The mean increase in fasting insulin from randomisation at Week 24 was 3.3% in the quetiapine group, 8.5% in the olanzapine group, and 11.9% in the risperidone groups. The mean relative changes from randomisation at Week 24 in AUC 0-2h of plasma insulin values was 13.2% in the quetiapine group, 24.5% in the olanzapine group, and 10.7% in the risperidone group. The ISI results showed 10.8% mean decrease from randomisation at Week 24 in the quetiapine group, 19.1% in the olanzapine group, and 15.8% in the risperidone group. The HOMA results showed a mean increase of 6.4% in the quetiapine group, 11% in the olanzapine group, and 16.8% in the risperidone group.

Few and very moderate mean changes in lipid levels were seen at Week 24 in all treatment groups, and the mean values in the population were close to normal. There was a slight mean increase in total cholesterol in the quetiapine group, a greater increase in the olanzapine group, and no change in the risperidone group. No mean change in HDL was observed at Week 24 in any of the treatment groups. The mean LDL level increased at Week 24 by about 10% in the quetiapine group, and slightly more in the olanzapine group. No change was observed in the risperidone group. The mean triglyceride level increased at Week 24 in the olanzapine group, but not in the quetiapine and risperidone groups.

No differences in metabolic syndrome risk factors were seen between the treatment groups. At Week 24, about 19% of patients developed =3 risk factors included in the definition of metabolic risk syndrome. Between 17% and 41% of patients in each treatment group moved from =3 risk factors to <3 risk factors at the end of treatment.

The mean increase in weight at Week 24 was 3.65 kg in the quetiapine group, 4.58 kg the olanzapine group, and 3.57 kg in the risperidone group. The corresponding increases were observed in mean BMI (1.294, 1.639 and 1.279 kg/m^2, respectively). The mean

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waist circumference increased at Week 24 by 3.2 cm in the quetiapine group, 4.4 cm in the olanzapine group, and 3.0 cm in the risperidone group.

Other safety results

Two patients who had been treated with risperidone died during the 30-day follow-up period of this study, but the deaths were considered unrelated to the study treatment. No deaths were reported in the quetiapine and olanzapine groups.

Generally, all 3 treatments were well tolerated. The rate of serious adverse events (SAEs) was low in all 3 treatment groups (see Table S6). The most commonly observed SAE was hospitalisation due to worsening of schizophrenia or due to symptoms associated with schizophrenia. In the quetiapine group, no SAEs were judged by the investigator to be related to the investigational product.

Discontinuation rates due to AE were approximately the same in the quetiapine and risperidone groups, and less in the olanzapine group. In the quetiapine group, discontinuations due to AEs (DAEs) were mostly due to worsening of symptoms associated with schizophrenia. In the olanzapine group, the discontinuations were due to tolerability reasons, and in the risperidone group due to worsening of the disease or tolerability reasons.

Table S6 Adverse events in different categories during the treatment and follow-up period (safety population)

Category of adverse event	Quetiapine N=169	Olanzapine N=168	Risperidone N=172
	n (%)	n (%)	n (%)
Adverse events[a]	101 (59.8)	79 (47.0)	116 (67.4)
Serious adverse events[a]	17 (10.1)	4 (2.4)	13 (7.6)
Serious adverse events leading to death[a]	0	0	2 (1.2)
Serious adverse events not leading to death[a]	17 (10.1)	4 (2.4)	12 (7.0)
Drug-related adverse events[a, b]	57 (33.7)	36 (21.4)	87 (50.6)
Adverse events leading to discontinuation[a]	17 (10.1)	3 (1.8)	14 (8.1)
Total number of adverse events[c]			
Adverse events[c]	243	196	320
Serious adverse events[c]	20	4	15
Drug-related adverse events[b, c]	94	45	177

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] As judged by the investigator.
[c] If a patient has multiple events in the same category all events are counted.

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The pattern of common AEs observed in the 3 treatment groups (see Table S7) conformed to what was anticipated based on known data and the pharmacological profiles of the investigational products

Table S7 Common adverse events during treatment and follow-up period by MedDRA term (safety population)

MedDRA preferred term[a]	Quetiapine N=169 n (%)	Olanzapine N=168 n (%)	Risperidone N=172 n (%)
Extrapyramidal disorder	3 (1.8)	3 (1.8)	42 (24.4)
Insomnia	11 (6.5)	7 (4.2)	25 (14.5)
Somnolence	17 (10.1)	6 (3.6)	8 (4.7)
Akathisia	2 (1.2)	3 (1.8)	22 (12.8)
Schizophrenia	12 (7.1)	2 (1.2)	8 (4.7)
Sedation	11 (6.5)	5 (3.0)	5 (2.9)
Dizziness	9 (5.3)	0	6 (3.5)

[a] Patients with multiple events falling under the same term are counted only once in that term.
Note: Common adverse event: adverse events occurring at an incidence of ≥5% in any randomised treatment group.
Note: Sorted by decreasing order of frequency as summarized over all treatment groups.

The rate of EPS-related AEs was low in the quetiapine and olanzapine groups, in comparison to the risperidone group, which was supported by the results on use of anticholinergic medication at Week 24, mean SAS total score in mean BARS Global Clinical Assessment of Akathisia score at Week 24.

The mean level of prolactin decreased at Week 24 in the quetiapine and olanzapine treament groups, while in the risperidone group, on the contrary, the mean prolactin level increased. The proportion of patients with abnormal prolactin level was reduced in the quetiapine group from 50.0% at randomisation to 7.9% at Week 24, and from 55.9% to 34.2% in the olanzapine group. In the risperidone group, this proportion increased from 46.3% at randomisation to 78.4% at Week 24.

Findings on clinically important laboratory values, vital signs, or ECG abnormalities were sporadic. Expected small increase in pulse rate was seen in the quetiapine group. There were no instances of agranulocytosis.

Overall, no new safety issues were identified for the investigational products.