AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Quetiapine fumarate
Study Code	5077IL/0089
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A Multicenter, Open-label, Flexible-dose, Parallel-group Evaluation of the Cataractogenic Potential of Quetiapine Fumarate (SEROQUEL™) and Risperidone (RISPERDAL™) in the Long-term Treatment of Patients with Schizophrenia or Schizoaffective Disorder [CLEARS]

Study dates:	First patient enrolled: 30 September 2003 Last patient completed: 22 October 2008
Phase of development:	Therapeutic use (4)
International Co-ordinating Investigator:	None assigned

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

Study centers

The study randomized 1098 patients at 82 centers in the United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the relative cataractogenic potential of quetiapine and risperidone with respect to nuclear opalescence (N), cortical (C) or posterior subcapsular opacification (P) for events over 2 years of exposure	Presence/absence of cataractogenic potential as measured by increase in lens opacity grade events in patients with 2 years of exposure (minimum 21 months) including patients withdrawn for an event (Events of N, C, or P as agreed by 2 independent treatment-masked non-consulting ophthalmologists at the 24-month visit or earlier for patients who withdrew due to the event)	Safety
Secondary	**Secondary**	
To characterize the long-term safety and tolerability of quetiapine and risperidone as measured by adverse events (AEs), clinical laboratory assessments, physical exams, electrocardiograms (ECGs), Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS)	Incidence, severity, and causality of all AEs, serious adverse events (SAEs), AEs leading to death, withdrawals due to AEs, and AEs of special interest Changes from baseline in vital signs, clinical laboratory assessments, physical examinations, and ECGs Change in SAS total score, one item of BARS (the 4th item, Global Assessment of Akathisia), and AIMS total score from baseline to final assessment, and a 7-item AIMS total score (AIMS-7)	Safety
To characterize the long-term treatment effects on efficacy using the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (CGI), and relapse criteria for quetiapine in comparison with risperidone	PANSS total score, positive sub-score, negative sub-score, and psychopathology subscale score at each assessment and change from baseline CGI Severity of Illness score and Global Improvement at each post-baseline assessment	Efficacy
To compare time to first relapse of schizophrenia or schizoaffective disorder	Time to first relapse and number of relapses of schizophrenia or schizoaffective disorder	Efficacy
To characterize the long-term treatment effects on quality of life using the Quality of Life Enjoyment and Satisfaction Short Form Questionnaire (Q-LES-Q SF) and Personal Evaluation of Transitions in Treatment (PETiT) for quetiapine in comparison with risperidone	Change in total score for Q-LES-Q SF from baseline and for each assessment Change in total score of PETiT and PETiT total treatment satisfaction subscore (6 items) from baseline and for each assessment	HEOR

AE Adverse event; AIMS Abnormal Involuntary Movement Scale; BARS Barnes Akathisia Rating Scale; C Cortical; CGI Clinical Global Impression; ECG Electrocardiogram; HEOR Health economics and outcomes research; N Nuclear opalescence; P Posterior subcapsular opacification; PANSS Positive and Negative Syndrome Scale; PETiT Personal Evaluation of Transitions in Treatment; SAE Serious adverse event; SAS Simpson-Angus Scale; Q-LES-Q SF Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form.

Study design

This was a randomized, 24-month, multicenter, evaluator (ophthalmologist)-masked, open-label, flexible-dose, parallel-group study to compare the cataractogenic potential in

patients treated for schizophrenia or schizoaffective disorder with quetiapine versus risperidone. All patients were to have eye examinations, including slit lamp assessments, to detect any increases in Lens Opacities Classification System II (LOCS II) lens opacity grade every 6 months for a 2-year period (24 months from randomization into the study). Patients who discontinued study treatment had the option to continue with the study-scheduled eye assessments for up to a total of 2 years.

Target subject population and sample size

The target population was male and female patients between the ages of 18 and 65 years with the diagnostic criteria of schizophrenia or schizoaffective disorder (according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition), with both eyes present and lenses intact, and a qualifying LOCS II slit lamp score assessment by 2 independent treatment-masked ophthalmologists.

The study sample size estimation was based on the simultaneous testing of 3 non-inferiority hypotheses for each primary endpoint (nuclear opalescence [N], cortical opacification [C], posterior subcapsular opacification [P]). Non-inferiority was to be established if the absolute risk difference Pi (quetiapine) – Pi (risperidone) was less than 10% where Pi was the proportion of patients experiencing a cataractogenic event for each i = N, C, P. With 170 evaluable patients per group, the power to reject all 3 null hypotheses would be at least 86% assuming all three event rates were at 7%. Assuming 40% of patients would complete at least 21 months of treatment without significant protocol violations or deviations, 535 and 465 randomized patients in the quetiapine and risperidone treatment groups, respectively, would be necessary to obtain 170 evaluable patients per treatment group.

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

Quetiapine was titrated as follows: 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3, 300 mg on Day 4, 400 mg on Days 5 through 7, 600 mg on Day 8; thereafter, the dosage was adjusted for efficacy and tolerability to within the dosing range of 200 to 800 mg/day. Risperidone was administered 2 mg/day on Days 1 through 5, 3 mg/day on Days 6 and 7, and 4 mg/day on Day 8; thereafter, the dosage was adjusted for efficacy and tolerability to within the dosing range of 2 to 8 mg/day. Study drug was administered orally twice daily (BID) during titration, and following titration (Day 8 onwards) quetiapine could be given BID or three times daily and risperidone could be given once daily or BID.

Treatment was provided orally in tablet form: *25-mg quetiapine tablets*: 6500J and 7527F; *100-mg quetiapine tablets*: 6513J, 6514J, 6515J, 6516J, 7511H, 7530K, 7532K, 7536F, and LK4600; *1-mg risperidone tablets*: 3NG599, 4LG557, 4MG628, 4NG708, 5AG766, 5GG099, 5JG254, 5KG348, 6CG830, 6JG201, 6MG507, 7GG065, and 93P0107. Quetiapine was provided as the immediate release (IR) formulation.

Duration of treatment

24 months.

Statistical methods

Mantel-Haenszel estimates with a 95% confidence interval were produced to evaluate the difference in proportion of patients with cataractogenic potential events between quetiapine and risperidone for each type of event (N, C, or P). Also, Mantel-Haenszel estimates with a 95% confidence interval were calculated for each proportion of events in the quetiapine and risperidone treatment groups for each type of event (N, C, or P). No formal statistical tests were done on secondary efficacy, safety, and tolerability variables except for extrapyramidal effects: Simpson-Angus Scale total score, 4th item of the Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale total score, and time to first relapse of schizophrenia or schizoaffective disorder.

Subject population

The numbers of patients enrolled and randomized were 1837 and 1098, respectively (596 patients in the quetiapine group and 502 patients in the risperidone treatment group). Randomized patients were provided from 82 centers in the United States. In total, 375 (34.2%) patients completed the study, with 723 patients discontinuing early (408 [68.5%] patients in the quetiapine and 315 [62.7%] patients in the risperidone treatment groups).

A total of 329 patients (161 quetiapine, 168 risperidone) were included in the primary analysis set for eye evaluations, which included all randomized patients who met eye eligibility, had a valid baseline LOCS II evaluation, had reached the study endpoint of either a LOCS II identified increase in lens opacity grade or were administered study medication for 21 months without a LOCS II identified increase in lens opacity grade, and had no major protocol deviations. The Safety analysis set included 587 quetiapine and 495 risperidone patients.

Approximately 60% of the patients in the study were men. The mean age of randomized patients was approximately 40 years. Approximately 50% of the randomized patients were Caucasian and approximately 40% of patients were Black. Cataract risk factors at baseline (including family history of cataracts, previous eye injury, outdoor occupation of >2 years, exposure to high levels of radiation for cancer treatment, known history of diabetes mellitus, and smoking status) were similar at baseline. Psychiatric history data at baseline were similar between treatment groups. The mean Positive and Negative Syndrome Scale (PANSS) total scores and Clinical Global Impression Severity of Illness (CGI-S) baseline scores were similar in both groups. The randomized patient populations were representative of the general schizophrenia or schizoaffective disorder population, and the 2 groups were well matched in number, demographics, and baseline disease characteristics.

Summary of efficacy results

All efficacy objectives were secondary (see Table S1). The efficacy results based on open-label measurements showed similar mean PANSS and Clinical Global Impression (CGI) scores at 24 months when compared to baseline for both treatment groups. Similarly, mean Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q SF) and

Personal Evaluation of Transitions in Treatment (PETiT) data were comparable between treatment groups.

A slightly higher proportion of patients reported first relapse in the quetiapine group for time points starting at 6 months or beyond compared to patients in risperidone treatment group. At 24 months, 30.5% patients and 26.0% patients in the quetiapine and risperidone treatment groups, respectively, experienced first relapse. The numbers of all reported relapses, including patients with multiple relapses, were similar between the 2 treatment groups.

Summary of safety results

Primary objective

The primary analysis assessed the relative cataractogenic potential of quetiapine and risperidone at 24 months. Over the 2-year study period, the increase in lens opacification in patients receiving quetiapine was not inferior to that in patients receiving risperidone (which is not identified in its prescribing information as cataractogenic). There were numerically more identified cataractogenic events in the risperidone treatment group than the quetiapine group (Table S2).

Table S2 Risk differences[a] between quetiapine and risperidone for the proportion of patients for each type of increase in lens opacity event (E2PP analysis set)

					Difference vs risperidone[b]		
Type of event	**Treatment group**	**Number (%) of patients**	**Number (%) of patients with event**	**Estimate of event rate (95% confidence interval)**	**Difference**	**95% Confidence interval (lower, upper[c])**	**p-value**
C	Quetiapine	161 (48.94)	2 (1.24)	0.0124 (0.0015, 0.0442)	-0.035	(-0.072, 0.001)	0.063
	Risperidone	168 (51.06)	8 (4.76)	0.0476 (0.0208. 0.0917)			
N	Quetiapine	161 (48.94)	0	0 (0, 0.0227)	-0.012	(-0.028, 0.004)	0.165
	Risperidone	168 (51.06)	2 (1.19)	0.0119 (0.0014, 0.0423)			
P	Quetiapine	161 (48.94)	4 (2.48)	0.0248 (0.0068, 0.0624)	-0.017	(-0.055, 0.022)	0.396
	Risperidone	168 (51.06)	7 (4.17)	0.0416 (0.0169, 0.0840)			
Any[d]	Quetiapine	161 (48.94)	6 (3.73)	0.0372 (0.0138, 0.0793)	-0.058	(-0.111, -0.005)	0.035
	Risperidone	168 (51.06)	16 (9.52)	0.0952 (0.0554, 0.1501)			

[a] The Mantel-Haenszel analysis includes a term for treatment.
[b] A negative difference compared to risperidone indicates a lower proportion of patients with lens opacification events for quetiapine compared with risperidone.
[c] If the upper limit of the 95% confidence interval <0.1 for each type of the three lens opacification event types, the conclusion is that quetiapine is non-inferior to risperidone.
[d] Patients with multiple events (C, N, or P) are counted only once. Thus, the total number of patients with any event may not equal the sum of the number of N, C, and P events. This was a post-hoc analysis.
C Cortical opacification; E2PP Two-year eye evaluation per protocol analysis set; N Nuclear opalescence; P Posterior subcapsular opacification.

Additional safety assessments

Quetiapine and risperidone were similarly tolerated with the adverse events (AEs) reported generally conforming to those anticipated based on the known pharmacological profile for the respective products.

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

Table S3 Number (%) of patients who had at least 1 AE in any category and the number of AEs in each category (safety analysis set)

	Number (%) of patients[a]		
	Quetiapine N=586	Risperidone N=496	Total N=1082
Number (%) of patients who had at least 1 AE in any category			
Any AE	545 (93.0)	440 (88.7)	985 (91.0)
Any AE with outcome = death	7 (1.2)	2 (0.4)	9 (0.8)
Any SAE (including events with outcome = death)	151 (25.8)	114 (23.0)	265 (24.5)
Any AE leading to discontinuation of treatment	117 (20.0)	78 (15.7)	195 (18.0)
Any treatment-related AE[b]	370 (63.1)	287 (57.9)	657 (60.7)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] In the opinion of the investigator.
Note: All AEs reported occurred from start of study treatment to 30 days after last dose of study treatment or study termination, if a patient continued in the study after premature discontinuation of the randomized study medication.
AE Adverse event; N Number of patients in a treatment group; SAE Serious adverse event.

Nine deaths occurred during the study (7 in the quetiapine and 2 in the risperidone treatment groups, respectively). The Medical Dictionary of Regulatory Activities preferred terms reported for the deaths in the quetiapine treatment group were accidental overdose (1 patient), arteriosclerosis (1 patient), completed suicide (2 patients), metastases to liver (1 patient), pneumonia (1 patient), and respiratory fume inhalation disorder and thermal burn (1 patient). For the 2 patients who died in the risperidone treatment group, 1 patient completed suicide and the other patient died due to illicit drug toxicity. None of the AEs with an outcome of death were considered by the investigator to be related to study treatment.

The most common AEs (>10% patients) in the quetiapine treatment group were somnolence, sedation, headache, insomnia, dizziness, dry mouth, anxiety, weight increased, depression, and fatigue. For risperidone, the most common AEs (>10% patients) were insomnia, headache, somnolence, anxiety, depression, sedation, dizziness, and nasopharyngitis. In this study, somnolence was the most commonly reported AE, occurring at approximately twice the frequency in the quetiapine group compared to the risperidone group. Sedation and dry mouth were reported in more patients in the quetiapine treatment group compared to the risperidone treatment group. Insomnia, akathisia, and tremor were more common in the risperidone treatment group than the quetiapine treatment group.

For a summary of prespecified AEs of special interest, see Table S4.

Table S4 Number (%) of patients with prespecified AEs of special interest

	Number (%) patients		
	Quetiapine N=586	**Risperidone N=496**	**Total N=1082**
AEs potentially associated with extrapyramidal symptoms	73 (12.5)	106 (21.4)	179 (16.5)
Tardive dyskinesia	5 (0.9)	5 (1.0)	10 (0.9)
AEs potentially associated with QT prolongation	4 (0.7)	0	4 (0.4)
AEs potentially associated with diabetes mellitus	18 (3.1)	26 (5.2)	44 (4.1)
AEs potentially associated with neutropenia or agranulocytosis	6 (1.0)	9 (1.8)	15 (1.4)
AEs potentially associated with suicidality	28 (4.8)	23 (4.6)	51 (4.7)
AEs potentially associated with somnolence	293 (50.0)	118 (23.8)	411 (38.0)

AE Adverse event; n Number of patients with an event within a treatment group; N Total number of patients in a treatment group.

A Columbia type suicidality analysis was conducted, comparing the quetiapine and risperidone treatment groups. No difference in suicidal behavior/ideation or possible suicidal behavior/ideation between the treatment groups was observed.

Mean changes from randomization to final visit and shifts at any time for hematology and clinical chemistry parameters, vital signs, and ECG parameters were small and in line with the known pharmacological profiles of the respective compounds.

There were shifts to clinically important (CI) high glucose values (≥7 mmol/L) in both treatment groups during the study. For assumed fasting glucose (where blood samples were collected >8 hours since the assumed last meal), 65 (18.3%) quetiapine-treated patients and 57 (19.6%) risperidone-treated patients shifted from normal to CI levels. A small shift to CI high values for glycosylated hemoglobin (>7.5%) was observed, with 17 (3.5%) quetiapine-treated patients and 20 (4.9%) risperidone-treated patients shifting from normal to CI high glycosylated hemoglobin levels. Shifts to CI values were seen for lipids in both treatment groups. There were 71 (16.9%) quetiapine-treated and 52 (14.5%) risperidone-treated patients who had shifts from normal to CI high cholesterol values (≥6.21 mmol/L). There were 102 (29.7%) quetiapine-treated and 74 (25.8%) risperidone-treated patients who had shifts

from normal to CI high triglyceride values (≥2.26 mmol/L). There were shifts to CI high values for thyroid function assessments and prolactin in both treatment groups; however, there were more patients with a CI shift for prolactin in the risperidone group.

There were similar reports of ≥7% weight gain at the end of treatment visit in both treatment groups (quetiapine 118 [21.9%] patients and risperidone 95 [20.7%] patients). The incidence of patients with a shift from <3 metabolic risk factors to ≥3 metabolic risk factors at the end of treatment was comparable for the quetiapine (41 [12.9%] patients) and risperidone (32 [12.7%] patients) groups.