AstraZeneca

Drug product:	SEROQUEL	**SYNOPSIS**	
Drug substance(s):	Quetiapine fumarate		
Study code:	5077US/0043		
Date:	26 September 2005		

A Multicenter, Double-blind, Randomized Comparison of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) and Risperidone (RISPERDAL™) in the Treatment of Patients with Schizophrenia

International Coordinating investigator

None for this study.

Study center(s)

This study was conducted in 78 centers in the United States.

Publications

None at the time of writing of this study report.

Study dates		**Phase of development**
First subject enrolled	28 June 2001	Therapeutic use (IV)
Last subject completed	4 September 2002	

Objectives

Primary: The primary objective of this trial was to demonstrate non-inferior efficacy of quetiapine compared with that of risperidone in the treatment of patients with schizophrenia.
Secondary: The secondary objective was to assess the tolerability and safety of quetiapine administered twice daily as compared with that of risperidone administered twice daily in patients with schizophrenia.
Other objectives:

- To compare the effects of quetiapine and risperidone on quality of life as assessed by the Modified Outcome Scale Short Form (SF-36).
- To compare the efficacy of quetiapine and risperidone in the treatment of the cognitive and functional aspects of psychosis.

Study design

This trial was a multicenter, double-blind, randomized, comparison of the effectiveness of quetiapine with that of risperidone in acutely hospitalized patients who have schizophrenia.

Target patient population and sample size
A total of 297 male and female patients in the per protocol population (those in the modified intent-to-treat population who did not have any protocol violations or deviations that could substantially affect efficacy), aged between 18 and 65 years inclusive, at least moderately ill with catatonic, disorganized, paranoid or undifferentiated subtypes of schizophrenia patients, derived from an estimated 330 randomized patients were required per treatment group for 90% power with $\alpha = 0.05$ to test for statistical non-inferiority assuming an equivalence margin of 6 points in the Positive and Negative Syndrome Scale (PANSS) total score.

Investigational product and comparator(s): dosage, mode of administration and batch numbers
Quetiapine (SEROQUEL ™) 100 to 400 mg orally twice daily, or risperidone (RISPERDAL ™) 1 to 4 mg orally twice daily, or placebo (for titration period). Doses were administered as identically encapsulated tablets. Batch numbers were: quetiapine 25 mg tablets, ST75019-001-FA03; quetiapine 100 mg tablets, ST75020-001-FA03, ST75020-001-FA05; risperidone 1 mg tablets, ST75021-001-FA03, ST75021-001-FA04, ST75021-001-FA06; placebo capsules, ST75022-001-FA01.

Duration of treatment
The treatment period lasted 8 weeks, with dose titration on Days 1 through 5.

Criteria for evaluation (main variables)
Efficacy

- Primary variable: Change from baseline in PANSS total score at the final assessment in the per protocol (PP) population.
- Secondary variables: Change from baseline at each visit in the PANSS total score and in the Positive, Negative, and General Psychopathology scales in the Modified Intent-to-Treat (MITT) population, treatment response (≥30% decrease from baseline) in PANSS total, Positive, Negative and General Psychopathology scales, alternative criteria for PANSS scales responses (≥20%, ≥40%, ≥50%), Change from baseline in Clinical Global Impression (CGI) Severity of Illness score at each visit for the MITT population, proportion of patients with CGI Global Improvement scores of "very much improved" or "much improved" at each visit in the MITT population, SF-36 scores.
- Other variables (exploratory, but not designated as supportive of the primary outcome variable): Serial Verbal Learning Test (SVLT), computerized continuous performance tests (AX CPT, IP CPT, Flanker CPT), computerized PENN Emotional Affect Test (PEAT), Trail Making Tests A and B, two verbal fluency tests (Animal Naming test and F-A-S test), Medication Management Ability Assessment (MMAA), and the Social Skills Performance Assessment (SSPA).

Safety
Standard safety assessments included adverse event reports, clinical laboratory data (haematology, liver, renal and thyroid function tests, electrolyte concentrations, prolactin concentration, fasting glucose concentrations, lipid panel), vital signs, electrocardiograms

(ECGs) and physical examination. Secondary outcome variables were analyzed with ANCOVA or Chochran-Mantel-Haenszel methods in the MITT or Safety populations, as appropriate.

Statistical methods

The primary outcome variable was evaluated for non-inferiority by analysis of covariance (ANCOVA) of the per-protocol population. Secondary variables were analyzed with ANCOVA or Cochran-Mantel-Haenszel methods, as appropriate.

Subject population

Patients in the quetiapine and risperidone treatment groups were well-matched as to number and demographic and baseline disease characteristics. The mean patient age was approximately 40 years, and approximately three quarters of the patients were male. Somewhat more than half were black and almost 40% were white. The mean screening PANSS total score was approximately 92 points. Approximately half of the randomly assigned patients in both groups completed the protocol. The primary reason for discontinuation in both groups was lack of efficacy, followed by withdrawal of consent. Similar proportions of the two treatment groups were assigned to the PP population.

Table S1 Subject disease characteristics and disposition

		Quetiapine		Risperidone		Total	
Baseline disease characteristics							
DSM-IV diagnosis [N and (%)]							
Disorganized		9	(3.0)	6	(2.0)	15	(2.5)
Catatonic		0	(0)	1	(0.3)	1	(0.2)
Paranoid		256	(85.3)	258	(85.1)	514	(85.2)
Undifferentiated		35	(11.7)	38	(12.5)	73	(12.1)
Screening PANSS total score [Mean (SD)]		92.1	(18.60)	91.2	(17.31)	91.6	(17.96)
Disposition							
N (% of randomized) of subjects who	Completed	154	(45.6)	168	(50.1)	322	(47.8)
	Discontinued	184	(54.4)	167	(49.9)	351	(52.2)
N analyzed for safety[a]		338		334		672	
N analyzed for efficacy (MITT)		328		320		648	
N analyzed for efficacy (PP)		300		303		603	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing.

DSM-IV=Diagnostic and Statistical Manual of the American Psychiatric Association, version IV; N=number; SD=standard deviation.

Efficacy results

The comparison of change from baseline in PANSS total score for the two treatment groups demonstrated the non-inferiority of quetiapine to risperidone. Analysis of the MITT population produced similar, statistically significant results as the primary analysis of the PP population. Over the course of the study, the mean change from baseline for the risperidone group was slightly more pronounced. Among patients in the MITT population who showed >30% response, the mean median dose for quetiapine was 561 mg/day and for risperidone was 6 mg/day. All quetiapine responders received a median dose between 200 mg/day and 800

mg/day. Non-equivalence analyses (superiority test) showed a statistically significant advantage for risperidone in the PANSS Positive subscale, however not for PANSS total. The statistical advantage did not reach the criterion for clinical relevance. Analysis of secondary outcome variables also supported the non-inferiority of quetiapine to risperidone. Results were similar for the PP and MITT populations for the PANSS Positive and PANSS Negative subscales.

Table S2 Efficacy results

Outcome Variable	Quetiapine	Risperidone	Quetiapine vs Risperidone 95% CI/Confidence limits	p-value
PANSS total change from baseline (mean) (PP)	-15.59	-18.10	5.01[a]	0.0108 (non-inferiority) 0.0973 (superiority)
PANSS Positive change from baseline (mean) (MITT)	-4.54	-5.55	0.10, 1.93	0.0306 (superiority)
PANSS Negative change from baseline (mean) (MITT)	-3.73	-4.15	-0.45, 1.27	0.3512 (superiority)
PANSS General Psychopathology change from baseline (mean) (MITT)	-7.02	-8.16	-0.41, 2.68	0.1481 (superiority)
PANSS total 30% improvement (%)(MITT)	27.4	27.7	NC	0.3856 (superiority)
PANSS Positive 30% improvement (%) (MITT)	35.4	36.2	NC	0.8326 (superiority)
PANSS Negative 30% improvement (%) (MITT)	28.1	27.1	NC	0.7903 (superiority)
PANSS General Psychopathology 30% improvement (%) (MITT)	25.3	27.4	NC	0.7599 (superiority)
CGI Severity of Illness (mean) (MITT)	-0.67	-0.86	0.05, 0.33	
CGI Global Improvement (%)(MITT)	39.0	41.8	NC	0.6711 (superiority)

CI Confidence interval; NC Not computed; Superiority=non-equivalence test; PP Per protocol population; MITT Modified intent-to-treat population.

[a] Test of non-inferiority yields one-sided confidence limits. Non-inferiority margin is 6 points on PANSS total.

Quality of life parameters as defined by SF-36 findings for both Physical Component Summary and Mental Component Summary scores did not show any meaningful differences between the two treatment groups. Among the 8 individual scales, the Role-Emotional score change from baseline for patients who completed the protocol exhibited a statistically significant advantage for quetiapine.

Safety results

Clinical adverse events were predominantly of the nervous and gastrointestinal systems and were generally consistent with current prescribing information for both quetiapine and

risperidone. Somnolence, headache, weight gain, dizziness, dyspepsia, nausea and pain were noted with greater than 5% incidence in both treatment groups. Asthenia and agitation were reported for approximately 5% of quetiapine-treated patients, and pharyngitis, akathisia, vomiting and dystonia were reported for 5% or more of risperidone patients. Extrapyramidal (EPS) findings were noted more frequently for risperidone-treated patients compared to quetiapine-treated patients. Approximately 13% of quetiapine patients and 22% of risperidone patients were reported to have experienced an EPS-related adverse event (AE). Among those patients who withdrew in association with adverse events, approximately 17% of quetiapine-treated patients and 44% of risperidone-treated patients exhibited increases in Abnormal Involuntary Movement Scale (AIMS) Total scores. Of the 14 patients who withdrew from the trial in association with EPS-related AEs, 1 had been treated with quetiapine, and 13 had been treated with risperidone. Diabetes-related adverse events were reported with a 15.1% incidence in quetiapine-treated patients and a 13.8% incidence in risperidone-treated patients. The event of "weight gain" was the predominant diabetes-related adverse event for both treatment groups. Both treatment groups exhibited increases in fasting glucose of approximately 4.5 mmol/L, and 10% to 11% of patients in the two groups had a shift from low or normal concentrations of glucose to high concentrations. Both treatment groups showed elevated mean prolactin concentrations at baseline. Following study treatment, mean prolactin concentrations declined among quetiapine-treated patients and increased among risperidone-treat patients. Risperidone-treated patients who did not have potentially clinically important prolactin concentrations at baseline exhibited approximately a 64% rate of shift to potentially clinically important concentrations while quetiapine-treated patients exhibited approximately a 1% shift rate. Most of the increased prolactin activity associated with risperidone administration was among female patients.

Table S3 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]			
	Quetiapine (N=338)		Risperidone (N=334)	
Any adverse events	258	(76.3)	256	(76.6)
Serious adverse events				
Serious adverse events leading to death	0	(0)	0	(0)
Serious adverse events not leading to death	14	(4.1)	9	(2.7)
Discontinuations of study treatment due to adverse events	20	(5.9)	23	(6.9)
Extrapyramidal-related adverse events	43	(12.7)	73	(21.9)
Diabetes-related adverse events	51	(15.1)	46	(13.8)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

N=number.

Table S 4 **Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of incidence within the quetiapine group (safety population)**

	Treatment			
	Quetiapine N=338		Risperidone N=334	
COSTART preferred term	**N**	**%**	**N**	**%**
Somnolence	89	26.3	66	19.8
Headache	51	15.1	56	16.8
Weight gain	48	14.2	45	13.5
Dizziness	48	14.2	32	9.6
Dry mouth	41	12.1	17	5.1
Dyspepsia	22	6.5	26	7.8
Nausea	21	6.2	22	6.6
Pain	20	5.9	24	7.2
Asthenia	17	5.0	14	4.2
Agitation	17	5.0	10	3.0
Pharyngitis	15	4.4	24	7.2
Akathisia	13	3.8	28	8.4
Vomiting	13	3.8	18	5.4
Dystonia	1	0.3	18	5.4

This table uses a cut-off of 5% in either treatment group.

Date of the report

26 September 2005