SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: SEROQUEL

ACTIVE INGREDIENT: Quetiapine

Trial title (number): A Multicentre, Double-Blind Randomised Comparison of SEROQUEL™ and Risperidone in the Treatment of Schizophrenic Patients with Acute Exacerbation (5077IL/0053)

Clinical phase: IIIb

First subject recruited: 6 May 1996
Last subject completed: 26 September 1997
Zeneca approval date: 12 June 1998

Principal investigator and location: No principal investigator was assigned to this trial.

Publications: There were no publications relating to this trial at the time this report was written.

OBJECTIVES

Primary objectives: To demonstrate equivalent efficacy of SEROQUEL and risperidone over a 10-week period in the treatment of schizophrenic patients with acute exacerbation; and to show a difference in the incidence of extrapyramidal symptoms (EPS) in patients treated with SEROQUEL compared with risperidone, as assessed by the proportion of patients receiving anticholinergic medication during the 10-week trial period.

Secondary objective: To compare the safety and tolerability of SEROQUEL and risperidone over this 10-week trial period.

METHODS

Design: This was a multicentre, double-blind, randomised, parallel-group comparison of SEROQUEL and risperidone in the treatment of patients with acute exacerbation of schizophrenia. The trial was designed to assess whether the 2 treatments were equivalent in efficacy, based on whether the 90% confidence interval of the difference between SEROQUEL and risperidone in mean change from baseline to Weeks 4 and 10 in PANSS total score was within the predetermined range of -9 to +9. This range of -9 to +9 was identified as being representative of a range over which treatment differences were unlikely to be of any clinical relevance.

Population: A total of 400 patients (200 in the SEROQUEL group and 200 in the risperidone group) with acute exacerbation of schizophrenia were to be recruited.

Key inclusion criteria: Male or female aged 18 to 65 years; satisfaction of the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria for either catatonic, disorganised, paranoid or undifferentiated schizophrenic subtypes; Clinical Global Impression (CGI) Severity of Illness rating of at least 4 (moderately ill); Positive and Negative Syndrome Scale (PANSS) total score of at least 60; PANSS score of at least 4 (moderate) on one or more of the following individual items: delusions, conceptual disorganisation, hallucinatory behaviour, suspiciousness/persecution.

Key exclusion criteria: Known sensitivity to SEROQUEL or risperidone; total white cell count (WCC) less than the lower limit of the reference range of the laboratory used for haematological monitoring; history of idiopathic or drug-induced agranulocytosis.

Dosage: SEROQUEL or risperidone was taken orally twice a day (morning and evening). There was an initial 4-day titration phase followed by 24 days of treatment with a fixed dose of either 300 mg/day of SEROQUEL or 6 mg/day of risperidone. At Week 4, patients who had not achieved at least a 30% decrease from baseline in PANSS total score had their dosage increased to either SEROQUEL 600 mg/day or risperidone 10 mg/day for a further 6 weeks. Patients who did achieve a 30% decrease in PANSS total score continued to receive the same dose of SEROQUEL or risperidone for the final 6 weeks. All of the tablets (SEROQUEL) and capsules (risperidone) were presented in “double-dummy” fashion.

Formulation and batch numbers were as follows: SEROQUEL 25 mg (F7202, 37406C96, 28046/95); placebo to SEROQUEL 25 mg (F7153, 28060/90); SEROQUEL 100 mg (F7201, 28049/95, 37404I96); placebo to SEROQUEL 100 mg (F7207, 28116/95, 34581/94); SEROQUEL 200 mg (F7200, 28035/95, 37405F96); placebo to SEROQUEL 200 mg (F7208, 28003/95, 28006/95); risperidone 1 mg (F11373, 28015/95, 39636K96); placebo to risperidone 1 mg (F11379, 34582/94); risperidone 2 mg (F11375, 28016/95, 39637H96); placebo to risperidone 2 mg (F11379, 34582/94); risperidone 3 mg (F11376, 28017/95, 39639B96); placebo to risperidone 3 mg (F11379, 34582/94); risperidone 4 mg (F11377, 39638E96, 28061/95); placebo to risperidone 4 mg (F11379, 34582/94).

Key assessments:

Efficacy: Patient’s schizophrenic symptoms were assessed using the PANSS and CGI psychiatric rating scales, with Brief Psychiatric Rating Scale (BPRS) scores being derived from the PANSS assessments. The primary efficacy endpoint was the change in the PANSS total score from baseline to Weeks 4 and 10. The secondary efficacy endpoints were as follows: the change in PANSS Positive, Negative and General Psychopathology Subscale scores from

baseline to Weeks 4 and 10; the CGI Global Improvement item at Week 10; the change in the CGI Severity of Illness score from baseline to Weeks 4 and 10; the number of patients who responded at Weeks 4 and 10, defined by a decrease in PANSS total score of at least 30% or at least 40% from baseline; and the change from baseline to Weeks 4 and 10 in the derived BPRS total score, Positive Subscale score and Mood Cluster score. All of the secondary endpoints were analysed using analysis of covariance, except the CGI Global Improvement Item was analysed using analysis of variance and the proportion of patients responding was analysed using logistic regression.

Safety and tolerability: Safety and tolerability assessments included the recording of anticholinergic medication use, adverse events, clinical laboratory values (including serum prolactin), and scores on the Barnes Global Akathisia scale, Simpson Scale and Abnormal Involuntary Movement Scale (AIMS). The primary safety endpoint was the proportion of patients receiving anticholinergic medication during the 10-week trial period (to assess the incidences of EPS); these data were analysed using logistic regression. The secondary safety endpoints included the following: the proportion of patients receiving anticholinergic medication between baseline and Week 4; the proportion of patients whose Simpson Scale total score exceeded the baseline value at any time during the periods from baseline to Weeks 4 and 10; the change in serum prolactin concentration from baseline to Week 10; the proportion of patients whose Barnes Global Akathisia score exceeded the baseline value at any time during the periods from baseline to Weeks 4 and 10; and the proportion of patients experiencing adverse events related to EPS. All of the secondary endpoints were analysed using logistic regression, except for the change in serum prolactin concentration, which was analysed using analysis of covariance.

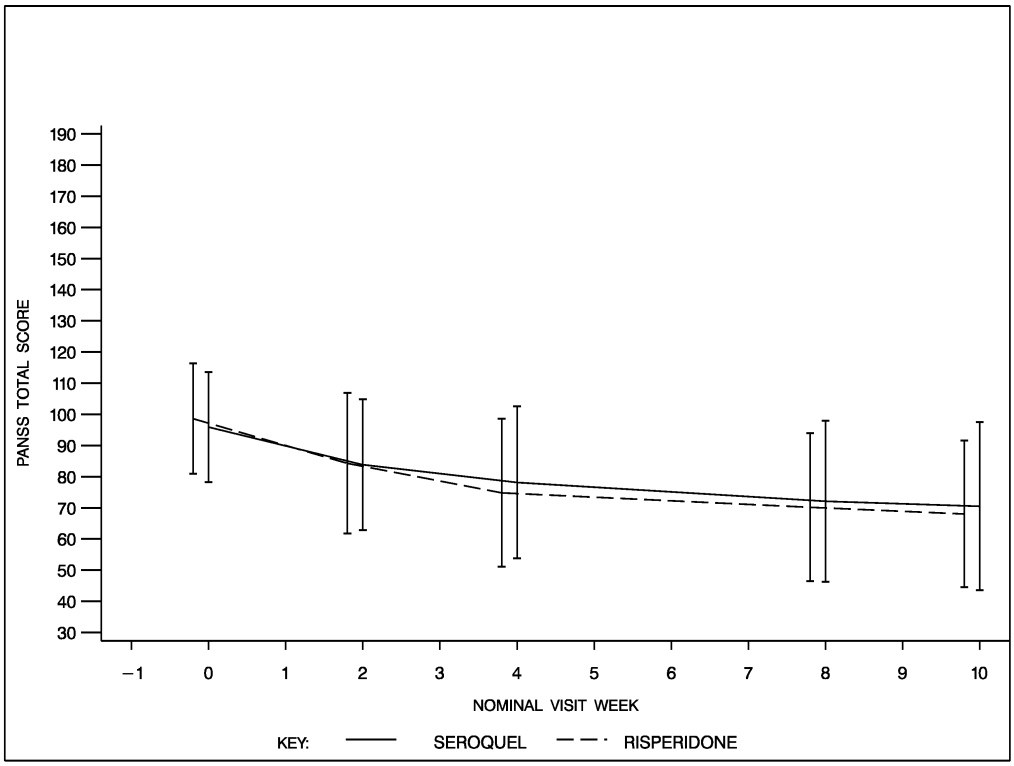
RESULTS

Demography: A total of 408 patients (200 in the SEROQUEL group and 208 in the risperidone group) were randomised to trial treatment from 65 centres. Mean age was 35 years (range 18 to 65 years) in the SEROQUEL group and 37 years (range 18 to 66 years) in the risperidone group; most patients in both groups were male (64.5% and 61.1%) and Caucasian (89.5% and 87.0%). These data indicate that the 2 groups were similar demographically. The 2 groups were also well matched in terms of schizophrenic subtype (71% from each group had paranoid schizophrenia) and baseline severity of illness (similar baseline psychiatric rating scale scores).

Of the 408 patients randomised, 3 were withdrawn before starting treatment (2 in the SEROQUEL group and 1 in the risperidone group) and a further 145 were withdrawn during treatment (78 and 67, respectively). The most common reason for withdrawal of SEROQUEL was “condition deteriorated” (30/200 patients [15.0%]) and for risperidone was “adverse event” (24/208 patients [11.5%]).

Efficacy: Both SEROQUEL and risperidone were associated with marked mean reductions in PANSS total score (the primary efficacy endpoint) over time, indicating clinically meaningful improvements in the symptoms of schizophrenia; profiles of these reductions over time were similar in the 2 groups (Figure I).

Figure I Mean (SD) PANSS total scores over time (last-value-carried-forward [LVCF] analysis on per-protocol [PP] population)



Results of the main analysis (LVCF analysis on PP population) of the treatment differences in change from baseline in PANSS total scores are shown in Table I.

Table I Analysis of covariance of change from baseline in PANSS total score (LVCF analysis on PP population)

Trial week	Change from baseline				Difference between treatments			
	SEROQUEL		Risperidone					
	n	lsmean	n	lsmean	Diff	SE	LCL	UCL
4	179	-15.52	192	-20.38	4.86	2.13	1.35	8.37
10	179	-20.32	192	-25.01	4.69	2.41	0.71	8.67

lsmean Least squares mean
Diff Estimated treatment difference
SE Standard error of difference
LCL Lower 90% confidence limit
UCL Upper 90% confidence limit

SEROQUEL and risperidone treatments can be considered to be clinically equivalent in efficacy, because the 90% confidence interval for the difference between the 2 treatments falls wholly within the predetermined range of -9 to +9.
Both treatments were associated with improvements on all secondary efficacy endpoints. At Week 10, risperidone was associated with statistically significantly greater reductions than SEROQUEL on the PANSS Positive and General Psychopathology Subscales, the derived BPRS total and Positive Subscales, and the CGI Global Improvement scale; the absolute magnitudes of the differences between treatments, on all scales, were modest. Interpreting such small differences between groups on mean changes in rating scale scores is inherently difficult and confounded by problems, such as the non-linearity of the rating scales. As a result, many investigators have adopted response rates (defined in this trial as improvements from baseline of greater than or equal to 30% or 40% in PANSS total scores) as an indicator of the clinical significance of treatment effects. There was a statistically significant difference between treatments, in favour of risperidone, using the less stringent criterion of a 30% improvement. However, using the more demanding criterion of a 40% improvement, a clinically significant benefit was seen with both treatments in over one-third of patients, with no statistically significant difference between treatments.
Safety and tolerability: Table II indicates there was a statistically significant difference in favour of SEROQUEL in the proportion of patients who received anticholinergic medication at any time during the 10-week trial period (primary safety and tolerability endpoint) and also from randomisation to Week 4 (secondary safety and tolerability endpoint).

Table II Proportion of patients who received anticholinergic medication during the trial period: results of logistic regression analysis (ITT population)

	SEROQUEL		Risperidone		Odds ratio	95% LCL	95% UCL	p-value
	Number assessed	Number (%) who received medication	Number assessed	Number (%) who received medication				
Randomisation to Week 4	198	23 (11.6)	207	51 (24.6)	0.37	0.21	0.64	<0.001
Within 10-week trial period	198	30 (15.2)	207	63 (30.4)	0.38	0.23	0.64	<0.001

LCL Lower confidence limit UCL Upper confidence limit

The data in Table II strongly suggest that SEROQUEL is associated with fewer EPS than risperidone, an interpretation which was supported by the analysis of additional safety and tolerability endpoints (eg, proportions experiencing adverse events related to EPS and proportions whose Simpson Scale and Barnes Global Akathisia scores exceeded the baseline score from baseline to Weeks 4 and 10).
The incidence of adverse events in the SEROQUEL group was 64.0% (128/200 patients) compared with 75.0% (156/208 patients) in the risperidone group. A higher proportion of patients treated with risperidone (51.9%) than with SEROQUEL (40.0%) reported adverse events related to the nervous system, especially adverse events related to EPS, eg, akathisia,

hypertonia and tremor (but not extrapyramidal syndrome). Other noteworthy events that were reported with a higher frequency in patients treated with risperidone than with SEROQUEL included anxiety, headache, rhinitis, abnormal ejaculation, abnormal vision, nervousness, insomnia, and increased salivation. SEROQUEL was associated with higher incidences of dry mouth, dizziness, hostility and agitation than risperidone.

One patient died after risperidone (suicide) but there were no deaths in the SEROQUEL group. Similar proportions of patients withdrew because of adverse events (22/200 [11.0%] in the SEROQUEL group and 24/208 [11.5%] in the risperidone group). The most common adverse event leading to withdrawal in the SEROQUEL group was agitation (5 patients), compared with akathisia (9 patients) in the risperidone group. Similar proportions of patients also reported serious adverse events (12/200 [6.0%] in the SEROQUEL group and 13/208 [6.3%] in the risperidone group), with no noteworthy differences between the groups in events classed as serious (no serious adverse event was reported by more than 2 patients in either group).

Clear differences (statistically significant) were seen between the 2 treatments in effect on serum prolactin concentration (secondary safety and tolerability endpoint): risperidone was associated with a mean increase whilst SEROQUEL was associated with a mean decrease over the period from pre-trial screen to end of treatment. More patients treated with risperidone than with SEROQUEL also had adverse events possibly related to elevations in serum prolactin concentration. Changes in other clinical laboratory variables were observed occasionally in both treatment groups (eg, decreases in white cell count, elevated ALT and altered thyroid hormone concentrations). These changes were not associated with clinical sequelae, although 1 patient treated with SEROQUEL, who had a history of viral hepatitis and alcohol abuse, developed evidence of diffuse liver disease and jaundice and was withdrawn from the trial. No important changes were apparent in either treatment group from examination of vital sign and physical examination data.