SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: SEROQUEL

ACTIVE INGREDIENT: Quetiapine

Trial title (number): A Multicentre, Double-Blind, Randomised Trial to Compare the Effects of SEROQUEL and Chlorpromazine in Patients with Treatment Resistant Schizophrenia (5077IL/0054 [TRESS])

Clinical phase: IIIb

First patient recruited: 20 May 1996
Last patient completed: 8 December 1998
Zeneca approval date: 13 November 2000

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

OBJECTIVES
The primary objective of this trial was to compare the efficacy of quetiapine and chlorpromazine in patients with schizophrenia who had previously failed to respond to antipsychotic treatment (treatment-resistant). Secondary objectives were to compare the safety of quetiapine and chlorpromazine in the same patient population and to compare additional measures of efficacy.

METHODS
Design: This was an international, multicentre, double-blind, randomised, parallel-group trial. A 2-week dose-titration period was followed by treatment for a further 8 weeks at a fixed dose.
Population: In total, 242 patients with treatment resistant schizophrenia - 121 per randomised treatment group - were to be recruited to achieve 90% power for the assessment of the primary endpoint.
Key inclusion criteria: Male or female patients aged 18 to 65 years inclusive; diagnosis of schizophrenia, according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders,

4th edition); at least two 6-week periods of treatment with different antipsychotic agents (at doses equivalent to or greater than 700 mg/day of chlorpromazine) in the preceding 5 years with no evidence of significant improvement between the 2 treatment periods[1], and with persistence of at least 1 positive symptom and 1 or more major areas of functioning (eg, work, interpersonal relations) markedly below the level achieved prior to this period; a total score of at least 60 on the Positive and Negative Syndrome Scale (PANSS); a score of at least 4 (moderately ill) on the Clinical Global Impressions (CGI) Severity of Illness item.

Key exclusion criteria: Patients with chlorpromazine resistance; patients who had not previously responded to treatment with clozapine; a total white blood cell count below the lower limit of the reference range for the laboratory used for haematological monitoring; known sensitivity to quetiapine or chlorpromazine; a history of idiopathic or drug-induced agranulocytosis.

Dosage: All tablets were taken by mouth twice a day (morning and evening). Daily doses of quetiapine and chlorpromazine were titrated over a 2-week period to 600 mg/day and 900 mg/day, respectively; thereafter, medication was maintained at these fixed doses for a further 8 weeks.

Formulation and batch numbers were as follows. Quetiapine 25 mg (F7202, 28046/95, and 37406C96) and placebo to match (F7153, 28060/95, and 34580/94); 100 mg (F7201, 28049/95, and 37404I96) and placebo to match (F7207, 28116/95, 34581/94, and 36161E96); 200 mg (F7200, 28035/95, and 37405F96) and placebo to match (F7208, 28003/95). Chlorpromazine 25 mg (F12022, 27171/95) and placebo to match (F12023, 27194/95); 50 mg (F12020, 27172/95) and placebo to match (F12021, 27193/95); 100 mg (F12018, 27176/95, and 37198I96) and placebo to match (F12019, 27192/95, 38261H96, and 39276D96).

Key assessments:

Efficacy: Severity of schizophrenic symptomatology was measured using the PANSS and the Severity of Illness and Global Improvement items of the CGI scale at baseline, Week 4, and Week 10, or on withdrawal from the trial. The primary efficacy endpoints were the proportion of patients responding to treatment at Week 10 (defined as a reduction from baseline of 20% or more in PANSS total score and a CGI Severity of Illness score of 3 or less) and the change in PANSS total score from baseline to Week 10.

The secondary efficacy endpoints were the proportion of patients responding to treatment shown by a decrease in PANSS total score of 20% or more from baseline to Week 10, the proportion of patients responding to treatment shown by a CGI Severity of Illness score of 3 or less at Week 10, change in PANSS total score from baseline to Week 4, change in PANSS subscale scores (positive, negative, and general psychopathology) from baseline to Week 10, change in the derived Brief Psychiatric Rating Scale (using a severity scale of 1 to 7 [BPRS (1-7)]) total scores, positive subscale, and mood cluster scores from baseline to Week 10, change in the CGI Severity of Illness score from baseline to Week 10, and the CGI Global Improvement score at Week 10.

Response to treatment was analysed using logistic regression, which included an assessment of the centre-by-treatment interaction. The primary analyses of response to treatment were

[1] Although the protocol stated “no significant improvement between the 2 treatment periods”, this was in error. What was intended, and was explained to the investigators, was that there was to have been “no significant improvement during the 2 treatment periods”.

performed on the intention-to-treat (ITT) population which consisted of all randomised patients who received treatment and provided efficacy data for at least 1 post-baseline visit. Additional analyses were performed on the per-protocol (PP) population which excluded all patients with major protocol violations or deviations.
The change in PANSS total score, PANSS subscale scores, derived BPRS (1-7) scores, and CGI Severity of Illness score were analysed using analysis of covariance, including baseline score, treatment, centre, and centre-by-treatment interaction as factors. The CGI Global Improvement score at Week 10 was assessed using an analysis of variance. The population assessed in the main analysis of changes from baseline in rating scales was the ITT population using a last-value-carried-forward (LVCF) approach. Additional analyses were performed on the ITT population without LVCF (ie, an observed case population) and an LVCF analysis on the PP population.
Safety: Possible neurological side effects were measured using the Simpson Scale, which included an item for akathisia, and the Abnormal Involuntary Movement Scale (AIMS); assessments were made at baseline and at Weeks 4 and 10, or on withdrawal from the trial. Statistical analyses were performed on the ITT and PP populations for the proportion of patients who experienced an increase in Simpson Scale score from baseline at any time, the proportion who developed clinically significant extrapyramidal symptoms (EPS) during the trial (as measured by the proportion of patients who had an increase from baseline in Simpson Scale total score and who had a Simpson Scale total score of at least 14 at any time during the trial), the proportion of patients receiving anticholinergic medication at any time from baseline onwards, and the proportion of patients experiencing worsening or developing EPS adverse events from baseline onwards. Changes in serum prolactin concentration between the pre-trial screen and Week 10 were analysed using the observed case ITT population (main analysis), and the observed case PP population. All adverse events were reported during the course of the trial were monitored until resolution, routine clinical laboratory tests, vital sign measurements, and body weight assessments were also performed.

RESULTS
Demography: A total of 256 different patients were recruited for this study from 32 active centres. Of these, 4 patients were screened twice and were allocated 2 different randomisation numbers and 1 patient completed the study twice, receiving both quetiapine and chlorpromazine. In total 236 patients were randomised (117 to quetiapine and 119 to chlorpromazine) including the patient who completed the study twice. The quetiapine and chlorpromazine groups were well matched demographically: most patients in each group were male (54.7% versus 57.1% for the quetiapine and chlorpromazine groups, respectively), Caucasian (80.3% versus 81.5%, respectively), in their late 30s (mean age was 39 years in both groups) with a mean weight of 71 kg in both groups. The quetiapine and chlorpromazine groups were also well matched with respect to schizophrenic subtype and baseline severity of illness: most patients in each group had paranoid schizophrenia (62.4% versus 65.5%, respectively) and most were moderately to markedly ill (mean baseline CGI Severity of Illness score was 5.4 and 5.5, respectively).
A total of 165 patients completed the trial (86 in the quetiapine group and 79 in the chlorpromazine group); the most common reason for withdrawal of treatment in both treatment

groups was adverse event. The ITT population comprised 116 patients in the quetiapine group and 118 in the chlorpromazine group; corresponding figures for the PP population were 75 and 80, respectively.

Efficacy: Both quetiapine and chlorpromazine gave similar results for response to treatment and reduction in PANSS total scores over time, and there was no statistically significant differences between the 2 treatment groups either in of these primary efficacy endpoints (Tables I and II).

Table I Proportion of patients responding to treatment[a] at Week 10 with quetiapine or chlorpromazine: results of logistic regression analysis (analysis on ITT population)

Quetiapine (N = 92)		Chlorpromazine (N = 89)		Odds ratio	LCL	UCL	p-value
n	%	n	%				
25	27.2	22	24.7	1.16	0.59	2.32	0.665

[a] ≥20% reduction from baseline in PANSS total score and a CGI Severity of Illness score ≤3 at Week 10.
N Number of patients with assessments at baseline and Week 10.
n Number of patients responding to treatment.
LCL Lower 95% confidence limit.
UCL Upper 95% confidence limit.

Table II Analysis of covariance of change in PANSS total score at Week 10 (LVCF analyses on ITT population)

Change from baseline				Difference between treatments				
Quetiapine		Chlorpromazine		Diff	SE	LCL	UCL	p-value
n	lsmean	n	lsmean					
115	-16.72	117	-18.85	2.14	2.66	-3.11	7.38	0.423

Diff Estimated treatment difference. LCL Lower 95% confidence limit.
lsmean Least squares mean. SE Standard error of difference.
UCL Upper 95% confidence limit.

The additional analyses on change in PANSS total score at Week 10 using a LVCF analysis on the PP population and an observed case analysis on the ITT population confirmed the results of the main analysis in both cases. For all secondary efficacy endpoints, there was no statistically significant difference between the quetiapine and chlorpromazine treatment groups, although both groups demonstrated beneficial changes in the rating scales used.

Safety: Secondary safety and tolerability endpoints of this trial were related to the development of EPS (increase in Simpson Scale scores, EPS-related adverse events, use of anticholinergic medication to treat EPS) and changes in serum prolactin concentration.

Statistically significant differences between the treatment groups were observed for changes in serum prolactin concentration ($p<0.001$) and adverse events related to EPS (ITT analysis; $p=0.045$), both in favour of quetiapine. The use of anticholinergic medication and the proportion of patients who had an increase from baseline in Simpson Scale total score and a Simpson Scale total score of at least 14 at any time during the trial were numerically in favour of quetiapine

although differences between the groups did not reach statistical significance. Further analysis of patients who started anticholinergic medication after randomisation showed statistical significance in favour of quetiapine.

The proportion of patients who reported at least 1 adverse event was similar in both the quetiapine (73.9%) and chlorpromazine (79.8%) groups, although there were some notable differences in the types of event reported. More patients treated with quetiapine, compared with chlorpromazine, reported vomiting, hostility, hypothyroidism, and constipation, a recognised anticholinergic effect of the drug. However, none of these events were reported in more than 10% of patients in this group. Dry mouth, another anticholinergic effect associated with quetiapine, was reported by a similar proportion of patients in each group.

A higher proportion of chlorpromazine patients, compared with quetiapine patients, reported EPS (akathisia, tremor, hypertonia), dizziness, nervousness, somnolence, postural hypotension, rash, and photosensitivity. Of these events only akathisia and somnolence were reported by more than 10% of patients in the chlorpromazine group. In patients who had a ≥30% or ≥40% reduction in PANSS total score, the proportion of patients with any EPS event, any EPS–related adverse event, or a Simpson Scale Score of ≥14 was lower in the quetiapine group compared to the chlorpromasine group. In addition, for patients who had a ≥40 % reduction in PANSS total score, the proportion of patients who received anticholinergic medication was lower in the quetiapine group than the chlorpromasine group.

In both treatment groups insomnia (a recognised symptom of schizophrenia) was the most frequently reported adverse event (22.7% of patients treated with quetiapine and 19.3% of patients treated with chlorpromazine). The proportion of patients who reported serious adverse events and adverse events leading to withdrawal was comparable for the 2 treatment groups; however, more patients in the quetiapine treatment group than in the chlorpromazine group were withdrawn as a result of hostility. No deaths were reported in either treatment group during this trial.