SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: **SEROQUEL™**

ACTIVE INGREDIENT: **Quetiapine**

Trial title (number): A Multicentre, Double-Blind, Randomised, Parallel-Group Comparison of Quetiapine and Haloperidol in the Treatment of Elderly Patients Presenting with Dementia and Psychoses (5077IL/0049)

Clinical phase: IIIb

First patient recruited: 19 February 1997
Last patient recruited: 9 October 1998
Zeneca approval date: 6 June 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 proportion of patients either developing or experiencing worsening of extrapyramidal symptoms (EPS) after treatment with quetiapine or haloperidol over a 6-week period in a patient population aged 65 years or more presenting with dementia and psychoses. Secondary objectives were to compare the effects of quetiapine and haloperidol on cognitive function, symptoms and behaviour, adverse events, and laboratory changes in the above population.

METHODS

Design: This was a multicentre, double-blind, randomised, parallel-group comparison of quetiapine and haloperidol in the treatment of elderly patients presenting with dementia and psychoses.

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Population: A total of 114 patients (57 per treatment group).
Key inclusion criteria: Male or female, aged 65 years or over; satisfaction of the ICD-10 (International Classification of Diseases) research diagnostic criteria for dementia in Alzheimer's disease, with the presence of predominantly delusional or hallucinatory symptoms; a score of at least 3 (mildly ill) on the Clinical Global Impressions (CGI) Severity of Illness item; a score between 10 and 26 from the Mini Mental State Examination.
Key exclusion criteria: Evidence of any significant clinical disorder or laboratory finding for this age group; patients with a history or clinical evidence on ECG of myocardial infarction within the last 3 months, or any clinically significant ECG result; total white blood cell count less than the lower limit of the reference range of the laboratory used for haematological monitoring; history of drug-induced agranulocytosis; satisfaction of diagnostic criteria for delirium superimposed on dementia.
Dosage: All tablets and capsules were taken by mouth twice a day (morning and evening). Doses of quetiapine and haloperidol were slowly titrated up to a maximum of 300 and 6 mg/day, respectively, depending on clinical response. Those patients who could not tolerate dose increases were still allowed to continue in the trial. Hence, patients could continue in the trial on 1 of 5 doses of quetiapine (50, 75, 100, 200, or 300 mg/day) or 1 of 5 doses of haloperidol (1, 1.5, 2, 4, or 6 mg/day). Formulation and batch numbers were as follows: quetiapine: 25-mg tablets (F7202; 28051/95, 37406C96) and placebo to match (F7153; 28060/95, 34580/94); 100-mg tablets (F7201; 28049/95, 37404I96) and placebo to match (F7207; 36161E96, 28116/95); haloperidol: 0.5-mg capsules (F8233; 35895H96, 00571F98) and placebo to match (F8236; 35894K96, 00569H98); 1.5-mg tablets (F8234; 27137/95, 00568K98) and placebo to match (F8237; 27138/95, 00570I98).
Key assessments:
Efficacy: Psychiatric assessments of patients were made at baseline and at Day 42 using the following rating scales: Neuropsychiatric Inventory (NPI), Montgomery and Asberg Depression Rating Scale (MADRS), CGI Severity of Illness (also assessed at Day 15), and Mini Mental State Examination (MMSE). Cognitive assessments using the Alzheimer's Disease Assessment Scale (ADAS) were also determined at baseline and at Day 42. Changes from baseline to Day 42 in these rating scale scores were secondary endpoints of the trial and were analysed by an analysis of covariance model. CGI Global Improvement was assessed only at Day 42 and was analysed by an analysis of variance model. Three separate analyses were performed: a last-value-carried forward (LVCF) analysis on an intention-to treat population (the primary analysis), an observed-case analysis on the intention-to-treat population, and an LVCF analysis on a per-protocol population.
Safety: The Simpson Scale was used to assess the development or worsening of EPS; scores were obtained at baseline and at Days 15 and 42. The proportion of patients with an increase from baseline in Simpson Scale total score (primary endpoint) and the proportion of patients developing clinically significant EPS during the trial, as measured by an increase from baseline in the Simpson Scale total score to ≥14 (secondary endpoint), were analysed using logistic regression. The use of anticholinergic medication to treat EPS and adverse events related to EPS were recorded and were additional secondary endpoints of the trial; these endpoints were also analysed using logistic regression. A survival-time analysis was also performed on the use of anticholinergic medication. Analyses of these endpoints were performed on both the

intention-to-treat (primary) and per-protocol populations. All adverse events were recorded for the safety population (which consisted of all patients who received at least 1 dose of trial treatment), and routine clinical laboratory tests, vital signs measurements, and ECGs were also performed.

RESULTS

Demography: Of the 140 patients screened, 112 from 18 centres were randomised to treatment: 55 to quetiapine and 57 to haloperidol. Thirty-four patients (34/112, 30.4%) withdrew, 17 from each treatment group (quetiapine: 17/55, 30.9%; haloperidol: 17/57, 29.8%); 2 of whom were withdrawn prior to receiving trial treatment. The 2 groups were well matched demographically: most patients were female (75.9%), Caucasian (99.1%), and >75 years old (77.7%). Late-onset dementia was the most frequently reported diagnosis (quetiapine: 46/55, 83.6%; haloperidol: 45/57, 78.9%) and the majority of patients had delusional symptoms associated with their disease (30/55, 54.5% and 43/57, 75.4%, respectively). The groups were also well matched in terms of baseline ADAS cognitive rating scale scores (30.8 and 28.7, respectively) and most were considered to be moderately ill (mean baseline CGI Severity of Illness scores of 4.0 and 3.9, respectively). The intention-to-treat population comprised 108 patients (quetiapine: 53; haloperidol: 55) whilst the per-protocol population consisted of 62 patients (31 from each treatment group).

Efficacy: No statistically significant differences were evident for the intention-to-treat (LVCF) population between the quetiapine and haloperidol treatment groups for the psychiatric and cognitive rating scales assessed; both treatments resulted in a substantial improvement in psychosis. The magnitude of the changes from baseline to Day 42 favoured quetiapine for both the NPI and MADRS total scores ($p = 0.156$ and $p = 0.065$, respectively). The additional analyses performed for the intention-to-treat (observed case) and per-protocol (LVCF) populations tended to confirm the results of the primary analysis. In 2 instances, significant differences were evident in the intention-to-treat (observed case) population; these were in favour of quetiapine for the MADRS total score (estimated treatment difference: -2.58; $p = 0.042$) but in favour of haloperidol for the MMSE total score (estimated treatment difference: -1.76; $p = 0.027$). In both of these cases, the results of the per-protocol populations confirmed the non-significant results seen for the primary analyses ($p = 0.223$ and $p = 0.310$, respectively).

Examination of the individual domains of the NPI revealed 2 significant differences between the treatment groups for the intention-to-treat (LVCF) population. A statistically significant difference was found in favour of quetiapine for the NPI depression/dysphoria domain score ($p = 0.027$). The additional analysis for the intention-to-treat (observed case) population confirmed this result ($p = 0.026$); however, the analysis of the per-protocol (LVCF) population was not statistically significant ($p = 0.141$). A statistically significant difference was also evident for the primary analysis of the change from baseline to Week 6 in the NPI anxiety domain score in favour of quetiapine ($p = 0.043$). However, the additional analyses for the intention-to-treat (observed case) and per-protocol (LVCF) populations were not statistically significant ($p = 0.141$ and $p = 0.562$, respectively).

Safety: No statistically significant difference was evident between the treatment groups for either the proportion of patients whose Simpson Scale total score exceeded the baseline value during the trial period (Table I) or for the proportion developing clinically significant EPS ($p = 0.598$), for the intention-to-treat population. The additional analyses for the per-protocol population confirmed these results.

Table I Results of logistic regression analysis of the proportion of patients whose Simpson Scale total score exceeded baseline at any time point (ITT population)

Number (%) of patients				Odds ratio	LCL	UCL	p-value
Quetiapine (n = 53)		Haloperidol (n = 55)					
26	(49.1)	24	(43.6)	1.24	0.57	2.71	0.590

ITT Intention to treat; LCL Lower 95% confidence limit; UCL Upper 95% confidence limit.

No statistically significant differences were reported between the treatment groups for the proportion of patients who experienced adverse events related to EPS or received anticholinergic mediation to treat EPS ($p = 0.447$ and $p = 0.254$, respectively).

Adverse events were reported by 38 patients from both treatment groups (quetiapine: 38/54, 70.4%; haloperidol: 38/56, 67.9%). Somnolence (12/54, 22.2%), accidental injury (8, 14.8%), and dry mouth (6, 11.1%) were the most prevalent events in the quetiapine group. In comparison, somnolence (10/56, 17.9%), asthenia (5, 8.9%), and tremor (5, 8.9%) were the most frequently reported events with haloperidol. Adverse events led to the withdrawal of 9 patients (16.7%) from the quetiapine group and 11 patients (19.6%) in the haloperidol group. Serious adverse events were reported marginally more frequently in the quetiapine group (quetiapine: 11/54 patients, 20.4%; haloperidol: 9/56, 16.1%). There were 4 deaths reported, 3 (5.6%) in the quetiapine group and 1 (1.8%) in the haloperidol group; none was considered to be related to treatment.

There were no clinically significant changes in laboratory data. Four patients in the quetiapine group and 1 from the haloperidol group had leucopenia reported as an adverse event; none had a reduction in WCC below 2.9×10^9 cells/l or an ANC below 1.5×10^9 cells/l.

No clinically significant changes from baseline were observed for either mean blood pressure or pulse rate. Significant ECG changes were evident for 4 quetiapine (4/54, 7.4%) and 8 haloperidol-treated patients (8/56, 14.3%).