SUMMARY

ASTRAZENECA

FINISHED PRODUCT: SEROQUEL™

ACTIVE INGREDIENT: Quetiapine

Trial title (number): A Multicentre, Double-blind, Randomised Trial to Compare the Effects of Quetiapine and Haloperidol Treatment Strategies on Treatment Outcomes (5077IL/0050 [ESTO])

Clinical phase: IIIb

First patient recruited: 2 May 1996
Last patient completed: 21 May 1999
AstraZeneca approval date: 09 April 2001

Principal investigators and locations (centre numbers): No principal investigator was appointed for this trial.

Publications: Drummond MF, Knapp MRJ, Burns TP, Miller KD, Shadwell PJ. Mental Health Policy Econ 1998;1:15-22.
Drummond MF, Knapp MRJ, Burns TP, Miller KD, Ruiz R. Eur Neuropsychopharmacol 1996:6 (suppl 4):S4-126, [abstract P.3.070].

OBJECTIVES
The primary objective of this trial was to show a difference between the quetiapine treatment group and the haloperidol treatment group in the number of patients who discontinued randomised treatment.
The secondary objectives were: to compare treatment strategies (all treatments received by each patient over the 52-week trial period regardless of whether they remained on randomised double-blind treatment) by comparing patient outcome and resource use; to compare the actual randomised double-blind treatments using the same criteria as for the comparison of the treatment strategies; and to assess the safety and tolerability of quetiapine and haloperidol.

METHODS

Design: This was an international, multicentre, double-blind, randomised trial. A 1-week dose-titration period was followed by treatment for a further 51 weeks at a flexible dose.

Population: In total, 380 patients with schizoaffective disorder or a schizophrenic subtype of either catatonic, disorganised, paranoid, or undifferentiated - 190 per randomised double-blind treatment group - were to be recruited to achieve 80% power at the 5% significance level for the assessment of the primary endpoint.

Key inclusion criteria: Male or female patients aged 18 years or over; diagnosis of 1 of the schizophrenic subtypes given above, according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition); at least 1 hospital admission or documented evidence of acute exacerbation of the patient's disorder within the 3 years immediately before entering the trial; a score of at least 4 (moderately ill) on the Clinical Global Impressions (CGI) Severity of Illness item; a total score of at least 60 on the Positive and Negative Syndrome Scale (PANSS); able to stop all psychotropic medication (a list defining all psychotropic medications is presented at the end of this summary) for 48 hours before randomisation with long-acting depot antipsychotic medication being stopped 1 dose interval before randomisation (in Germany pre-trial psychotropic medication was only to be withdrawn 48 hours before randomisation if, in the investigator's opinion, it was medically justifiable; the investigator considered the patient was capable of being followed-up for at least 12 months.

Key exclusion criteria: Pregnancy or lactation in females, or female patients at risk of becoming pregnant (in Canadian Centre 0026, women who had not undergone surgical sterilisation or who were pre-menopausal were excluded, in Australian Centre 0004 women using oral and/or barrier methods of contraception were excluded); a total white blood cell (WBC) count below the lower limit of the reference range for the laboratory used for haematological monitoring; a history of idiopathic or drug-induced agranulocytosis; known sensitivity to quetiapine or haloperidol; evidence of chronic or severe disease; (Germany only) patients who required depot neuroleptics or neuroleptics with a long half-life, had suicidal tendencies, or were in care or legally committed.

Dosage: All tablets were taken by mouth twice a day (morning and evening). Daily doses of quetiapine and haloperidol were titrated over 4 or 5 days, respectively, up to 300 mg/day and 10 mg/day, respectively; thereafter, the option was available to allow titration of medication up to a maximum of quetiapine 600 mg/day and haloperidol 20 mg/day for a further 51 weeks. Formulation numbers were as follows: quetiapine 25 mg and placebo to match (F7202[1] and F7153[2], respectively); 100 mg (F7201 and F12157)[3] and placebo to match (F7207[4]); 200 mg (F7200 and F12158)[5] and placebo to match (F7208[6]). Haloperidol 0.5 mg and placebo to match

[1] Batch numbers: 28028/95, 37406C96.

[2] Batch numbers: 34580/94, 28060/95.

[3] Batch numbers: 28026/95, 28049/95, 35480C96, 37404I96, 28050/95, 36574D97.

[4] Batch numbers: 34581/94, 36161E96.

[5] Batch numbers: 28033/95, 28030/95, 28058/95, 37405F96, 28029/95, 36576I97.

[6] Batch numbers: 28007/95, 28008/95, 28005/95, 28004/95, 28012/95, 28001/95, 28009/95, 28011/95.

(F8233 and F8236, respectively)[7]; 1.5 mg and placebo to match (F8234 and F8237, respectively)[8]; 5.0 mg and placebo to match (F8235b[9] and F8238[10], respectively).

Key assessments:

Efficacy: The primary efficacy endpoint was the proportion of patients who discontinued randomised double-blind trial treatment. Secondary endpoints included: time to discontinuation of randomised double-blind treatment; change from baseline to Weeks 24 and 52 in PANSS total and subscale (positive, negative, and general psychopathology) scores, CGI Severity of Illness score, derived Brief Psychiatric Rating Scale (BPRS) total and subscale (positive and mood cluster) scores, and quality of life (QoL); proportion of patients with a ≥ 40% reduction in PANSS total score from baseline at Weeks 24 and 52; proportion of patients with a ≥ 40% reduction in derived BPRS total score from baseline at Weeks 24 and 52; change in impact of the disease on family or caregiver from baseline to Week 52. The secondary efficacy endpoints were assessed in the treatment strategy and randomised treatment populations. The treatment strategy population was defined as all patients who had remained in the trial for the entire 52-week trial period regardless of whether or not they remained on randomised double-blind therapy. The randomised treatment population was comprised of all patients whilst they remained on randomised treatment only.

The proportion of patients who discontinued randomised double-blind treatment was analysed using logistic regression, which included an assessment of the centre-by-treatment interaction. The change in PANSS total score, PANSS subscale scores, derived BPRS scores, CGI Severity of Illness score, and QoL scores were analysed using analysis of covariance, including baseline score as a covariate and treatment, centre and centre-by-treatment interaction as factors. The CGI Global Improvement score was assessed using an analysis of variance.

Economic: In this clinical trial report (CTR), economic assessments employed were: change in Client Service Receipt Inventory (CSRI) from baseline to Week 52 in the amount of care per Week from informal carers, number of day care attendances, contact with community psychiatric nurse, and contact with social worker; number and proportion of days hospitalised. A full economic cost-consequence report is being prepared separately from this CTR.

Safety: The proportion of patients who experienced an increase in Simpson Scale score from baseline onwards, and the proportion who developed clinically significant extrapyramidal symptoms (EPS) during the trial, as measured by patients who had a Simpson Scale total score of 14 or more, were analysed as secondary safety and tolerability endpoints. Other secondary endpoints were proportion of patients receiving anticholinergic medication at any time from baseline onwards and proportion of patients experiencing EPS adverse events from baseline onwards. Routine clinical laboratory tests and vital sign measurements were also performed as was the monitoring of adverse events and the assessment of changes in abnormal involuntary movement scale (AIMS) scores over the trial.

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[7] Batch numbers: 27135/95 and 27136/95 for active drug and placebo, respectively.

[8] Batch numbers: 27137/95 and 27138/95 for active drug and placebo, respectively.

[9] Batch numbers: 27140/95, 27139/95, 39368G97.

[10] Batch numbers: 27141/95, 27142/95, 39369D97.

RESULTS

Demography: Of the 418 patients screened, 381 from 53 centres were randomised to treatment: 193 to quetiapine and 188 to haloperidol. Three-hundred and three, 154/193 (79.8%) from the quetiapine treatment group and 149/188 (79.3%) from the haloperidol treatment group, discontinued randomised double-blind treatment prior to Week 52. One hundred and twenty-one patients (quetiapine 61/193 [31.6 %]: haloperidol 60/188 [31.9%]) withdrew prior to Week 52. The 2 groups were well matched demographically: most patients were male (63.0%), Caucasian (89.5%), and 40 to 49 years old (22.8%); weight at baseline was very similar for the 2 groups (quetiapine 76.7 kg: haloperidol 77.3 kg). Paranoid schizophrenia was the most common diagnosis (quetiapine 120/193 [62.2%]; haloperidol 117/188 [62.2%]). Both groups were matched in terms of time since first diagnosis (quetiapine 7.3 years; haloperidol 7.4 years). The groups were also well matched in terms of baseline PANSS total score (quetiapine 92.4; haloperidol 91.0) and most were considered to be moderately ill (mean baseline CGI score: quetiapine 5.0; haloperidol 4.9).

Efficacy: The results of the analysis of the proportion of patients who discontinued from randomised double-blind treatment are presented in Table I and shows that there was no statistically significant difference between the randomised treatment groups in the proportion of patients who discontinued randomised treatment.

Table I Proportion of patients discontinuing from randomised double-blind treatment with quetiapine or haloperidol: results of logistic regression analysis (intention-to-treat population)

Quetiapine (N = 193)		Haloperidol (N = 188)		Odds ratio[a]	95% confidence interval	p value
n	%	n	%			
154	79.8	149	79.3	1.03	0.62, 1.71	0.910

[a] Odds ratio calculated for the quetiapine:haloperidol comparison. An odds ratio of greater than 1.00 indicates that quetiapine was associated with a greater proportion of patients discontinuing from randomised double-blind treatment.

N Number of patients in randomised treatment group.

n Number of patients discontinuing randomised treatment.

The majority of patients who discontinued randomised treatment did so as a result of a deterioration in condition in the quetiapine group and because of adverse events in the haloperidol group.

For the secondary endpoint of time to discontinuation of randomised double-blind treatment, patients in the quetiapine group tended to stay on randomised treatment longer than those patients in the haloperidol group. Mean (median) time to discontinuation of randomised treatment was 87.7 (74.5) days and 69.1 (35.0) days for the quetiapine and haloperidol groups, respectively. However the difference between treatments was not statistically significant ($p = 0.188$). This may, in part, be explained by the observed difference between the groups in the reasons for the majority of patients discontinuing: patients in the haloperidol group were more likely to discontinue randomised treatment as a result of adverse events which were

reported earlier in the trial than the discontinuations as a result of a deterioration in condition, the reason for the majority of quetiapine patients discontinuing. Thus, it is possible that the early onset of adverse events would mean that patients who were treated with haloperidol discontinued before any deterioration in condition was observed.

The results of the changes in PANSS scores, BPRS scores, and CGI items appear to give conflicting results in the analysis of the randomised double-blind treatment and the treatment strategy populations. In the randomised treatment population a direct clinical comparison between quetiapine and haloperidol is being made. The results of this analysis showed that quetiapine was significantly more effective in PANSS total, PANSS negative subscale, PANSS GP scale, derived BPRS total, and derived BPRS mood cluster scores when compared with haloperidol after 52 weeks of treatment. The treatment strategy results also shows significant differences between treatments for PANSS total, PANSS positive subscale, BPRS total, and BPRS positive but in favour of patients who started treatment with haloperidol. No statistically significant differences were seen between treatments in the proportion of patients with a reduction from baseline of ≥40% in PANSS total score or derived BPRS total score in both the randomised treatment analysis or treatment strategy analyses at Weeks 24 and 52. However, advantages were seen for the quetiapine group at Week 24 for both the randomised treatment and treatment strategy analyses and this benefit appeared to be maintained at the Week 52 analysis for the analysis of randomised treatment. No statistically significant differences were seen between treatments in CGI Severity of Illness or Global Improvement scores at Week 24 or Week 52 in the analysis of the randomised treatment population. However, in the treatment strategy analysis, a statistically significant advantage was seen for haloperidol at Weeks 24 and 52 for the CGI Global Improvement score and at Week 52 for the severity of Illness score. It must be remembered that the treatment strategy approach was as an aid in the investigation of the health economic aspects of the trial and patients included in this analysis were likely to have received a variety of neuroleptic medications. There were no statistically significant differences between treatments in the QoL and Experience of Caregiving Inventory (ECI) assessments. These assessments were performed on the treatment strategy populations and so a direct comparison between quetiapine and haloperidol was not possible.

Economic: The economic results presented in the CTR are part of a larger cost-consequence analysis which will be presented as an addendum to this report.

The results show little difference between the treatment groups in terms of the economic endpoints. A wide range of economic data were captured by the CSRI and basic descriptive statistics were calculated for the parameters of employment, income, type of accommodation, and other services used; preliminary analyses of these data failed to demonstrate a clear difference between the treatment groups. However, the results of these individual comparisons of parameters should be viewed with caution. The data collection instrument used, the CSRI, is not intended to provide input to such analyses. The full economic report will provide analysis using multivariate techniques and will provide interpretation based on these analyses.

Safety: Secondary safety and tolerability endpoints were related to the concomitant use of anticholinergic medication, development of EPS (increase in Simpson Scale scores, EPS-related adverse events), adverse events, and laboratory results.

Statistically significant differences between the treatment groups were observed for concomitant use of anticholinergic medication, EPS-related adverse events, and increase in Simpson Scale

scores (Simpson Scale score increased from baseline and a Simpson Scale total score of at least 14 at any time) all in favour of quetiapine. These differences were observed during the randomised double-blind and strategy treatment phase.

With the exception of adverse events relating to EPS, which were reported by significantly more patients treated with haloperidol, the adverse event profile of the 2 treatments was similar, although a slightly greater proportion of patients in the haloperidol group reported adverse events compared with the quetiapine group. Quetiapine therapy was associated with a greater incidence of dry mouth, anxiety, and somnolence than haloperidol, whereas, in addition to the EPS-related events, haloperidol was associated with a greater incidence of increased salivation and depression. The events of dry mouth and increased salivation are likely to be related to the pharmacological properties of the treatments. Overall, the majority of adverse events were mild or moderate in intensity and were considered to be non-serious. No new adverse events that were not consistent with the known safety profile of each treatment were reported in clinically significant numbers. The safety profile of both drugs remained similar during both the randomised double-blind and treatment strategy phases.

The incidence of adverse events leading to discontinuation of randomised treatment was dominated by EPS-related events in the haloperidol group. The adverse event data and the results of neurological assessments, which showed significantly fewer patients developing EPS symptoms, confirm that quetiapine has a superior EPS safety profile compared with haloperidol. The results of the recorded AIMS scores, although not subjected to formal statistical analysis, shows a trend for decreasing mean AIMS score and increasing proportion of patients with a score of 0 in patients treated with quetiapine. This trend suggests that quetiapine has a better safety profile regarding involuntary movements when compared with haloperidol.

In both treatment groups only a small number of patients experienced changes in clinically laboratory parameters. The majority of WBC count changes were non-serious and were without clinical symptomatology; all incidences of changes in WBC counts resolved without sequelae. Two patients in each group discontinued the randomised treatment because of a decrease in WBC count. Changes in liver function tests were unremarkable for both groups. During the randomised double-blind phase hypothyroidism was reported in 6 patients who were receiving quetiapine although no patients reported clinical symptoms.

Neither of the treatments was associated with clinically significant changes in vital signs.