SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: ZOMIG™ 2.5 mg tablet

ACTIVE INGREDIENT: zolmitriptan

Trial title (number): A Randomised, Double-Blind, Parallel Group Multicentre Trial to Compare the Efficacy and Safety of Zolmitriptan 2.5 mg, Zolmitriptan 5.0 mg and Sumatriptan 50 mg in the Treatment of Migraine Headache (311CIL/0070 [ZEUS]) (6-Attack Analysis).

Clinical phase: IIIb

First patient recruited: 13 January 1997
Last patient completed: 19 August 1998
Zeneca approval date: 3 May 1999

Publications: There were no publications arising from this study at the time that this report was prepared.

OBJECTIVES

The primary objectives of this trial were to assess whether zolmitriptan (2.5 mg and 5.0 mg) and sumatriptan 50 mg were equivalent, in terms of efficacy, for the treatment of the first migraine headache experienced by patients during the trial, and to assess the efficacy of zolmitriptan (2.5 mg and 5.0 mg) compared with sumatriptan 50 mg, over 6 migraine headaches (including the first headache)[1]. The secondary objective of this trial was to assess the safety and tolerability of zolmitriptan (2.5 mg and 5.0 mg) and sumatriptan 50 mg.

[1] Only the second primary objective is addressed in this report. An earlier interim report (311CIL/0070 - first attack analysis) addressed the efficacy of zolmitriptan and sumatriptan in the treatment of the first migraine headache.

METHODS

Design: Randomised, double-blind, parallel-group trial conducted on an international, multicentre basis.

Population: It was intended that 500 patients should be enrolled into each arm of the study so that, allowing for withdrawals and unevaluable data, there would be 450 evaluable patients in each treatment group. This number of patients would provide a 90% chance of showing equivalence between zolmitriptan (2.5 mg or 5.0 mg) and sumatriptan 50 mg.

Key inclusion criteria: Male or female patients aged 18 to 65 years inclusive; willing and able to give informed consent; an established diagnosis of migraine, with or without aura and as defined by International Headache Society criteria.

Key exclusion criteria: History of basilar, opthalmoplegic or hemiplegic migraine headache; non-migraine headaches on 10 or more days per month over the preceding 6 months; history or symptoms of ischaemic heart disease or other vascular disease, including Prinzmetal angina, Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathways or arrhythmias; if female, not at risk of pregnancy.

Dosage: Patients were randomised to receive zolmitriptan 2.5 mg, zolmitriptan 5.0 mg (administered as 2 x 2.5 mg doses) or sumatriptan 50 mg in a ratio of 1:1:1. Sufficient trial medication was supplied for the initial treatment of 3 migraine attacks as well as recurrent or persistent symptoms. Patients were required to return to the clinic within 2 weeks of any treated attack for assessment and for further supplies of trial drug until a total of 6 migraines had been treated. The batch numbers used in this trial were: zolmitriptan 2.5 mg: JMP 2051; placebo to zolmitriptan: EX960121; sumatriptan: F94/177A and F96/137B; placebo to sumatriptan: F94/006C and F96/127B.

Endpoints:

Primary: Headache response by 2 hours after dosing, defined as an improvement of migraine headache from severe or moderate pain to mild or no pain.

Secondary: Headache response by 1 and 4 hours after dosing; consistency of headache response; meaningful migraine relief (MMR) by 1, 2 and 4 hours; 24-hour pain relief (none, partial or full); sustained (24-hour) pain relief; patients' global impression of treatment.

Key assessments: This report only considers the results from the analysis of the 6-attack data. Patients were provided with a simple calendar for the duration of the study and asked to record the occurrence of all migraine attacks and, if applicable, menstrual flow dates. The occurrence of adverse events was reviewed by the investigator at each study visit.

Diary cards were used to record data on each migraine headache immediately before and by 1, 2 and 4 hours after taking trial medication. Data recorded were as follows: intensity of headache pain (none, mild, moderate or severe), MMR, migraine recurrence, nausea, photophobia, phonophobia and use of escape medication.

Statistical analyses were performed to detect any differences between the efficacy of zolmitriptan (2.5 mg or 5.0 mg) and sumatriptan 50 mg. Consistency of headache response and global impression were analysed using logistic regression which allowed for the effects of treatment, country and average baseline headache intensity. Headache response, MMR, 24-hour pain relief and sustained relief were analysed using a Generalised Estimating Equations (GEE) approach. The model for GEE allowed for the effects of treatment, country, baseline headache intensity and attack number. The significance level for all analyses was 2% and hence

98% confidence intervals (CIs) have been presented. The analyses presented are based on an intention-to-treat (ITT) population (which included all patients who completed at least 2 diary cards according to randomised treatment); an additional analysis was performed on a per-protocol population for the primary endpoint.
Safety: All patients who received at least 1 dose of trial medication were included in the safety population and were assessed according to the treatment actually received. Medical examinations, including haematology and clinical chemistry laboratory tests, were performed at the pre-trial screening visit. Adverse events and use of concomitant medications were reviewed with each patient by the investigator at each visit and recorded on the patient's case report form (CRF). Serum human chorionic gonadotrophin (HCG) pregnancy tests were performed on women of child-bearing potential at the pre-trial screening visit.

RESULTS
Demography: In total 1787 patients who suffered from migraine, recruited from 166 centres in 21 countries, were randomised to treatment. A total of 121 patients withdrew before starting treatment and 144 completed less than 2 diary cards and were therefore excluded from the ITT population which, consequently, consisted of 1522 patients. Of these 500 were randomised to zolmitriptan 2.5 mg, 514 to zolmitriptan 5.0 mg and 508 to sumatriptan 50 mg. The majority (95.3%) of patients were Caucasian; 14.7% (223/1522) of the population were male and 85.3% (1299/1522) were female. Demographic characteristics and migraine associated characteristics were well balanced across the treatment groups. The average age was 41.9 years (range 17 to 67 years), mean weight was 68 kg (range 34 to 130 kg) and mean height was 166.1 cm (range 147 to 198 cm).
Efficacy:
Headache response:
The headache response rate over all attacks for each treatment group by 1, 2 and 4 hours after treatment is given in Table I together with the odds ratios and 98% confidence intervals for the comparisons between zolmitriptan and sumatriptan. No statistically significant differences were observed between the 2 doses of zolmitriptan and sumatriptan 50 mg. Similarly, analysis of consistency of headache response showed no statistically significant differences between treatments in the percentage of patients responding in at least 80% or 100% of attacks.

Table I Headache response rates and statistical analyses of comparisons between treatments by 1, 2 and 4 hours after dosing

Time after dosing (h)		Treatment group		
		Zolmitriptan 2.5 mg	Zolmitriptan 5 mg	Sumatriptan 50 mg
2	Response rate	62.9% (1632/2594)	65.7% (1771/2695)	66.6% (1760/2642)
	Odds Ratio (98% CI)	0.87 (0.71,1.07)	1.02 (0.83, 1.26)	
1	Response rate	36.9% (975/2639)	39.5% (1074/2716)	38.0% (1013/2667)
	Odds Ratio (98% CI)	0.97 (0.79, 1.19)	1.11 (0.90, 1.37)	
4	Response rate	70.3% (1775/2526)	72.9% (1898/2602)	72.2% (1828/2532)
	Odds Ratio (98% CI)	0.93 (0.75, 1.15)	1.09 (0.88, 1.36)	

CI confidence interval

MMR: MMR was assessed by patients 1, 2 and 4 hours after treatment. Only small differences in the proportion of patients in each group who reported MMR at the 3 assessments were observed. The range across the groups was 34.7% (925/2665) to 39.2% (1075/2743) by 1 hour, 63.9% (1699/2658) to 68.2% (1870/2741) by 2 hours and 76.6% (2009/2624) to 80.0% (2176/2719) by 4 hours. The analyses found no statistically significant differences between the 2 doses of zolmitriptan and sumatriptan 50 mg; the odds ratios (98% CI) for zolmitriptan 2.5 mg versus sumatriptan 50 mg by 1, 2 and 4 hours were 0.87 (0.71 to 1.07), 0.88 (0.72 to 1.06) and 0.88 (0.71 to 1.10), respectively. The corresponding values for zolmitriptan 5.0 mg versus sumatriptan 50 mg were 1.08 (0.88 to 1.33), 1.07 (0.88 to 1.31) and 1.11 (0.88 to 1.38), respectively.

Other efficacy endpoints: An analysis of pain relief response over 24 hours following treatment grouped patients into 3 categories (full relief, partial relief and no relief) and took into account both the initial response and any subsequent recurrence. Analysis of this endpoint showed no statistically significant differences between zolmitriptan 2.5 mg and sumatriptan 50 mg (odds ratio 0.92; 98% CI, 0.78 to 1.10) or between zolmitriptan 5.0 mg and sumatriptan 50 mg (odds ratio 1.06; 98% CI, 0.89 to 1.26). Similarly analysis of sustained (24 hours) pain relief, comparing the proportion of patients with a full response, demonstrated no statistically significant difference between zolmitriptan 2.5 mg and sumatriptan 50 mg (odds ratio 0.94; 98% CI, 0.78 to 1.14), or between zolmitriptan 5.0 mg and sumatriptan 50 mg (odds ratio 1.07; 98% CI, 0.89 to 1.29).

Analyses of global impression also showed no statistically significant differences between zolmitriptan 2.5 mg and sumatriptan 50 mg (odds ratio 1.09; 98% CI, 0.83 to 1.44), or between zolmitriptan 5.0 mg and sumatriptan 50 mg (odds ratio 1.20; 98% CI, 0.91 to 1.58).

Migraine recurrence, alleviation of non-headache symptoms, use of escape or further trial medication, consistency of MMR, consistency of pain free response and response by all patient subgroups were all summarised but not formally analysed. There were no notable differences between zolmitriptan (2.5 mg or 5.0 mg) and sumatriptan 50 mg for all these additional endpoints.

Safety:

The safety population was comprised of all patients who received at least one dose of study treatment and contained a total of 1666 patients (551 zolmitriptan 2.5 mg, 560 zolmitriptan 5 mg

and 555 sumatriptan 50 mg). Overall, adverse events were reported by 35.7% (594/1666) of patients in the safety population. These were distributed evenly across the 3 treatment groups; 34.8% (192/551), 37.7% (211/560) and 34.4% (191/555) for the zolmitriptan 2.5 mg, 5.0 mg and sumatriptan 50 mg groups, respectively.

Across all treatment groups, 31.8% (529/1666) of patients reported an adverse event that was considered to be related to trial medication. The most frequently reported adverse events (ie, those with an incidence of greater than 4%) were asthenia, aggravation reaction, tightness, dizziness, paresthesia and somnolence; these were mostly recognised class effects of $5HT_{1B-1D}$ agonists.

Approximately 3% of patients in each group withdrew from the trial because of an adverse event. The most common adverse events leading to withdrawal were vomiting (6 patients), unintended pregnancy (6 patients) and dizziness (5 patients).

One patient died and 6 other patients reported serious adverse events before taking randomised treatment; these events were therefore not considered to be drug related. Twenty-eight patients experienced serious adverse events while taking trial medication, though none of these was considered to be related to trial medication. Nine women had unintentional pregnancies after taking trial medication; 3 appeared to undergo spontaneous abortion (not considered to be related to trial therapy) and the remaining 6 were withdrawn from treatment.

In summary all 3 preparations were well tolerated and the safety analysis did not raise any concerns regarding the use of zolmitriptan 2.5 mg, 5.0 mg or sumatriptan 50 mg.