SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ZOMIG™ (Nasal spray)

ACTIVE INGREDIENT: Zolmitriptan

Trial title (number): A Randomised, Double-Blind, Double-Dummy, Parallel Group, Multicentre Trial to Compare the Efficacy and Safety of Four Fixed Doses of Intranasal Zolmitriptan with an Oral Dose of Zolmitriptan and Placebo in Patients with Migraine Headache (311CIL/0077)

Clinical phase: II/III

First patient recruited: 31 December 1997
Last patient completed: 4 February 1999
AstraZeneca approval date: 7 September 1999

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

OBJECTIVES

The primary objective of this trial was to compare the efficacy of 5.0 mg, 2.5 mg, 1.0 mg and 0.5 mg zolmitriptan administered via the intranasal route and placebo in the acute treatment of migraine headache.

The secondary objectives were to compare the efficacy of 5.0 mg, 2.5 mg, 1.0 mg and 0.5 mg zolmitriptan administered via the intranasal route with 2.5 mg zolmitriptan administered orally in the acute treatment of migraine headache, and to compare the safety and tolerability of zolmitriptan administered via the intranasal route with those of zolmitriptan administered orally.

METHODS

Design: Randomised, double-blind, double-dummy, placebo-controlled, parallel-group trial, conducted on an international, multicentre basis, in patients with an established diagnosis of migraine.

Population: It was intended that 1440 patients with migraine (240 per treatment group) would be recruited to the trial and randomised evenly to the 6 treatment groups. Each centre was required to provide a minimum of 30 and a maximum of 150 patients.
Key inclusion criteria: Male and female patients aged 18 to 65 years, inclusive; an established diagnosis of migraine, as defined by the International Headache Society Criteria.
Key exclusion criteria: History of basilar, ophthalmoplegic or hemiplegic migraine headache; history of, or symptoms suggestive of, ischaemic heart disease or other vascular disease, including Prinzmetal angina, Wolff-Parkinson-White Syndrome or other cardiac accessory conduction pathways or arrhythmias; moderate or severe hypertension, and mild uncontrolled hypertension; if female, not to be at risk of pregnancy.
Dosage: Patients were randomised, in a 1:1:1:1:1:1 ratio, to receive intranasal zolmitriptan at a dose of 5.0 mg, 2.5 mg, 1.0 mg or 0.5 mg, or oral zolmitriptan at a dose of 2.5 mg, or placebo as a single acute treatment for each of 3 moderate or severe migraine headaches. For each migraine attack, a nasal spray and tablet were administered at the same time. For patients receiving zolmitriptan, one of these preparations was placebo. Patients in the placebo group received both placebo nasal spray and placebo tablet.
The batch numbers used in this trial are listed in Table I.

Table I Batch numbers used in the trial

Preparation	Zolmitriptan dose (mg)	Batch number
Zolmitriptan intranasal solution	5.0	37981D97; 39082J97; 01249B98; 00464F98
Zolmitriptan intranasal solution	2.5	37900E97; 38911C9700; 00321C98; 00795I98; 01803F98
Zolmitriptan intranasal solution	1.0	37805G97; 38380H97; 01733J98; 00277C98
Zolmitriptan intranasal solution	0.5	37501A97; 38381E97; 37501A9701; 00157E98; 01400B98
Placebo to match zolmitriptan intranasal solution	0	37161H97; 37161H9701
Zolmitriptan oral tablet	2.5	39486A96
Placebo to match zolmitriptan oral tablet	0	39485D96

Key assessments:
Efficacy: Diary cards were used to record data on each migraine attack immediately before and at specified times after taking trial medication. The primary efficacy endpoint was headache response at 2 hours after administration of trial medication, defined as an improvement of migraine headache from severe or moderate pain to mild or no pain. Secondary efficacy endpoints were: headache response at 15, 30 and 45 minutes, and at 1 and 4 hours following treatment; absence of pain, reduction of pain and meaningful migraine relief (MMR) at 15, 30 and 45 minutes, and at 1, 2 and 4 hours following treatment; use of escape medication. The main statistical analyses were performed on the intention-to-treat population. The endpoints of headache response, absence of pain, reduction in pain, and MMR were analysed as binary responses using a generalised linear mixed model with a pseudo-likelihood approach to model the odds of response. Further secondary efficacy endpoints not subjected to formal statistical analysis were: time to resumption of normal activities; incidence and time to headache recurrence within 24 hours of dosing; patient global satisfaction rating; improvement of photophobia, phonophobia, nausea and somnolence; consistency of headache response.
Safety: Medical examinations were performed before entry to the trial. Haematology and clinical chemistry laboratory tests, blood pressure, pulse rate and electrocardiograms were

monitored before and after the trial. Nose and throat examinations were performed before and after the trial at predetermined trial centres. Serum human chorionic gonadotrophin pregnancy tests were performed on women of child-bearing potential before entry to the trial. Patients were required to record the details of any adverse events on their diary cards during the course of the trial. Safety data were not subjected to formal statistical analysis.

RESULTS

Demography: A total of 1547 migraine sufferers were recruited from 42 centres in 11 countries. Randomisation to treatment was as follows: 259 (intranasal zolmitriptan 5.0 mg), 259 (intranasal zolmitriptan 2.5 mg), 258 (intranasal zolmitriptan 1.0 mg), 256 (intranasal zolmitriptan 0.5 mg), 256 (oral zolmitriptan 2.5 mg), 259 (placebo). The safety population consisted of 1376 patients as 171 patients failed to treat at least 1 attack. Five patients failed to treat headaches of moderate or severe baseline intensity and were excluded from the intention-to-treat (ITT) population which comprised 1371 patients. The majority of patients were female (1137/1371, 82.9%). Demographic characteristics and migraine-associated characteristics were well balanced across the treatment groups. Mean age of the population was 40.6 years (range, 18 to 65 years), mean weight was 68.9 kg (range, 40 to 126 kg) and mean height was 167.4 cm (range, 143 to 198 cm).

Efficacy:

There was some evidence to suggest that use of medication for the treatment of a 3rd attack was dependent upon the response to treatment in the first 2 attacks. Patients receiving a higher dose of intranasal zolmitriptan were more likely to treat a 3rd attack. In order to counteract any bias resulting from non-random drop out, only data from attacks 1 and 2 were subjected to statistical analysis.

Primary endpoint:

Analysis of the primary endpoint, headache response at 2 hours, showed statistically significant differences between each of the intranasal zolmitriptan treatment groups and placebo in favour of zolmitriptan (Table II) with response rates of 70.2%, 58.8%, 55.1% and 41.4% for the intranasal zolmitriptan 5.0 mg, 2.5 mg, 1.0 mg and 0.5 mg groups, respectively, in comparison with 30.2% for placebo.

Table II Statistical analysis of headache response[a] at 2 hours (intranasal zolmitriptan versus placebo)

Treatment comparison versus placebo	Odds ratio	95% CI	p-value
Intranasal zolmitriptan 5.0 mg	5.75	(4.09, 8.07)	0.0001
Intranasal zolmitriptan 2.5 mg	3.62	(2.59, 5.08)	0.0001
Intranasal zolmitriptan 1.0 mg	3.05	(2.20, 4.21)	0.0001
Intranasal zolmitriptan 0.5 mg	1.79	(1.28, 2.51)	0.0007

[a] Response was defined as an improvement in headache intensity from moderate or severe to mild or none.
CI Confidence interval.

The primary endpoint for the secondary objective of this trial compared each dose of intranasal zolmitriptan with oral zolmitriptan 2.5 mg in the acute treatment of migraine headache at 2 hours after dosing. A statistically significant difference was evident between response rates for intranasal zolmitriptan 5.0 mg (70.2%) and oral zolmitriptan 2.5 mg (61.3%) with superiority for the former (p=0.025). Headache response rates for the intranasal zolmitriptan 2.5 mg and 1.0 mg

groups did not differ significantly from that of the oral zolmitriptan group whilst the intranasal zolmitriptan 0.5 mg group was significantly inferior to oral zolmitriptan 2.5 mg ($p<0.001$). Intranasal zolmitriptan 5.0 mg was effective, as measured by 2 hour headache response, in treating migraine headaches associated with nausea, or aura, attacks that were present upon awakening and menstrually related migraine. Response rates for these difficult-to-treat attacks were numerically superior for the intranasal zolmitriptan 5.0 mg group when compared with the oral zolmitriptan group. There was an apparent trend for intranasal zolmitriptan to be more effective at treating these attack types with increasing dose.

There was no statistical evidence of any relationship between 2 hour headache response rates and either gender or weight, although an interaction was evident between age and treatment ($p=0.046$) with a higher response rate in the lower age group (18 to 39 years) for the intranasal zolmitriptan 5.0 mg and 2.5 mg groups and in the higher age group (40 to 65 years) for oral zolmitriptan. The clinical relevance of these findings is unclear.

Secondary endpoints:

In general, all doses of intranasal zolmitriptan were superior to placebo. There was a consistent dose-response relationship for all secondary endpoints; differences between intranasal zolmitriptan and placebo increased with dose and time. Statistical comparison of the response rates for headache response, absence and reduction in pain, and MMR are presented in Table III.

Table III Summary of statistical analyses of secondary endpoints (attacks 1 and 2)

Endpoints	Intranasal zolmitriptan (dose)	Comparison intranasal zolmitriptan vs placebo/oral zolmitriptan 2.5 mg Time after dosing					
		15 min	30 min	45 min	1 h	2 h	4 h
Headache response							
	5.0 mg	+ / +	+ / +	+ / +	+ / +	+ / +	+ / ns
	2.5 mg	ns / ns	+ / ns	+ / ns	+ / ns	+ / ns	+ / ns
	1.0 mg	na / ns	ns / ns	+ / ns	+ / -	+ / ns	+ / -
	0.5 mg	na / ns	na / ns	ns / ns	ns / -	+ / -	+ / -
Absence of pain							
	5.0 mg	na / na	+ / +	+ / +	+ / ns	+ / ns	+ / ns
	2.5 mg	na / na	+ / ns	+ / ns	+ / ns	+ / -	+ / -
	1.0 mg	na / na	+ / ns	+ / ns	+ /ns	+ / -	+ / -
	0.5 mg	na / na	ns / ns	ns / ns	ns / -	ns / -	+ / -
Reduction in pain							
	5.0 mg	+ / +	+ / +	+ / +	+ / +	+ / +	+ /ns
	2.5 mg	+ / ns	+ / ns	+ / ns	+ / ns	+ / ns	+ / ns
	1.0 mg	ns / ns	+ / ns	+ / ns	+ / ns	+ / -	+ / -
	0.5 mg	na / ns	ns / ns	ns / ns	ns / -	+ / -	+ / -
MMR							
	5.0 mg	ns / ns	+ / +	+ / +	+ / +	+ / ns	+ / +
	2.5 mg	na / ns	ns / ns	+ / ns	+ / ns	+ / ns	+ / ns
	1.0 mg	na / ns	na / ns	+ / ns	+ / ns	+ / ns	+ / -
	0.5 mg	na / ns	na / ns	ns / -	ns / -	+ / -	+ / -

\+ Statistically significant difference in favour of the intranasal zolmitriptan dose ($p<0.05$).

\- Statistically significant in favour of the oral zolmitriptan 2.5 mg dose ($p<0.05$).

ns Not significant.

na Not analysed - data were assessed using a step-down approach. Response rates for absence of pain at 15 min were not analysed as the statistical model would not converge to provide a result.

Superior response rates reaching statistical significance were evident for intranasal zolmitriptan 5.0 mg over oral zolmitriptan 2.5 mg in terms of headache response at 15, 30 and 45 minutes, 1 hour and 2 hours. At 4 hours, the response rate was greater in the zolmitriptan 5.0 mg group compared with the oral zolmitriptan group (78.9% and 72.0%, respectively), although the difference between treatments no longer attained statistical significance. Intranasal zolmitriptan 5.0 mg conferred significant benefit compared with oral zolmitriptan 2.5 mg in terms of pain-free response at both the 30 and 45 minute time points highlighting the faster onset of action.

Intranasal zolmitriptan 5.0 mg demonstrated the highest efficacy of all the dose groups and, in general, was superior to oral zolmitriptan (2.5 mg) in terms of the other endpoints evaluated, ie, use of escape medication, time to resumption of normal activities, time to recurrence, complete response, improvements in associated symptoms of photophobia, phonophobia, nausea and somnolence, and consistency of response. Patient satisfaction was also highest for the intranasal zolmitriptan 5.0 mg group.

Safety:

Of the 1376 patients who were evaluated in the safety population, 33.9% (467/1376) reported adverse events. There was evidence of a dose-related increase in adverse events for the intranasal formulation with 49.2% (116/236) of patients, 43.9% (98/223), 31.8% (75/236) and 22.4% (50/223) of patients from the intranasal zolmitriptan 5.0 mg, 2.5 mg, 1.0 mg and 0.5 mg groups, respectively, experiencing adverse events. The percentage of patients reporting adverse events in the oral zolmitriptan and placebo groups was 38.8% (90/232) and 25.2% (57/226), respectively. The higher incidence of adverse events in the intranasal zolmitriptan 5.0 mg and 2.5 mg groups in comparison with the oral zolmitriptan group was attributable to a dose-dependent increase in nasopharyngeal events associated with the intranasal route of administration. The incidence of most of the other adverse events tended to be lower in each of the intranasal groups than in the oral zolmitriptan 2.5 mg group.

The majority of adverse events reported were considered to be drug-related but most were of short duration and were described as either mild or moderate in intensity. With the exception of nasopharyngeal effects, the adverse events reported were consistent with the pharmacological effects of 5-HT receptor agonists. The most widely reported adverse event reported in the intranasal zolmitriptan groups was a bitter or unpleasant taste in the mouth (COSTART term: taste perversion) reported by between 4.9% (0.5 mg dose) and 21.2% (5.0 mg dose) of patients. In the oral zolmitriptan and placebo groups, the most frequently reported adverse event was paraesthesia (5.2% and 4.9% of patients, respectively).

Twelve patients (12/1376, 0.9%) from the safety population were withdrawn due to an adverse event. These included 9 patients (9/918, 1.0%) taking intranasal zolmitriptan (3, 1, 3 and 2 patients, respectively, from the 5.0 mg, 2.5 mg, 1.0 mg and 0.5 mg groups) and 2 patients (2/232, 0.9%) and 1 patient (1/226, 0.4%) from the oral zolmitriptan and placebo groups, respectively. A bitter or unpleasant taste in the back of the mouth (COSTART term: taste perversion) led to the withdrawal of 2 patients; single adverse events were responsible for the other withdrawals. The frequency of withdrawal because of adverse events was low in all treatment groups.

Fourteen patients (14/1376, 1.0%) reported serious adverse events. One patient experienced a serious adverse event following randomisation but did not take trial medication. A further 3 patients experienced serious adverse events prior to taking trial medication and 10 patients

reported serious adverse events after taking trial medication; none was considered by the investigator to be drug related. No deaths were reported during the course of this trial. Those events not considered to be associated with the route of administration were consistent with the well-known pharmacological effects of this class of compound (5-$HT_{1B/1D}$ receptor agonists), and have been reported at similar frequencies in previous trials.
All 5 preparations were well tolerated and the safety data did not raise any concerns regarding the use of intranasal zolmitriptan 5.0 mg, 2.5 mg, 1.0 mg, or 0.5 mg or oral zolmitriptan 2.5 mg for the acute treatment of migraine headache.