SUMMARY

ASTRAZENECA

FINISHED PRODUCT: ZOMIG™ 2.5 mg tablets

ACTIVE INGREDIENT: Zolmitriptan

Trial title (number): A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Trial to Assess the Efficacy of Oral Zolmitriptan 2.5 mg in the Acute Treatment of Migraine During the Mild Intensity Phase of an Attack in Patients Highly Disabled by Migraine (MIDAS Grades III and IV) (311CIL/0111)

Clinical phase: IIIB

First patient recruited: 20 December 2000
Last patient completed: 30 June 2001
AstraZeneca approval date: 3 May 2002

Publications: None at the time this report was prepared.

OBJECTIVES

Primary: To compare the efficacy of oral zolmitriptan 2.5 mg and placebo at 2 hours in the treatment of mild migraine headache in patients highly disabled by migraine (MIDAS grades III and IV)**.**

Secondary: To compare other efficacy measures at defined time points. The incidence and nature of adverse events occurring within 24 hours of treatment with trial medication was also evaluated.

METHODS

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

Population: Adult patients who experienced moderate to severe migraine-related disability, as assessed by the Migraine Disability Assessment (MIDAS) questionnaire. Patients usual migraine headaches were those starting as mild pain, but that usually progressed to moderate or severe.

Key inclusion criteria: Males and females aged 18 to 65 years, inclusive; established diagnosis of migraine, as defined by the International Headache Society Criteria; MIDAS Grade III or IV (ie, at least 11 days with substantially reduced productivity at work, school or leisure because of headache in last 3 months); migraine attacks that were initially mild but became worse; ability to identify a migraine headache while it was still mild.
Key exclusion criteria: History of basilar, ophthalmoplegic or hemiplegic migraine (zolmitriptan has not been evaluated in these types of migraine); frequent non-migraine headaches; evidence of cardiovascular conditions that might place the patient at risk from treatment with a triptan (history or symptoms suggestive of ischaemic heart disease, other vascular disease, other cardiac accessory conduction pathways, or arrhythmias; risk factors for ischaemic heart disease; moderate or severe hypertension); risk of pregnancy.
Dosage: Single dose of oral zolmitriptan 2.5 mg or matching placebo. A second dose (or an approved escape medication) could be taken >2 hours after the first dose, for treatment of persistent or recurrent headache of moderate to severe pain intensity. Formulation numbers: zolmitriptan F012092, placebo F012134. Batch numbers: zolmitriptan JMP2081, placebo 980281.
Key assessments:
Efficacy: Diary cards were used to record headache pain intensity and other data immediately before and at specified times after dosing. The time between the onset of headache and taking of trial treatment was also recorded.
Primary efficacy endpoint: Pain-free response rate at 2 hours post-dose.
Secondary efficacy endpoints: These examined 3 areas of interest: pain-free response at time points earlier than 2 hours post-dose; non-progression of headache; and impact on normal activities. A range of endpoints was used in each area (Table I).

Table I Secondary efficacy endpoints

Pain-free response	Pain-free response rate at 30 minutes, 1 h and 1.5 h; Time to pain-free response
Non-progression of headache	Non-progression of headache within 2 h post-dose and 12 h post-dose; Time to progression; Use of further medication within 24 h; Time to use of further medication; % of patients with moderate or severe headache pain at 30 min and 1, 1.5 and 2 h; area under the pain intensity/time curve (AUC) over the first 2 h post-dose
Impact on normal activities	Ability to perform normal activities at 30 min and 1, 1.5 and 2 h post-dose; Reduction in impact on usual activities at 2 h

All binary (yes/no) endpoints (eg, pain-free responses) were analysed by logistic regression. Time-to-event endpoints were analysed by Cox's regression model. Analyses of all endpoints were conducted using an intention-to-treat (ITT) population. A per-protocol (PP) population was assessed for the primary endpoint only. The ITT population was the primary population of interest for efficacy assessments.

Safety: Adverse events were recorded by patients on diary cards and transcribed by the investigator onto case report forms at the next clinic visit. Non-serious events occurring more than 24 hours after dosing were not transcribed. All patients who took trial treatment were analysed for safety.

RESULTS

Demography, baseline characteristics and patient withdrawals: A total of 302 migraine patients were recruited from 24 centres in 3 countries (Table II). In the ITT efficacy population (Table III), the treatment groups were well balanced in all demographic and baseline characteristics. In both groups, patient characteristics were similar to those in most acute migraine studies, being predominantly female and with a mean age of 41.7. Both groups showed a considerable level of headache-related disability, with mean MIDAS scores of 29.6 (zolmitriptan) and 27.6 (placebo) respectively, indicating that the trial patients suffered severe migraine-related disability. The number (and proportion) of patients withdrawn by the investigator from the study was similar in the two treatment groups, ie, 12 (8.0%) and 14 (9.2%) in the zolmitriptan and the placebo groups respectively. The most common reason for withdrawal was also similar between the groups. Eight (5.3%) and 12 (7.9%) patients in the zolmitriptan and the placebo groups were withdrawn due to protocol non-compliance. Other reasons for withdrawal in the zolmitriptan group were “patient lost to follow-up” (2 patients) and “pregnancy” (1 patient who was withdrawn prior to taking trial medication) and “other reason” (1 patient). In the placebo group, 1 patient was “lost to follow-up” and 1 patient was withdrawn for “other reason”. No patient in the study was withdrawn due to an adverse event.

Table II Populations analysed

Population	Zolmitriptan 2.5 mg	Placebo
N of patients randomised	150	152
N of patients analysed for safety	138	142
N of patients analysed for efficacy (ITT population)	138	142
N of patients analysed for efficacy (PP population)	126	126

Table III Demographic and baseline characteristics (ITT population)

Characteristic	Parameter		Zolmitriptan 2.5 mg N=138		Placebo N=142	
Gender	n (%) of patients	Female	114	(82.6)	127	(89.4)
		Male	24	(17.4)	15	(10.6)
Age in years	Mean±SD (range)		41.4±11.3	(19.0 to 65.0)	42.0±10.3	(18.0 to 64.0)
Race	n (%) of patients	White	131	(94.9)	134	(94.4)
		Black	2	(1.4)	6	(4.2)
		Hispanic	3	(2.2)	1	(0.7)
		Other	2	(1.4)	1	(0.7)
MIDAS score	Mean±SD (range)		29.6±21.3	(11 to 137)	27.6±17.5	(11 to 111)
MIDAS grade	n (%) of patients	III	59	(42.8)	58	(40.8)
		IV	79	(57.2)	84	(59.2)

MIDAS Migraine disability assessment. Score is number of days with substantial reduction in productivity (at work, school, or leisure) due to headache in previous 3 months. Grade III is 11 to 20, Grade IV is ≥21.
ITT Intention to treat; PP Per protocol; SD Standard deviation.

Efficacy: The mean time between the onset of headache and taking of trial treatment was 1.0 hours in the zolmitriptan group (range 0.0 to 6.8 hours) and 0.8 hours in the placebo group (range 0.0 to 4.1 hours).
Primary efficacy endpoint: Pain-free response rates at 2 hours after dosing are shown in bold figures in Table IV. (To show the time course of response, this table also contains pain-free response rates at earlier time points, which are secondary endpoints.)

Table IV Pain-free response rates (ITT population)

Timepoint	Zolmitriptan 2.5 mg			Placebo			Statistical analysis (logistic regression): Zolmitriptan 2.5 mg vs placebo		
	n	N	(%)	n	N	(%)	Odds ratio	95% CI	P-value
30 minutes	7	136	(5.1)	2	141	(1.4)	3.88	0.79 to 19.08	0.09559
1 hour	21	137	(15.3)	14	141	(9.9)	1.66	0.80 to 3.41	0.17086
1.5 hours	40	136	(29.4)	20	141	(14.2)	2.48	1.36 to 4.52	0.00298
2 hours	**59**	**136**	**(43.4)**	**26**	**141**	**(18.4)**	**3.28**	**1.90 to 5.66**	**0.00002**

CI Confidence interval; n number of patients pain-free;
N number of patients assessed.

After treatment of mild migraine headache with zolmitriptan 2.5 mg, significantly more patients (43.4%) were pain-free at 2 hours compared with placebo (18.4%). In the subgroup of patients treating their mild headache early, ie, within 15 min of onset, the difference in 2 hour pain free rates between zolmitriptan and placebo was remarkably larger than when dosing later, being 56.6% vs 20.0% for active vs placebo respectively.

Secondary efficacy endpoints:

- **Pain-free response rates over time:** See Table IV. Significantly more patients on zolmitriptan were pain free not only at 2 hours but also at 1.5 hours compared with patients in the placebo group (29.4% vs 14.2%). No significant differences were found at 30 min and 1 hour. The time to pain-free response was significantly shorter in patients on zolmitriptan vs on placebo ($p<0.0001$) in a survival analysis.

- **Non-progression of headache:** Treatment of migraine headache with zolmitriptan in the mild phase reduced progression of headache to more severe intensity. At 2 and 12 hours there was a significant difference in favour of zolmitriptan in the proportion of patients not having progressed to moderate or severe headache (46.3% vs 29.6% at 2 hours and 40.3% vs 21.5% at 12 hours). The time to progression to more severe headache was significantly prolonged in patients on zolmitriptan vs on placebo in a survival analysis ($p=0.01$). The proportion of patients on zolmitriptan requiring further medication within 24 hours was significantly smaller compared with placebo (46.4% vs 71.1%) and those who did was also treating significantly later than on placebo, as confirmed in a survival analysis ($p<0.00001$). The total median pain intensity over first 2 hours (AUC0-2) was significantly lower in patients on zolmitriptan ($p<0.001$) and fewer patients on zolmitriptan had moderate or severe headache at time points 1, 1.5, and 2 hours (approximately 35% on all time points vs 46.8% to 65.2% in patients on placebo).

- **Ability to return to normal function:** At 2 hours, 68.4% of patients on zolmitriptan were able to perform usual activities and this was significantly more than in placebo patients (50.7%, $p<0.01$).

- **Impact on normal activity:** Treatment of mild headache with zolmitriptan reduced the perceived impact of the migraine attack on usual activities at 2 hours after dosing in the majority of patients who usually experience migraine related impact. For patients typically impacted on usual activities (99.3%), almost twice as many patients in the zolmitriptan group experienced a reduced impact, when compared to patients in the placebo arm (54.3% vs 28.2%, $p<0.0001$). The difference between treatments was especially marked in the relatively large group of patients dosing within 15 min of onset of attack with 63.5% of patients reporting a reduced impact on zolmitriptan vs 27.3% on placebo.

Safety: An overview of the patients with adverse events is given in Table V.

Table V Overview of patients with adverse events[a] (safety population)

Category[b]	Zolmitriptan 2.5 mg N=138		Placebo N=142	
	n	(%)	n	(%)
Number of patients with adverse events within 24 h of treatment [c]	43	(31.2)	16	(11.3)
Number of patients with drug-related adverse events [d]	38	(27.5)	14	(9.9)
Number of patients with serious adverse events (during the study)	1	(0.7)	0	(0)
Before treatment	0	(0)	0	(0)
Within 24 h after treatment	1	(0.7)	0	(0)
More than 24 h after treatment	0	(0)	0	(0)
Number of patients died	0	(0)	0	(0)
Number of patients with adverse events leading to withdrawal	0	(0)	0	(0)
Number of patients pregnant	0	(0)	0	(0)

[a] Adverse events with missing or partial onset dates are included in this table.
[b] Patients may fall into more than 1 category.
[c] Includes all adverse events occurring within 24 hours of treatment; all serious adverse events; all adverse events with the COSTART term “unintended pregnancy”; all adverse events leading to withdrawal or death.
[d] Drug-related events are counted only if they occurred within 24 hours of treatment or were serious.

Adverse events were reported by 43 (31.2%) of 138 patients in the zolmitriptan treatment group and by 16 (11.3%) of 142 patients in the placebo treatment group. The majority of these adverse events were considered drug-related by the investigator. The majority of adverse events reported were transient, self-limiting and mild to moderate in intensity. The adverse event profile was consistent with results from previous trials with zolmitriptan oral tablets. The most frequently reported adverse events were those commonly associated with the triptan class of drugs such as asthenia, heaviness, tightness and paraesthesia. Only one serious adverse event was reported and was an allergic reaction deemed attributable to the study medication. No patients were withdrawn from the trial due to adverse events although only a single attack was studied making this unlikely.