SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: ZOMIG™

ACTIVE INGREDIENT: Zolmitriptan

Trial title (number): A Multicentre, Randomised, Double-Blind Trial to Compare the Efficacy and Safety of ZOMIG 2.5 mg, NARAMIG 2.5 mg and Placebo in the Acute Treatment of Adult Patients with Migraine (311CIL/0099)

Clinical phase: IIIb

First patient recruited: 24 June 1998
Last patient completed: 28 July 1999
AstraZeneca approval date: 5 October 2000

Publications: There are no publications relating to this trial.

OBJECTIVES

The primary objective of this trial was to evaluate the efficacy of ZOMIG 2.5 mg and NARAMIG 2.5 mg in the acute treatment of migraine. The secondary objective of this trial was to compare the safety and tolerability of ZOMIG 2.5 mg and NARAMIG 2.5 mg in the acute treatment of migraine.

METHODS

Design: This was a multicentre, randomised, double-blind trial to compare the efficacy and safety of ZOMIG 2.5 mg, NARAMIG 2.5 mg and placebo in the acute treatment of migraine. The trial consisted of 2 parts: Part 1 where patients were randomised to treat Attack 1 with either ZOMIG 2.5 mg, NARAMIG 2.5 mg or placebo and Part 2 where patients were re-randomised to treat Attacks 2 to 4 with either ZOMIG 2.5 mg or NARAMIG 2.5 mg.

Population: In total, 570 patients were to be recruited to give at least a 90% chance of observing a difference in headache response between ZOMIG 2.5 mg and NARAMIG 2.5 mg at 1 and 2 hours after dosing at a 5% level of significance, assuming 10% of patients would withdraw or be unevaluable. Patients were recruited by their primary care physician or neurologist.
Key inclusion criteria: Patients were to: have had an established diagnosis of migraine as defined by the International Headache Society (IHS) Criteria with an age at onset of less than 50; have experienced at least 1 migraine headache per month before the start of the trial; be between 18 and 65 years old; be able to differentiate between migraine and non-migraine headaches.
Key exclusion criteria: Patients were excluded if they: had a history of basilar, ophthalmoplegic or hemiplegic migraine headache; had non-migraine headaches on more than 6 days per month over the preceding 6 months; had history or symptoms suggestive of ischaemic heart disease or other vascular disease; systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 95 mmHg; had current or anticipated use of methysergide or methylergotamine in the 2 weeks before randomisation; had recent history of abuse of alcohol or other drugs; were pregnant or breast-feeding; had a previous unacceptable adverse experience following use of ZOMIG, NARAMIG or other 5-HT agonist drug, or known hypersensitivity; had hepatic or renal failure or impairment.
Dosage: Patients were randomised to receive oral doses of either ZOMIG 2.5 mg, NARAMIG 2.5 mg or placebo to treat Attack 1, and then re-randomised to either ZOMIG 2.5 mg or NARAMIG 2.5 mg to treat Attacks 2 to 4. For all attacks, migraine headache intensity was to be moderate or severe. If necessary, patients could take a second dose of trial medication 4 hours after the initial dose.
Key assessments: The primary endpoints were headache response (defined as improvement from severe or moderate pain to mild or no pain) at 2 hours after dosing in Part 1, and consistency of headache response at 2 hours over Attacks 2 to 4 in Part 2. The secondary efficacy endpoints were: headache response at 1 hour after dosing (and consistency in Part 2), area under the curve (AUC) for headache relief between 30 minutes and 4 hours after dosing (Part 1 only), an additional analysis of headache response at 2 hours across Attacks 2 to 4, proportion of patients pain-free 2 hours after dosing (and consistency in Part 2), patient satisfaction and patient preference (Attacks 1 and 2 only). The safety endpoint was the incidence of triptan-related adverse events defined as heaviness, pressure, stiffness, tightness, chest pain, paraesthesia, intranasal paraesthesia, hyperaesthesia and vasodilatation.
Logistic regression analyses were performed for all endpoints except for the following: AUC of headache relief (analysed using analysis of variance [ANOVA]), the additional analysis of headache response at 2 hours across Attacks 2 to 4 (generalised linear mixed model [Wolfinger and O'Connell 1993] with a pseudo likelihood approach) and patient preference (Prescott's test). The primary analysis was done on the intention-to-treat (ITT) population, consisting of all patients who treated a migraine attack with trial treatment and recorded at least 1 post-dose efficacy assessment.

RESULTS
Demography - Part 1
Of the 553 patients randomised into the trial, 440 treated an attack and had efficacy data, of whom 174 each were in the ZOMIG 2.5 mg and NARAMIG 2.5 mg groups and 92 in the

placebo group; these patients were included in the ITT and safety populations. There were 369 females (83.9%) and 71 males (16.1%). In total, 16 patients (3.6%) withdrew from Part 1 of the trial. Migraine headache history, recorded at baseline, was similar across the treatment groups. The incidence of withdrawals was low, with similar rates in the ZOMIG 2.5 mg and placebo groups (just over 5%), and lower in the NARAMIG 2.5 mg group (2.3%). The most common reason for withdrawal was due to an adverse event: 6 patients (1.4%) withdrew for this reason.

Demography - Part 2

Of the 438 patients randomised into Part 2 of the trial, 384 treated at least 1 attack and had efficacy data, of whom 200 patients were in the ZOMIG 2.5 mg group and 184 in the NARAMIG 2.5 mg group. Fourteen patients, who were randomised to Part 1 but did not treat an attack, went on to treat at least 1 attack in Part 2 and are included in the ITT population in Part 2. Demographic variables in Part 2 were similar to those in Part 1.

In total, 58 patients withdrew from Part 2 of the trial; there was a similar incidence of withdrawals across the 2 treatment groups with 30 (13.3%) and 28 (13.2%) patients withdrawing from the ZOMIG 2.5 mg and NARAMIG 2.5 mg groups, respectively. The most common reason for withdrawal was that patients were lost to follow up: 11 patients (4.9%) and 16 (7.5%) from the ZOMIG 2.5 mg and NARAMIG 2.5 mg groups, respectively, withdrew for this reason.

Efficacy - Part 1

The 2-hour headache response rate was highest in the ZOMIG 2.5 mg group (54.1%), with response rates of 50.0% and 23.3% in the NARAMIG 2.5 mg and placebo groups, respectively. There was a statistically significant difference in the 2-hour headache response rate between ZOMIG 2.5 mg and placebo, and a numerical advantage for the 2-hour headache response rate of ZOMIG 2.5 mg compared with NARAMIG 2.5 mg, although this difference was not statistically significant (Table I). The results of the per protocol analysis supported the results of the ITT analysis, with a statistically significant difference between ZOMIG 2.5 mg and placebo, but not between ZOMIG 2.5 mg and NARAMIG 2.5 mg.

It is important to note that there was a higher proportion of patients with an attack that was of severe intensity at baseline in the ZOMIG 2.5 mg group (32.8%) than in the NARAMIG 2.5 mg group (18.4%). As expected, response rates for these severe attacks were considerably lower, with rates of 33.3%, 25.0% and 16.7% for ZOMIG 2.5 mg, NARAMIG 2.5 mg and placebo, respectively. Because of this imbalance, and as the observed response rates combine data from moderate and severe attacks, a statistical model was used which included the term baseline intensity to provide model-based estimates and thus allow a direct comparison between the treatment groups. The model-based estimated response rates were 54.5%, 46.6% and 21.3% for ZOMIG 2.5 mg, NARAMIG 2.5 mg and placebo, respectively.

Table I Analysis of headache response at 2 hours after dosing (ITT population)

Comparison	Odds ratio	95% confidence interval	p-value
Part 1			
ZOMIG 2.5 mg versus NARAMIG 2.5 mg	1.38	(0.88, 2.17)	0.159
ZOMIG 2.5 mg versus placebo	4.46	(2.45, 8.10)	<0.001

ZOMIG 2.5 mg had a statistically significant superior 1-hour headache response rate compared with both NARAMIG 2.5 mg (p=0.012) and placebo (p<0.001).
ZOMIG 2.5 mg also showed a significant superiority in pain-free at 2 hours compared with both NARAMIG 2.5 mg (p=0.009) and placebo (p=<0.001). Further evidence of superiority in relief of pain was obtained from the AUC endpoint, where ZOMIG 2.5 mg showed a significant difference from both NARAMIG 2.5 mg (p=0.029) and placebo (p<0.001) in the amount of pain relief within the first 4 hours. Additionally, in the satisfaction category, ZOMIG 2.5 mg demonstrated a superiority in 'speed of pain relief' compared with NARAMIG (p=0.045). This result further supports the results of the analysis of the 1-hour headache response and 2 hour pain-free endpoints.

Efficacy - Part 2

Over Attacks 2 to 4, there was still a slightly higher proportion of patients in the ZOMIG 2.5 mg group with attacks of severe intensity (213 patients, 39.1%) than in the NARAMIG 2.5 mg group (179 patients, 35.2%), although the difference was not as marked as in Part 1 of the trial. The data for the primary endpoint in Part 2 are presented by average baseline intensity, as this was the statistically significant interaction term in the model.
In patients with a majority of attacks of severe baseline intensity there was a significant difference between ZOMIG 2.5 mg and NARAMIG 2.5 mg in the percentage of patients with at least 66% consistency of headache response at 2 hours (p=0.027) (Table II). However, in patients who treated a majority of moderate attacks, there was no statistically significant difference between ZOMIG 2.5 mg and NARAMIG 2.5 mg (p=0.623).
In the group of patients with 100% consistency of headache response the results were not statistically significant (p=0.093), although a higher proportion of patients receiving ZOMIG 2.5 mg had a consistent headache response than those receiving NARAMIG 2.5 mg. There were no differences between the 2 treatment groups for patients who treated a majority of moderate attacks (p=0.0829).

Table II Analysis of consistency of 2-hour headache response: ZOMIG 2.5 mg vs NARAMIG 2.5 mg

Baseline intensity	Consistency	Odds ratio	95% confidence interval	p-value
Majority severe	≥66%	2.46	(1.11, 5.47)	0.0266
	100%	2.83	(0.84, 9.49)	0.0930
Majority moderate	≥66%	0.88	(0.51, 1.49)	0.6231
	100%	0.94	(0.53, 1.66)	0.8294

[a] Grouped according to the intensity of the majority of attacks at baseline, ie, if a patient had >50% of attacks of severe intensity, then they are included in the 'majority severe' category, if ≥50% moderate, then they are included in the 'majority moderate' category.

ZOMIG 2.5 mg also demonstrated superiority to NARAMIG 2.5 mg for the secondary endpoints of consistency of 2-hour pain-free in 2 out of 3 attacks (p=0.043), consistency of 1-hour headache response (p=0.002), and overall 1-hour headache response (p=0.011).

Safety

In Part 1 of this study, there was a higher incidence of adverse events in the ZOMIG 2.5 mg group (30.5%) compared with the NARAMIG 2.5 mg (22.4%) and placebo groups (22.8%), and there was also a higher incidence of withdrawals due to adverse events in the ZOMIG 2.5 mg group. The majority of adverse events were mild or moderate in intensity. The incidence of severe adverse events was low and similar across all 3 treatment groups.

The highest incidence of adverse events occurred in the 'body as a whole' system, followed by the nervous system. The most common adverse event was paraesthesia, followed by dizziness and abdominal pain. Paraesthesia was more common in the ZOMIG 2.5 mg group, but dizziness and abdominal pain were evenly distributed across the treatment groups. Triptan-related adverse events, such as paraesthesia, hyperaesthesia and somnolence were particularly common (but such events were also reported in the placebo group).

In Part 2, there was no difference in the overall incidence of adverse events in the ZOMIG 2.5 mg group compared with NARAMIG 2.5 mg (37.5% and 38%, respectively), and the majority of events were mild or moderate in intensity. The percentage of patients who experienced a severe adverse event was marginally higher in the NARAMIG group (2.7%) compared with the ZOMIG group (1.5%). Although there were nearly twice as many withdrawals in the ZOMIG 2.5 mg group compared with the NARAMIG 2.5 mg group, the percentage withdrawing because of an adverse event was similar (2.0% and 1.6%, respectively). Again, the most common event was paraesthesia, reported by an equal percentage of patients in both treatment groups. Dizziness, somnolence and tightness were also commonly reported. These are all known class effects of triptans.

No deaths were reported during either Part 1 or Part 2 of the trial.

There were no obvious trends in the type or category of adverse event that led to withdrawal across or within the treatment groups.

No patients had serious adverse events during the treatment period for either part of this study. There were 5 serious adverse events that occurred in Part 1 of this study, but none in patients in the ZOMIG group. Four of these events occurred after randomisation, but before treatment with trial medication.

There was a total of 6 serious adverse events in Part 2 of this study, but all were outside of the treatment period, 3 each in the ZOMIG 2.5 mg and NARAMIG 2.5 mg groups. In all cases, the individual investigators stated that none of these was related to trial treatment. In addition, there were 5 serious adverse events in 4 patients that occurred after Attack 1 but before Attack 2.

In Part 1, the incidence of triptan-related adverse events was 13.8%, 6.3%, and 5.4% in the ZOMIG 2.5 mg, NARAMIG 2.5 mg and placebo groups, respectively, with paraesthesia being the most commonly reported triptan-related adverse event. There were statistically significant differences between ZOMIG 2.5 mg and placebo and between ZOMIG 2.5 mg and NARAMIG 2.5 mg. However, there were no significant differences in the global patient satisfaction endpoint for the question 'satisfaction with trial medication regarding side effects', indicating that patients were not unduly troubled by triptan-related adverse events.

In Part 2, the incidence of triptan-related adverse events was similar in the 2 treatment groups, and there was no statistically significant difference between ZOMIG 2.5 mg and NARAMIG 2.5 mg.