AstraZeneca

Drug product:	Zomig	**SYNOPSIS**	
Drug substance(s):	Zolmitriptan		
Document No.:	805-1221-AK-0009		
Edition No.:	1		
Study code:	311CIL/0120		
Date:	10 May 2004		

REALIZE (Real Life Intranasal Zolmitriptan Exposure study) A Multinational, Multicentre, Two Phase Study to Assess the Efficacy of and Satisfaction with Intranasal Zolmitriptan 5 mg in the Acute Treatment of Migraine When Taken as Required by the Patients,

International co-ordinating investigator

Prof. Dr Jürgen Aschoff
Outpatient Dept. Neurology
(Neurologische Ambulanz) -University of Ulm
Steinhövelstraße 9
D-89075 Ulm
Germany

Study centre(s)

This was a multinational study performed at 193 centres in Germany and 18 centres in Canada.

Publications

Aschoff J., Gawel M., Lee J., Charlesworth B. Zolmitriptan nasal spray is highly efficacious and very fast acting in the treatment of acute migraine in a real-life setting: results from phase I of the REALIZE study Cephalalgia, 2003;23;711, P5N73.

Aschoff J., Gawel M., Lee J., Charlesworth B. Zolmitriptan nasal spray is highly efficacious and very fast acting in the treatment of acute migraine in a real-life setting. results from phase I of the REALIZE study. 7th Congress of the European Federation of Neurological Societies; 2003 Aug 30 to Sep 2; Helsinki, Finland; P3081.

Gawel M., Aschoff J., Lee J., Charlesworth B. Zolmitriptan nasal spray is highly efficacious, very fast acting and produces sustained relief in the treatment of acute migraine in a real life setting results from phase I of the REALIZE study. Annuals of Neurology 2003;54(suppl 7):32

Gawel M., Aschoff J., Lee J., Charlesworth B. Zolmitriptan nasal spray is highly efficacious, very fast acting and produces sustained relief in the treatment of acute migraine in a real life setting results from phase I of the REALIZE study. Headache et al, 43;5; Abstract Addendum OR17.

Study dates		**Phase of development**
First patient enrolled	14 May 2002	Therapeutic use (IV)
Last patient completed	4 August 2003	

Objectives

Primary objectives

Phase 1

The primary objective of the first phase was to compare the efficacy of nasally administered zolmitriptan 5 mg nasal spray and placebo at 1 hour after dosing, in migraine of any intensity, treated according to the patients' normal dosing pattern. Efficacy was assessed by comparison of total symptom relief (defined as no headache pain, nausea, photophobia or phonophobia) in the two treatment groups.

Phase 2

The primary objective of the second phase was to observe how patients choose to use the nasal spray across several attacks when provided freedom with regard to dosing. Time of dosing from time of onset of headache was captured in diary cards.

Secondary objectives

Secondary objectives of the study were:

Phase 1

- to compare the efficacy of intranasal zolmitriptan and placebo at specified time points in terms of pain relief, relief of associated symptoms, sustained pain relief, reduction in impact on usual activities and time to return to normal activities
- to investigate tolerability by assessment of Adverse Events

Phase 2

- to assess patient satisfaction with the intranasal formulation of zolmitriptan and willingness to use the preparation to treat future migraine attacks by direct questioning at the end of the open phase

- to assess patient preference for the zolmitriptan 5 mg nasal spray over previous migraine therapies following repeated use by direct questioning at the end of the open phase

- to further monitor the repeated dose safety (already established) in repeated use by collection of adverse events

Study design

This was a multinational (Canada and Germany), multicentre, randomised, parallel group, double-blind (phase 1) and open (phase 2), two phase study to further assess the efficacy, safety and tolerability of intranasal zolmitriptan 5 mg in the acute treatment of migraine in adults, when taken as required by patients during any stage of the headache phase of a migraine attack.

Target patient population and sample size

Male and female patients, aged between 18 and 65 years with an established diagnosis of migraine as defined by the International Headache Society Criteria with an age at onset of less than 50. It was estimated that 1000 patients must be recruited to achieve 400 evaluable patients in each treatment group. The estimates were calculated using 90% power with a 5% significance level (two-tailed test).

Investigational product and comparator(s): dosage and mode of administration

Each nasal spray applicator delivered one dose of 100 µl volume, containing zolmitriptan at a strength of 50 mg/mL, giving a total dose of 5 mg per patient. In phase 1 the treatment was to be zolmitriptan 5 mg or placebo, and in phase 2 zolmitriptan 5 mg.

Duration of treatment

The phase 1 nasal sprays were to be used to treat an attack within 6 weeks after randomisation and the phase 2 nasal sprays within 6.5 months.

Criteria for evaluation (main variables)

Efficacy

- Primary variable, phase 1: Total symptom relief at one hour after dosing with study medication irrespective of baseline headache intensity. This was defined as being free from headache, nausea, photophobia and phonophobia.

- Primary variable, phase 2: Time to dosing from time of onset of headache, captured in diary cards.

Safety

- Frequencies and percentage of all SAEs (by patient and by attack) experienced at any time during the study

- Frequencies and percentage of all adverse events and treatment related AEs (by patient and by attack) experienced within 24 hours of taking study medication

Statistical methods

The primary population for statistical analysis was intention-to-treat (ITT) population. In addition, a secondary per-protocol (PP) was performed on the primary endpoint in phase 1 of the study.

The primary endpoint and all secondary endpoints relating to treatment efficacy and speed of action were analysed using logistic regression. Data collected for time to return to normal activities were summarised using Kaplan Meier curves. Data on patient satisfaction with study medication, preference over previous acute migraine therapy, prospective future use and dosing patterns were summarized using descriptive statistics.

Patient population

Table S1 Patient population and disposition

		Zolmitriptan 5 mg nasal spray		**Placebo**		**Total**	
Population							
N randomised (N planned)		527	(500)	517	(500)	1044	(1000)
Demographic characteristics							
Sex (n and % of patients)	Male	54	(11.6)	62	(13.7)	116	(12.7)
	Female	410	(88.4)	389	(86.3)	799	(87.3)
Age (years)	Mean (SD)	40.9	(10.6)	42.4	(9.9)	41.6	(10.3)
	Range	18 to 66		18 to 65		18 to 65	
Race (n and % of patients)	Caucasian	458	(98.7)	444	(98.4)	902	(98.6)
	Black	3	(0.6)	3	(0.7)	6	(0.7)
	Oriental	2	(0.4)	2	(0.4)	4	(0.4)
	Other	1	(0.2)	2	(0.4)	3	(0.3)
Baseline characteristics							
Mean (SD) age at onset of migraine (years)		21.0	(9.4)	21.5	(9.4)	21.3	(9.4)
Disposition							
N analysed for safety[a] phase 1		464		451		915	
N analysed for efficacy (ITT) phase 1		461		451		912	
N analysed for efficacy (PP) phase 1		448		439		887	
N analysed for safety[a] phase 2		853		—		—	

	Zolmitriptan 5 mg nasal spray	Placebo	Total
N analysed for efficacy (ITT) phase 2	851	—	—

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number; PP=Per-protocol

Overall, the treatment groups were comparable for demographic characteristics, baseline values and discontinuations. Not experiencing a migraine attack within 6 weeks of randomisation was the most common reason for discontinuation in phase 1. In phase 2, patients lost to follow up was the most common reason for discontinuation. The mean age was 41.6 years and a majority of the patients were female (87.5%): migraine is known to be most common in women aged between 25 and 55 (Lipton et al. 1994).

Efficacy results

In terms of the primary outcome variable (total symptom relief rate 1 hour post-dose) zolmitriptan 5 mg nasal spray was significantly superior to placebo (14.5% vs. 5.1% patients; p<0.0001). A statistically significant difference in total symptom relief rate was also demonstrated at 30 minutes post-dose, at which time 6.1% of zolmitriptan treated patients were free of pain, nausea, photo- and phonophobia vs. 2.1% of placebo patients (p=0.0032). At two hours post dose the difference was even more marked in favor of zolmitriptan nasal spray (32.6% vs. 8.5%; p<0.0001).

In terms of the traditional outcome variable of headache response, zolmitriptan 5 mg nasal spray produced a significantly higher headache response rate than placebo from 10 minutes (15.1% vs. 9.1%; p=0.0079), reaching a value comparable to previous studies at 2-hours post dose (64.8% vs. 23.9%; p<0.0001).

Table S2 Total symptom relief[a] by time window phase 1 (ITT population)

Time window	n (%) of patients with total symptom relief						Statistical analysis of symptom relief rates by time window
	Zolmitriptan 5 mg nasal spray N=461			Placebo N=451			Zolmitriptan 5 mg nasal spray vs. Placebo
	n	N*[b]	(%)	n	N*[b]	(%)	p-value
10 minutes	6	458	(1.3)	2	447	(0.4)	0.1472
30 minutes	27	444	(6.1)	9	433	(2.1)	0.0032
60 minutes	63	434	(14.5)	22	432	(5.1)	<0.0001
120 minutes	144	442	(32.6)	37	434	(8.5)	<0.0001

For individual patient data see listing G16. For p-values see Table 78.

[a] Total symptom relief is defined as no headache pain intensity and no symptoms of nausea, photophobia, phonophobia

[b] Number of patients with non-missing responses

The intention-to-treat population in Phase 2 consisted of 851 patients. Most patients (89.3%) used zolmitriptan nasal spray to treat 3 migraine attacks. In total, 2426 attacks were treated with zolmitriptan nasal spray. The mean time from migraine onset to treatment was 2 hours and 42 minutes, remaining constant across attacks (primary endpoint) and the median time was 1 hour and 15 minutes. Most patients reported being satisfied or very satisfied with zolmitriptan nasal spray overall (76.7%) and with regard to its speed of relief (76.9%), ease of use (92.8%), convenience (89.2%), and reliability (76.7%). Furthermore, the majority of patients agreed or strongly agreed that they would be willing to use zolmitriptan nasal spray in the future (60.6%) and that zolmitriptan nasal spray was preferred over previous therapies (58.5%).

Safety results

Overall zolmitriptan 5 mg nasal spray was well tolerated. In the first phase of the study adverse events were reported by 228 (49.1%) patients after zolmitriptan 5 mg nasal spray treatment and by 92 (20.4%) patients after placebo treatment. Eight patients in the zolmitriptan group and 3 patients in the placebo group discontinued from the study due to adverse events. Two of the patients in the zolmitriptan group discontinued prior to treatment and are therefore not included in the phase 1 safety population. One of the patients in the placebo group discontinued after entering the open-label phase but before receiving any open-label treatment. One patient in each treatment group experienced serious adverse events.

In phase 2 of the study, adverse events were reported by 430 (50.4%) patients in 967 (39.9%) attacks after zolmitriptan 5 mg nasal spray treatment. Fourteen patients discontinued due to adverse events, of which 2 discontinued before receiving any open-label treatment (not included in the phase 2 safety population). Two patients experienced serious adverse events (see Table 32). The majority of adverse events were transient, self-limiting and mild in intensity in both phases of the study. The types of adverse events were those seen in previous studies, being mainly known pharmacological effects of triptans (e.g. Dizziness, fatigue, paraesthesia, nausea, sensation of heaviness, somnolence, and throat tightness) or of drugs given via the nasal route (e.g. Dysgeusia, nasal passage irritation, throat irritation, dysphagia, pharyngitis, and dry mouth).

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events phase 1 (safety analysis set)

Category of adverse event	**N (%) of patients who had an adverse event in each category [a]**			
	Zolmitriptan 5 mg nasal spray N=464		**Placebo N=451**	
Any adverse events	228	(49.1)	92	(20.4)

Category of adverse event	N (%) of patients who had an adverse event in each category [a]			
	Zolmitriptan 5 mg nasal spray N=464		Placebo N=451	
Adverse events within 24 hours	228	(49.1)	91	(20.2)
Any drug related adverse events [b]	205	(44.2)	68	(15.1)
Serious adverse events	1	(0.2)	1	(0.2)
Before treatment of attack	0	(0)	0	(0)
During treatment of attack (<24 h)	1	(0.2)	0	(0)
After treatment of attack (>24 h)	0	(0)	1	(0.2)
Serious adverse events leading to death	0	(0)	0	(0)
Discontinuations of study treatment due to adverse events	6	(1.3)	3	(0.4)
Other significant adverse events	0	(0)	0	(0)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
[b] Adverse events judged by the investigator to be related to study medication

Table S4 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events phase 2 (safety analysis set)

Category of adverse event	N (%) of patients who had an adverse event in each category [a]	
	Zolmitriptan 5 mg nasal spray N=853	
Any adverse events	430	(50.4)
Adverse events within 24 hours	430	(50.4)
Any drug related adverse events [b]	410	(48.1)
Serious adverse events	2	(0.2)
During treatment of attack (<24 h)	1	(0.1)
After treatment of attack (>24 h)	1	(0.1)
Serious adverse events leading to death	0	(0)
Discontinuations of study treatment due to adverse events	12	(1.4)
Other significant adverse events	0	(0)

[=a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Adverse events judged by the investigator to be related to study medication

Conclusion(s)

The primary objective of total symptom relief has not previously been used in migraine clinical studies, but is very relevant to patients, due to the high prevalence of headache-associated symptoms during an attack (Lipton et al. 2001) and the considerable impact of such symptoms on quality of life (Terwindt et al., 2000; Solomon et al., 2000; Breslau and Rasmussen, 2001). Using the endpoint of total symptom relief, a significant difference from placebo was observed at 1 hour after treatment (the primary endpoint), but also at the earlier 30 minute time point. Since the total symptom relief endpoint requires the resolution of several variables, the response rates are lower than for the more commonly used primary endpoints of headache response or pain free outcome. However, in this study, zolmitriptan 5 mg nasal spray achieved total symptom relief in over 30% of patients by 2 hours after treatment.

Significant headache response and pain free rates were also seen at early timepoints with zolmitriptan 5 mg nasal spray. Zolmitriptan 5 mg nasal spray produced a significantly higher headache response rate than placebo from 10 minutes post-dose. Onset of efficacy has been reported 10 minutes after administration of sumatriptan 6 mg subcutaneous injection (Cady et al., 1991), 15 minutes after administration of sumatriptan 20 mg nasal spray (Ryan et al., 1997), and no earlier than 30 minutes with any oral triptan (Dahlöf, 2002). Zolmitriptan nasal spray may be more acceptable to patients than an injection, particularly since subcutaneous sumatriptan is associated with a high rate of adverse events such as injection site reactions (Cady et al., 1991). The 2-hour headache response rate after treatment with zolmitriptan 5 mg nasal spray was high, even in patients with severe baseline headache intensity. High 2-hour headache response rates were also seen in other studies of zolmitriptan 5 mg nasal spray (Charlesworth et al., 2003; Dowson et al., 2003). Thus, zolmitriptan 5 mg nasal spray provides the two attributes of migraine medication rated most highly by patients: high efficacy and rapid pain relief (MacGregor et al., 2003).

Pain-free rates were significantly higher after treatment with zolmitriptan 5 mg nasal spray, compared with placebo, from 30 minutes post-dose. These results are consistent with those seen in an earlier short-term study with zolmitriptan 5 mg nasal spray at the 5 mg dose (Charlesworth et al., 2003). Importantly, zolmitriptan 5 mg nasal spray was significantly superior to placebo in achieving sustained freedom from pain without the need for additional medication over 24 hours post-treatment. This was also reflected by usage of a second dose of study medication and usage of escape medication, which were much lower in zolmitriptan 5 mg nasal spray recipients.

Zolmitriptan 5 mg nasal spray reduced the impact of migraine on daily activities in almost half the patients at 2 hours of treatment. Among patients with severe headache at baseline, approximately one-third of patients were able to perform normal activities by 30 minutes post-dose. This result is likely to be important to patients, given the highly disruptive effect that migraine has on sufferers' work, social and home life (Lipton et al., 2001; Solomon et al., 2000; Von Korff et al., 1998).

Zolmitriptan nasal spray was generally well tolerated in phase 1, with very few patients in the zolmitriptan group withdrawing from the study due to adverse events. The most common adverse event in this group was dysgeusia (unusual taste). Unusual taste was also the most common adverse event in two long-term studies of zolmitriptan 5 mg nasal spray, although very few patients withdrew as a result of this adverse event (Dowson et al., 2003; 311CIL/0122). Together, these findings suggest that patients treated with zolmitriptan 5 mg nasal spray who experience dysgeusia do not find this adverse event to be particularly troublesome with this treatment.

The main focus of phase 2 was patient experience with zolmitriptan 5 mg nasal spray without a dictated regimen for dosing. The results indicate that most patients treat either within 30 minutes (35.1%) or >60 minutes (53.4%) after attack onset. The vast majority (76.6%) were very satisfied or satisfied with zolmitriptan 5 mg nasal spray overall. Patients were also highly satisfied with zolmitriptan 5 mg nasal spray with regard to its speed of relief, ease of use, convenience, and reliability. These attributes have previously been identified in satisfaction studies as being important or very important characteristics of an acute migraine therapy (Lipton et al. 2002; Pascual et al. 2001; Ryan 2001). Furthermore, the majority of patients agreed or strongly agreed when asked if willing to use zolmitriptan 5 mg nasal spray in the future and if zolmitriptan 5 mg nasal spray was preferred over previous therapies.

Zolmitriptan 5 mg nasal spray was equally well tolerated in phase 2, with very few patients withdrawing from the study due to adverse events. The most common adverse event, dysgeusia, again did not appear to be troublesome to patients and was typically reported as mild in intensity.

Date of the report

10 May 2004