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AstraZeneca

Drug product	Zomig® Nasal Spray	**SYNOPSIS**	
Drug substance(s)	Zolmitriptan		
Study code	311CUS/0022		
Date	19 October 2005		

A Multicenter, Randomized, Placebo-controlled, Double-blind, Parallel-group Trial to Evaluate Early Efficacy and Tolerability of Zolmitriptan (ZOMIG®) Nasal Spray in the Acute Treatment of Adult Subjects with Migraine

Principal investigator

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Study centre(s)

Patients were enrolled and randomized at 151 investigational sites in the United States (one additional site had no randomized patients).

Publications

None

Study dates		**Phase of development**
First patient enrolled	10 September 2002	Therapeutic confirmatory (IIIB)
Last patient completed	13 May 2003	

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Objectives

– The primary objective of the study was to evaluate early efficacy (as assessed by the percentage of responders) of a zolmitriptan 5-mg nasal spray dose in the acute treatment of migraine in adult patients.

– The secondary objective of this study was to further evaluate the efficacy, safety, and tolerability of a zolmitriptan 5-mg nasal spray dose in the acute treatment of migraine.

Study design

A multicenter, randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy and tolerability of a zolmitriptan 5-mg nasal spray dose in the acute treatment of migraine

Target patient population and sample size

Men and women aged 18 to 65 inclusive who had an established diagnosis of migraine, with or without aura, as defined by the International Headache Society criteria were eligible for entry into the trial. An enrollment of 1592 patients was planned in order to obtain 1384 evaluable patients (692 patients per treatment group). All trial patients who treated at least 1 migraine headache with trial treatment (up to 2 migraine headaches could have been treated with study medication) were evaluable.

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

Patients were randomized in a 1:1 ratio to either zolmitriptan 5-mg nasal spray or matching placebo. AstraZeneca supplied zolmitriptan 5-mg commercial nasal spray device (IPS batch BC612 [pharmaceutical batch #91806K02], formulation number F12441) and matching placebo for zolmitriptan nasal spray (IPS batch BC421 [pharmaceutical batch #91110E02], formulation number F12787).

Duration of treatment

Patients were to treat up to 2 migraine headaches of moderate or severe intensity over a 10-week period, and return to the investigational center for assessment within 1 to 2 weeks of treating their second attack, or up to 12 weeks after randomization, whichever occurred first. Each headache was to be treated initially with a single dose of trial medication. Patients who required additional treatment for migraine, may have taken an approved escape medication 4 hours after taking the initial dose of trial treatment and after completion of the 4-hour migraine headache assessment.

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Criteria for evaluation (main variables)

Efficacy

Headache response was defined as an improvement in migraine headache intensity from severe or moderate to mild or none. The analyses based on the first-attack data were the primary analyses.

- Primary endpoint: headache response at 2 hours, 1 hour, 30 minutes, and 15 minutes after the initial dose of trial treatment. (Since a step-down procedure was used to control the overall type-I error at 5% over the 4 timepoints starting at 2 hours, the primary endpoint was achieved if statistical superiority was observed at the 2-hour timepoint)
- Secondary endpoints:
  - headache response at 4 hours after dosing
  - time to onset of headache response for the first attack
  - pain-free response rate at 30 minutes and at 1, 2, and 4 hours after dosing
  - 24-hour sustained headache response rate
  - 24-hour sustained pain-free response rate
  - return to normal activities at 30 minutes and at 1, 2, and 4 hours after dosing
  - incidence of and time to use of escape medication
  - resolution of migraine headache associated symptoms (ie, nausea, photophobia, phonophobia, vomiting) at 15 and 30 minutes and at 1, 2, and 4 hours after dosing
  - patient's global satisfaction rating (global impression)

Safety

- The incidence and nature of adverse events, serious adverse events, and causally related adverse events
- Changes in vital signs, laboratory findings, physical examination, nose and throat examination, and electrocardiograms
- The incidence and nature of adverse events and patient discontinuation from the trial

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Statistical methods

Binary response data were analyzed using logistic regression for a single migraine attack (first treated migraine) and generalized estimating equations for multiple headaches. The primary analysis was based on the first-attack data in the intention-to-treat (ITT) population; the per protocol population was also assessed. Between-treatment group comparisons of headache response rates were performed using the logistic regression with treatment, region, and baseline headache intensity in the model. A step-down approach was used to account for the multiple testing on the primary endpoints of headache response at 2 hours, 1 hour, 30 minutes, and 15 minutes for the first attack. The odds ratio and confidence interval (CI) were obtained by taking the antilogarithms of the estimate and 95% CI of the treatment effect.

AstraZeneca performed an interim analysis of efficacy data based on the first-attack data in order to provide the US Food and Drug Administration with validated, unblinded efficacy data from a subset of 210 patients who treated the first migraine headache attack with study medication, including the 5-mg nasal spray device proposed for marketing.

All formal statistical tests for treatment differences were performed using a 2-sided hypothesis test with a significance level of 0.050, unless otherwise specified. No correction to the reported p-values was made for the analysis of secondary measures. Secondary efficacy endpoints of headache response, pain-free response, sustained headache response, sustained pain-free response, return to normal activities, and resolution of non-headache symptoms were analyzed in the same manner as for the primary endpoint.

Time-to-event data were graphically summarized for each attack using Kaplan-Meier estimation. Differences between treatment groups were assessed using the Cox proportional hazards model, adjusting for treatments, region, and baseline pain intensity.

Data on satisfaction were analyzed using ordered logistic regression using the proportional odds model. Preference data were analyzed via binary logistic regression, with covariates of treatment, region, and average baseline pain intensity. Data on prospective future use and ease of use were summarized using descriptive statistical methods only.

Demographics, baseline characteristics, and safety data were summarized descriptively using summary statistics for continuous variables and frequency counts, proportions, and shift tables for categorical variables.

Patient population

Demographic and baseline characteristics for the ITT population and the disposition of all patients in the trial are shown in Table S1. A total of 2122 patients were enrolled and randomized to zolmitriptan (n = 1066) or placebo (n = 1056) at 151 centers in the US. The first patient entered the study on 10 September 2002, and the last patient completed the final visit on 13 May 2003. The treatment groups appeared well balanced, and 918 and 903 patients in the zolmitriptan and placebo groups, respectively, completed the study. The most common reasons for discontinuation in both treatment groups were protocol noncompliance (8% in each group) and lost to follow-up (3% and 4% in the zolmitriptan and

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placebo groups, respectively). The study population was primarily female and Caucasian, with a mean age of 41 years, which was reflective of the target population for the investigational product.

Table S1 Patient population and disposition

		Zolmitriptan 5-mg nasal spray	Placebo	Total
Population				
N randomized (N planned)		1066 (796)	1056 (796)	2122 (1592)
Demographic characteristics[a]				
Sex (n [% of patients])	Male	139 (14.87)	109 (11.68)	248 (13.28)
	Female	796 (85.13)	824 (88.32)	1620 (86.72)
Age (years)	Mean (SD)	40.7 (10.4)	40.7 (10.3)	40.7 (10.4)
	Range	18 to 65	18 to 64	18 to 65
Race (n [% of patients])	Caucasian	783 (83.74)	784 (84.03)	1567 (83.89)
	Black	90 (9.63)	95 (10.18)	185 (9.90)
	Hispanic	31 (3.32)	34 (3.64)	65 (3.48)
	Asian	18 (1.93)	12 (1.29)	30 (1.61)
	Other[b]	13 (1.39)	8 (0.86)	21 (1.12)
Baseline characteristics[a]				
Average number of attacks/month[c]				
Mean (SD)		3.5 (1.3)	3.5 (1.3)	3.5 (1.3)
Minimum, maximum		2, 15	1, 12	1, 15
Disposition				
N (%) of patients who completed		918 (86.1)	903 (85.5)	1821 (85.8)
N (%) of patients who discontinued		148 (13.9)	153 (14.5)	301 (14.2)
N analyzed for safety[d]		935	934	1869
N analyzed for efficacy (ITT)		935	933	1868
N analyzed for efficacy (PP)		886	854	1740

[a] For the intention-to-treat population (935 patients on zolmitriptan and 933 patients on placebo).
[b] Other included any special subgroups.
[c] During the 3 months prior to trial entry.
[d] Number of patients who took any trial treatment.
ITT, intention to treat; N Number; PP Per-protocol; SD Standard deviation.

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Efficacy results

Results of analyses of the primary endpoints for the ITT and per protocol populations are shown in Table S2. Zolmitriptan 5-mg nasal spray was efficacious in the acute treatment of migraine with or without aura in adults. Statistically significant superiority compared with placebo in the primary endpoint (headache response) was observed at 2 hours, 1 hour, 30 minutes, and 15 minutes post dose. Statistical superiority compared with placebo was also obtained for all secondary parameters except resolution of vomiting at all timepoints ≥ 30 minutes and for many as early as 15 minutes postdose for the first attack and in the patient's global satisfaction rating. In the analysis of both attacks, statistical superiority compared with placebo was obtained for all secondary parameters at all timepoints, except resolution of photophobia at 15 minutes and resolution of vomiting at timepoints before 4 hours postdose.

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Table S2 Headache response rate (first attack) at 15 minutes, 30 minutes, 1 hour, and 2 hours post dosing

Timepoint, population	Zolmitriptan 5-mg nasal spray (n=935)		Placebo (n=933)		Statistical comparison (logistic regression)		
	Number assessed	Headache response (n [%])[a]	Number assessed	Headache response (n [%])[a]	Odds ratio	95% CI (L, U)	p-value
At 15 min							
ITT	927	170 (18.3)	923	105 (11.38)	1.782	(1.367, 2.324)	< 0.001
PP	847	156 (18.42)	811	93 (11.47)	1.770	(1.338, 2.343)	< 0.001
At 30 min							
ITT	919	360 (39.17)	918	221 (24.07)	2.119	(1.726, 2.603)	< 0.001
PP	839	329 (39.21)	805	187 (23.23)	2.221	(1.783, 2.766)	< 0.001
At 1 hour							
ITT	901	513 (56.94)	909	311 (34.21)	2.643	(2.177, 3.208)	< 0.001
PP	819	471 (57.51)	800	271 (33.88)	2.727	(2.220, 3.349)	< 0.001
At 2 hours							
ITT	926	641 (69.22)	922	347 (37.64)	3.837	(3.155, 4.665)	< 0.001
PP	845	596 (70.53)	813	313 (38.50)	3.916	(3.184, 4.817)	< 0.001

[a] Percentages are based on the total number of attacks in the population and timepoint assessed.
95% CI (L, U) Lower and upper 95% confidence limits of odds ratio of response rates for patients treated with zolmitriptan versus patients treated with placebo.
ITT, Intention to treat; PP, Per protocol.

Safety results

A summary of the number of attacks with an associated adverse event in each category of seriousness is presented in Table S3. A summary of the number of patients with an adverse event in each category of seriousness is presented in Table S4. The most common adverse events, as summarized by preferred term, are shown in Table S5.

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Table S3 Number (%) of attacks with an associated adverse event in any category, safety population

Category of adverse event	Number (%) of attacks associated with an adverse event in each category[a]			
	Zolmitriptan 5-mg nasal spray (n=1745)		Placebo (n=1718)	
Any adverse events	673	(38.57)	278	(16.18)
Drug-related adverse events	615	(35.24)	220	(12.81)
Serious adverse events	0	—	1	(0.06)
Serious adverse events leading to death	0	—	0	—
Serious adverse events not leading to death	0	—	1	(0.06)
Discontinuations of study treatment due to adverse events	6	(0.34)	3	(0.17)
Other significant adverse events	0	—	0	—

[a] Both attacks 1 and 2 are included. Attacks with multiple events in the same category are counted only once in that category. Attacks with events in more than 1 category are counted once in each of those categories.

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

Category of adverse event	N (%) of patients who had an adverse event in each category[a]			
	Zolmitriptan 5-mg nasal spray (n=935)		Placebo (n=934)	
Any adverse events	442	(47.27)	215	(23.02)
Drug-related adverse events	397	(42.46)	168	(17.99)
Serious adverse events	5	(0.53)	3	(0.32)
Serious adverse events leading to death	0	—	0	—
Serious adverse events not leading to death	5	(0.53)	3	(0.32)
Discontinuations of study treatment due to adverse events	6	(0.64)	3	(0.32)
Other significant adverse events	0	—	0	—

[a] Adverse events occurring within 24 hours after intake of study medication and serious adverse events occurring at any time during the study were included. 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.

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Table S5 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency in the zolmitriptan group, safety population

Adverse event (preferred term)	Zolmitriptan 5-mg nasal spray (n=935)		Placebo (n=934)		Total (N=1869)	
Dysgeusia	205	(21.93)	20	(2.14)	225	(12.04)
Nasal passage irritation	84	(8.98)	34	(3.64)	118	(6.31)
Dizziness	60	(6.42)	33	(3.53)	93	(4.98)
Throat irritation	52	(5.56)	29	(3.10)	81	(4.33)
Pharyngolaryngeal pain	36	(3.85)	6	(0.64)	42	(2.25)
Somnolence	35	(3.74)	11	(1.18)	46	(2.46)
Nausea	30	(3.21)	18	(1.93)	48	(2.57)
Postnasal drip	20	(2.14)	2	(0.21)	22	(1.18)
Rhinorrhoea	19	(2.03)	11	(1.18)	30	(1.61)
Throat tightness	19	(2.03)	0	—	19	(1.02)

[a] Events with an incidence of ≥ 2% in the zolmitriptan group are included in this table.

Zolmitriptan 5-mg nasal spray was safe and well tolerated. The overall incidence of adverse events or drug-related adverse events was generally higher in patients who were given zolmitriptan 5-mg nasal spray, compared with those who were given placebo. Most of this difference was due to the higher incidence of dysgeusia in the zolmitriptan group (21.93% vs 2.14% in the placebo group). Nasal passage irritation, dizziness, throat irritation, pharyngolaryngeal pain, somnolence, and nausea were also frequent (≥ 3% of patients on zolmitriptan) and were more frequent among zolmitriptan- than placebo-treated patients. Females were more likely than males to report adverse events, including those most frequently reported on zolmitriptan. Most adverse events were transient and mild or moderate in intensity. No deaths occurred during the study, and few events were serious or resulted in withdrawal from the study. No evidence for treatment-related adverse changes in clinical laboratory results, electrocardiography findings, vital signs, or physical examination was observed.

Conclusions

Zolmitriptan 5-mg nasal spray provided rapid relief in the treatment of migraine headache with or without aura in adults. Statistical superiority to placebo was achieved for the primary endpoint of headache response as early as 15 minutes post dose. Statistical superiority to placebo was also achieved for all secondary parameters except resolution of vomiting as early as 30 minutes and often within 15 minutes postdose. The use of zolmitriptan 5-mg nasal spray

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was safe and generally well tolerated. Most adverse events were transient and of mild to moderate intensity.

Date of the report

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