AstraZeneca

Drug product:	Zomig®	**SYNOPSIS**	
Drug substance(s):	Zolmitriptan		
Document No.:			
Edition No.:			
Study code:	311CUS/0016		
Date:	10 April 2006		

A Multicenter, Randomized, Open-label Comparison of the Effects of ZOMIG-ZMT® (zolmitriptan) and Usual Non-triptan Migraine Care on Work Loss, Productivity, and Patient Preference

International co-ordinating investigator

Not applicable

Study center(s)

This study was conducted in the US (177 centers).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	November 1, 2001	Therapeutic use (IV)
Last patient completed	July 30, 2002	

Objectives

The primary objective of this study was to compare the number of work-hours lost per migraine attack between patients treated with ZOMIG-ZMT® (orally disintegrating zolmitriptan; hereafter referred to as ZMT) and patients treated with non-triptans in the usual migraine therapy treatment arm.

The secondary objectives of this study were to evaluate:

- the number of work-hours lost over the entire 12-week study period;
- the impact of therapy on total work productivity lost per attack;
- the total productivity lost over the entire 12-week study period;

- the time to meaningful migraine relief following the first dose of study medication, categorized as follows: ≤15 minutes, 16 to 30 minutes, 31 to 45 minutes, 46 to 60 minutes, >1 hour to 2 hours, and >2 hours to 4 hours;
- the economic impact of therapy;
- in the groups treated with ZMT, the patients' overall preference for ZMT over their most recent previous migraine medication;
- and the safety of study treatment as indicated by the incidence, nature, and severity of treatment-emergent adverse events.

Study design

This study was a multicenter, randomized, open-label study to compare the effects of ZMT and usual non-triptan migraine therapy on patients' work loss, productivity, and treatment preference.

Target patient population and sample size

The study population was composed of male and female patients, aged between 18 and 65 years inclusive, with an established diagnosis of migraine headache (with or without aura) as defined by the International Headache Society diagnostic criteria (with a migraine-related disability of MIDAS grade II, III, or IV), and with an age at onset of less than 50 years. In addition, patients must have been working greater than 30 hours per week at a paid job (including self-employment) during the study.

Using an estimated standard deviation of 1.906 from Davies et al (1999), a 2 sample t-test with a 2-sided significance level of 0.05 (a step-down procedure for multiple comparisons was employed) would have 92% power to detect a difference in treatment means (1.5 hours for ZMT and 2.4 hours for non-triptan usual therapy) when there are 252 patients in each ZMT arm and a minimum of 70 patients in the non-triptan usual therapy arm (worst case assumption of only about 30% of those randomized to usual therapy using non-triptans). Assuming a withdrawal rate of 25%, the study required a total of 1008 enrolled patients.

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

At Visit 1, eligible patients were randomized to 1 of the following treatments in parallel fashion in a 1:1:1 ratio: ZMT 2.5 mg, ZMT 5 mg, or their usual migraine medication (may include triptans or non-triptans). The 5-mg dose initially consisted of two 2.5-mg ZMT tablets, but might have changed to one 5-mg ZMT tablet when it became commercially available. Study medication for each of the 3 treatment groups was prescribed by the investigator and supplied through licensed pharmacies.

Duration of treatment

Patient treated their migraine attacks during a 12-week open-label treatment period. The quantity of study medication prescribed at Visit 1 was sufficient to treat a maximum of 12 migraine attacks during each of two 6-week treatment periods. Additional headaches occurring during the study treatment period could be treated with the patient's usual migraine medication. Quantities prescribed for each of the treatment groups allowed for patients to take a second, equal dose of study medication for all 12 headaches, if necessary.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: number of work-hours lost per migraine attack (intention-to-treat [ITT] analysis set)
- Secondary variables:
  - number of work-hours lost over the 12-week study period (ITT)
  - total work productivity lost (hours) per treated migraine attack (ITT)
  - total work productivity lost (hours) over the 12-week study period (ITT)
  - time to meaningful migraine relief following the first dose of study medication (for each of the first 6 treated attacks in each 6-week treatment period) (ITT)
  - economic impact of therapy over the 12-week study period (ITT)
  - overall patient preference for ZMT over the most recent previous migraine medication (ITT)

Safety

Standard safety variables were assessed and included any adverse events (AEs), common AEs, serious AEs (SAEs), and AEs causing discontinuation. A clinical laboratory evaluation of biological samples (hematology, clinical chemistry, or urinalysis) was not conducted. A physical examination, including measurement of vital signs, was conducted at the baseline visit only; electrocardiograms (ECGs) were not measured. The safety analysis set consisted of all patients who were known to have received at least one dose of treatment and had some follow-up information to document any possible AEs. Patients did not need to have diary cards if follow-up visit information was available to indicate that the patient took medication (ie, either the patient reported an AE or the patient indicated that he/she took ZMT on the Patient Preference Questionnaire).

Statistical methods

Analysis of the efficacy endpoints was based on the principle of intention-to-treat, where all patients entering the study are included, provided they used study treatment and had baseline and post-baseline efficacy data for the same efficacy parameter for a minimum of 1 migraine headache. The attack-level analysis included attacks that were known to be treated and which contributed some post-treatment efficacy data.

A per-protocol (PP) analysis was performed on the primary endpoint. The PP analysis set was a subset of the ITT analysis set who did not have major violations or deviations from the protocol. For attack-level summaries and analyses, each attack was evaluated for the occurrence of a major protocol deviation. Thus, there are patients in the PP analysis set who have one or more attacks included in the analysis set and at least one attack excluded.

The primary endpoint of work-hours lost per treated migraine attack, and the key secondary endpoints (work hours lost for the study, hours of productivity lost per attack, hours of productivity lost for the study, economic impact of therapy in dollars, time to migraine relief for the first 6 attacks during each 6-week period, and patients' overall preference) were subjected to formal statistical analysis. Data summaries only were provided for the remaining efficacy endpoints. To control the Type I error at the 0.05 level for the primary endpoint, the comparison between the ZMT 5-mg and usual non-triptan groups was tested first. Only if the result of the first comparison was statistically significant was the ZMT 2.5-mg group compared with the usual non-triptan group. All other statistical tests for pair-wise differences between the ZMT and usual non-triptan groups were performed using 2-sided hypothesis tests with a significance level of 0.050.

All but the time to meaningful migraine relief and overall preference were analyzed with Pitman's permutation test, comparing each ZMT group with the usual non-triptan group, stratified on the baseline MIDAS grade. Pitman's permutation test replaced the originally proposed analysis of covariance (ANCOVA) model because the distribution of these data was extremely skewed, such that the validity of the ANCOVA method was questionable. For patients in the ZMT groups, patients' overall preference for ZMT compared with their usual migraine therapy was analyzed using a 1-sample binomial test with a null hypothesis of no preference, proportion = 0.50. The time to meaningful migraine relief was analyzed at the attack level with a Cochran-Mantel-Haenszel test using ridit scores, controlling for region, baseline MIDAS grade, and baseline headache intensity.

The safety analysis set consisted of all patients who were known to have received at least one dose of study treatment and had some follow-up information to document and possible AEs. Safety was assessed by evaluating the incidence, nature, and severity of treatment-emergent AEs: these included AEs occurring within 24 hours following a dose of study medication and SAEs occurring at any time subsequent to the first dose of study medication for each patient.

Patient population

Of 1056 patients randomized to treatment, 845 and 813 patients were included in the ITT and PP analysis sets, respectively. The number of randomized patients that completed the study

was 240, 248, 111, and 145 in the ZMT 5 mg, ZMT 2.5 mg, usual non-triptan, and usual triptan groups, respectively. The most common reasons for discontinuation from the study were lost to follow-up, protocol noncompliance, and the patient felt the study medication was ineffective. Patients in the ITT analysis set were predominantly Caucasian, women, had a mean age of 39 years, had a mean age of onset of migraine headaches of 22 years, and a baseline MIDAS grade of III to IV. The treatment groups were well balanced regarding demographic and baseline disease characteristics.

Table S1 Patient population and disposition

Demographic or baseline characteristic		Treatment group				All
		ZMT		Usual		
		5.0 mg	2.5 mg	non-triptan	triptan	
Population						
N randomized (N planned)		343 (336)	352 (336)	177 (93)	184 (243)	1056 (1008)
Demographic characteristics (ITT)						
Sex (n and % of patients)	Male	41 (14.6)	35 (12.5)	16 (13.1)	19 (11.7)	111 (13.1)
	Female	240 (85.4)	244 (87.5)	106 (86.9)	144 (88.3)	734 (86.9)
Age (years)	Mean (SD)	38.7 (10.0)	40.0 (10.5)	37.3 (10.4)	40.8 (9.2)	39.3 (10.1)
	Range	18-65	18-64	18-63	18-62	18-65
Race (n and % of patients)	Caucasian	245 (87.2)	249 (89.2)	108 (88.5)	147 (90.2)	749 (88.6)
	Black	19 (6.8)	17 (6.1)	6 (4.9)	10 (6.1)	52 (6.2)
	Oriental	6 (2.1)	4 (1.4)	2 (1.6)	0	12 (1.4)
	Hispanic	9 (3.2)	9 (3.2)	4 (3.2)	6 (3.7)	28 (3.3)
	Other	2 (0.7)	0	2 (1.6)	0	4 (0.5)
Baseline characteristics (ITT)						
Baseline MIDAS grade (n and % of patients)	I	2 (0.7)	3 (1.1)	0	0	5 (0.6)
	II	34 (12.1)	31 (11.1)	16 (13.1)	23 (14.1)	104 (12.3)
	III	82 (29.2)	84 (30.1)	31 (25.4)	46 (28.2)	243 (28.8)
	IV	163 (58.0)	161 (57.7)	75 (61.5)	94 (57.7)	493 (58.3)
Disposition						
N (%) of randomized patients who:						
Completed[b]		240 (70)	248 (70)	111 (63)	145 (79)	744 (70)
Discontinued		102 (30)	103 (29)	66 (37)	39 (21)	310 (29)
N analyzed for safety[a]		299	296	123	164	882
N analyzed for efficacy (ITT)		281	279	122	163	845

Demographic or baseline characteristic	Treatment group				All
	ZMT		Usual		
	5.0 mg	2.5 mg	non-triptan	triptan	
N analyzed for efficacy (PP)	270	269	112	162	813

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
[b] Completion data are missing for 1 patient in each of the ZMT groups.
ITT = Intention-to-treat; PP = Per-protocol; SD = Standard deviation

Efficacy results

Patients in the 2 ZMT and the usual non-triptan groups treated 5681 migraine attacks during the 12-week study period. For the primary efficacy variable of the mean number of work-hours lost per attack, the results were comparable in the ZMT 5-mg and 2.5-mg groups (0.8 and 0.7 hours, respectively), and each was significantly lower compared to usual non-triptan treatment (1.3 hours; ITT analysis set). The mean number of work-hours lost per attack for the usual non-triptan group was approximately twice that for either ZMT group.

Table S2 Number of work-hours lost per treated migraine attack (ITT)

	Treatment group			P-value[a] for Usual non-triptan versus:	
	ZMT		Usual	ZMT	
	5.0 mg	2.5 mg	non-triptan	5.0 mg	2.5 mg
N	281	278	122		
Mean (SD)	0.8 (1.3)	0.7 (1.1)	1.3 (2.4)	0.0033	0.0005
Median (range)	0.2 (0.0-8.7)	0.2 (0.0-7.7)	0.5 (0.0-16.0)		

[a] Monte Carlo estimate of exact p-value from permutation test using raw data as scores, stratified by Baseline MIDAS grade (grades I and II were pooled).
ITT = Intention-to-treat; SD = Standard Deviation

Results for all of the secondary efficacy variables were comparable between the 2 ZMT groups and each favored ZMT over usual non-triptan treatment. Compared to the usual non-triptan group, the number of work-hours lost over the 12-week study period and total productivity lost per treated migraine attack were significantly lower in the 2 ZMT groups. Although total productivity lost over the study period and the economic impact were lower in the 2 ZMT groups compared to the non-triptan group, the results did not reach statistical significance. On an annual basis, the mean economic loss resulting from migraine attacks was approximately $1026, $964, and $1295 in the ZMT 5-mg, ZMT 2.5-mg, and usual non-triptan groups, respectively.

Table S3 Secondary variables related to work-hours lost (ITT)

	Treatment group			P-value[a] for Usual non-triptan versus:	
	ZMT		Usual non-triptan	ZMT	
	5.0 mg	2.5 mg		5.0 mg	2.5 mg
Number of work-hours lost over 12-week study period[b]					
N	281	277	122		
Mean (SD)	5.6 (9.8)	5.8 (10.0)	8.5 (13.0)	0.0154	0.0264
Median (range)	1.8 (0.0-61.1)	1.2 (0.0-67.2)	2.8 (0.0-60.3)		
Total productivity lost (hours) per treated migraine attack					
N	277	278	120		
Mean (SD)	1.6 (2.0)	1.4 (1.5)	2.3 (3.2)	0.0133	0.0002
Median (range)	1.1 (0.0-20.0)	1.0 (0.0-9.5)	1.5 (0.0-26.0)		
Total productivity lost (hours) over the 12-week study period[b]					
N	277	277	120		
Mean (SD)	11.3 (14.5)	11.2 (14.7)	14.2 (16.3)	0.1027	0.0906
Median (range)	6.4 (0.0-101.8)	6.0 (0.0-95.9)	8.4 (0.0-73.0)		
Economic impact of therapy (dollars) over the 12-week study period					
N	277	276	120		
Mean (SD)	236.1 (349.5)	221.9 (334.4)	298.0 (407.8)	0.1618	0.0701
Median (range)	132.9 (0.0-2932.4)	104.9 (0.0-2510.2)	170.2 (0.0-2102.4)		

[a] Monte Carlo estimate of exact p-value from permutation test using raw data as scores, stratified by Baseline MIDAS grade (grades I and II were pooled).

[b] Normalized to 84 days

ITT = Intention-to-treat; SD = Standard deviation

In addition, meaningful migraine relief tended to occur faster in the 2 ZMT groups compared to usual non-triptan therapy; statistical significance versus the non-triptan group was achieved for both ZMT groups, primarily for attacks in the second 6-week study period. The percent of attacks with meaningful migraine relief within 2 hours of study treatment was 64%, 61%, and 53% for the ZMT 5-mg, ZMT 2.5-mg, and usual non-triptan groups, respectively. Significantly more than half of the patients in the ZMT 5-mg group (76%) and the ZMT

2.5-mg group (80%) preferred ZMT over their most recent previous migraine medication ($p<0.0001$ for each ZMT group).

Safety results

The ZMT 5-mg and 2.5-mg treatment regimens as well as the non-triptan and triptan usual therapies for the treatment of migraine attacks were safe and generally well tolerated. A higher percentage of patients in the ZMT groups experienced AEs compared to the usual therapy groups; however, most events were of mild to moderate intensity. Although the pattern of AEs at the attack level was similar to that observed at the patient level, the incidence of AEs at the attack level was substantially smaller (reduced by more than half) than that observed at the patient level for each treatment group. The incidence of AEs in the ZMT groups appeared to be dose-dependent. Of the AEs that occurred within 24 hours after taking study medication, AEs led to withdrawal from the study of 19 ZMT 5-mg patients, 8 ZMT 2.5-mg patients, and 1 usual triptan patient; most of these AEs were of mild to moderate intensity. Six SAEs occurred (4 in the ZMT 5-mg group, and 1 each in the ZMT 2.5-mg and usual triptan groups), but none were considered by the investigators to be related to study medication. There were no deaths during the study.

Table S4 Number (%) of patients who had at least 1 adverse event in any category (safety analysis set)

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]			
	ZMT		Usual	
	5 mg n=299	2.5 mg n=296	non-triptan n=123	triptan n=164
Any adverse events[b]	105 (35.1)	61 (20.6)	15 (12.2)	27 (16.5)
Serious adverse events[c]	4 (1.3)	1 (0.3)	0	1 (0.6)
Serious adverse events leading to death	0	0	0	0
Serious adverse events not leading to death	4 (1.3)	1 (0.3)	0	1 (0.6)
Study medication–related adverse event	73 (24.4)	36 (12.2)	4 (3.3)	13 (7.9)
Discontinued study due to adverse events	19 (6.4)	8 (2.7)	0	1 (0.6)

[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] The onset of an adverse event was within 24 hours after taking study medication.
[c] The onset of a serious adverse event could be any time after taking study medication.

Table S5 Number (%) of patients with the most commonly reported[a] adverse events by body system and preferred term (safety analysis set)

Body system	ZMT		Usual	
COSTART preferred term	5 mg n=299	2.5 mg n=296	non-triptan n=123	triptan n=164
Nervous system				
Dizziness	20 (6.7)	13 (4.4)	5 (4.1)	6 (3.7)
Paresthesia	16 (5.4)	11 (3.7)	1 (0.8)	0
Somnolence	14 (4.7)	5 (1.7)	1 (0.8)	1 (0.6)
Nervousness	6 (2.0)	0	0	0
Body as a whole				
Asthenia	19 (6.4)	5 (1.7)	0	2 (1.2)
Tightness	12 (4.0)	6 (2.0)	2 (1.6)	4 (2.4)
Pain	10 (3.3)	3 (1.0)	0	0
Digestive system				
Nausea	17 (5.7)	9 (3.0)	4 (3.3)	7 (4.3)
Dry mouth	8 (2.7)	2 (0.7)	1 (0.8)	0
Respiratory system				
Pharyngitis	10 (3.3)	4 (1.4)	2 (1.6)	1 (0.6)
Cardiovascular system				
Vasodilatation	6 (2.0)	4 (1.4)	1 (0.8)	3 (1.8)

[a] This table uses a cut-off of ≥2% in any treatment group.
The onset of an adverse event was within 24 hours after taking study medication; the onset of a serious adverse event could be any time after taking study medication.

Conclusion(s)

- Over the 12-week study period, significantly fewer mean work-hours were lost per migraine attack in both ZMT groups (5 mg = 0.8 hours, 2.5 mg = 0.7 hours) compared to the usual non-triptan group (1.3 hours).
- Total work productivity lost per treated migraine attack was significantly lower in the ZMT 5 mg group (1.6 hours) and 2.5 mg group (1.4 hours) compared to usual non-triptan treatment (2.3 hours).
- Patients demonstrated a significantly higher preference for ZMT (76% to 80%) over their most recent previous migraine medication; the preference was consistent (up to 90%) across individual preference categories.

- Mean total economic cost due to productivity loss for ZMT treatment was about 60 to 80 US dollars lower than for usual non-triptan treatment over the 12-week study period (approximately $270 to $330 on an annual basis).
- Meaningful migraine relief tended to occur faster in the 2 ZMT groups compared to usual non-triptan therapy.
- Patients treated with ZMT lost fewer mean total hours of household and leisure activities, and were less of a burden on family members compared with patients in the usual non-triptan therapy group over the 12-week study period.
- The need for escape medication, including a second dose of study medication, was lower in the ZMT groups compared to usual non-triptan treatment.
- Patients treated with ZMT experienced no treatment-related SAEs in this study. Most AEs were transient and of mild to moderate intensity.

Date of the report

10 April 2006