AstraZeneca

Drug product	Zomig®	**SYNOPSIS**	
Drug substance(s)	Zolmitriptan		
Study code	311CUS/0012		
Date	22 June 2006		

An Open, Randomized, Parallel-Group, Multicenter Study to Compare a Stratified Care Treatment Regimen based on Migraine Disability (MIDAS grade) versus Standard Therapy for the Acute Treatment of Migraine Headache

International coordinating investigator

Not applicable.

Study center(s)

This study was conducted in the US (613 investigators at primary care sites enrolled patients).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	25 July 2000	IV
Last patient completed	27 December 2002	

Objectives

The primary objective was to compare a stratified care treatment regimen based on the Migraine Disability Assessment (MIDAS) Grade, to standard therapy for the acute treatment of migraine headache.

Study design

This was an open-label, randomized, multicenter study. The study was conducted at 613 primary care sites in the United States.

Target patient population and sample size

Adult men and women, aged 18 to 65 years inclusive, with an established diagnosis of migraine as defined by the International Headache Society (IHS) criteria, were enrolled.

Patients were new to prescription pharmacological care for migraine or had not been receiving any triptan care in the past 3 months.

Study drug and comparator(s): dosage, mode of administration and batch numbers

Treatment for migraine headache (triptans, analgesics or a combination thereof) was prescribed by the investigator. For patients randomized to stratified care, the Sponsor provided for the cost of zolmitriptan (up to 18 tablets) and for generic Fioricet, Fiorinal, Midrin, and naproxen.

Duration of treatment

Patients treated their migraine headaches over a 3-month period. The total duration of the study was 12 months (a 9-month enrollment period).

Criteria for evaluation (main variables)

Efficacy variables

Primary variable: Improvers (patients whose final MIDAS score dropped by 50% or more when compared to their baseline MIDAS score) based on the MIDAS questionnaire.

Main secondary variables:

1. Change in migraine disability score from baseline to the end of the study treatment period, based on the MIDAS questionnaire.

2. Change in migraine-specific quality of life score from baseline to the end of the study treatment period, based on the physical and mental component scores of the 36-item short-form health survey questionnaire (SF-36).

3. Subject-rated global rating of treatment satisfaction.

Safety variables

1. Incidence of treatment-related adverse events leading to patient withdrawal.

2. Incidence, nature and severity of all serious adverse events (SAEs) (only patients who received zolmitriptan).

Patient-reported outcomes (PRO)

Pharmacoeconomics (healthcare utilization) of stratified care treatment regimen vs standard care as measured by self-reported visits to primary care physicians and specialists/neurologists, ER visits, diagnostic procedures (MRI, CT scans) corrected for education, salary range, employer or industry, insurance co-payment, and job information.

Statistical methods

The primary efficacy variable was assessed as the percent of patients in each treatment group who were classified as improvers. All binary data were analyzed using logistic regression, with the model including terms for treatment regimen, region, and baseline MIDAS grade. An analysis of covariance (ANCOVA) was used to assess the continuous response secondary endpoints including the change from baseline in MIDAS score and SF-36. This model included terms for treatment regimen, region, baseline MIDAS grade (except for MIDAS score), and baseline response value as covariates. Subject-rated global rating of treatment satisfaction was analyzed using Cochran-Mantel-Haenszel testing controlling for region and baseline MIDAS grade. As an exploratory analysis, the effects of other variables, including sex, race, age, and time of study treatment (relative to onset of migraine headache) on the primary endpoint, were investigated individually, together with their interactions with treatment. Descriptive statistics were provided for the subgroup analyses.

Patient population

A total of 2864 patients were randomized (stratified care n=1320; standard care, n=1544) and 1811 were included in the intent-to-treat (ITT) population (stratified care, n=825; standard care, n=986). The majority of patients in both treatment groups had baseline MIDAS grades III or IV. Approximately 92% of patients in the ITT population completed the study. The most frequent reason for study discontinuation was failure to respond (approximately 6% of the ITT population). Average age at onset of migraine headaches in the ITT population was 22 (range 1-83) years and average number of migraine headaches was 7 headaches per month. Demographic characteristics of the patient population are shown in Table S1. Demographic and baseline characteristics, as well as the proportion of patients completing the study, were similar in the stratified and standard care treatment groups.

Table S1 Demographic and baseline characteristics (ITT population)

Characteristic	Stratified (n=825)	Standard (n=986)	Total (n=1811)
Age at entry (years)	(n=821)	(n=979)	(n=1800)
Mean (SD)	37.94 (10.92)	38.75 (11.27)	38.38 (11.11)
Range	14-76	15-83	14-83
Sex (n and % of patients)	(n=823)	(n=984)	(n=1807)
Female	715 (86.88%)	874 (88.82%)	1589 (87.94%)
Male	108 (13.12%)	110 (11.18%)	218 (12.06%)
Race (n and % of patients)	(n=821)	(n=984)	(n=1805)
White	668 (81.36%)	809 (82.22%)	1477 (81.83%)
Black	65 (7.92%)	71 (7.22%)	136 (7.53%)
Asian	24 (2.92%)	15 (1.52%)	39 (2.16%)
Hispanic	55 (6.70%)	77 (7.83%)	132 (7.31%)
Other	9 (1.10%)	12 (1.22%)	21 (1.16%)

Efficacy results

Results of the primary efficacy outcome are summarized in Table S2. Results of key secondary outcomes in the overall ITT population and in patients with baseline MIDAS grades III and IV only (a pre-planned secondary analysis) are summarized in Table S3.

Table S2 Number (%) of patients classified as MIDAS score improvers (≥50% improvement in MIDAS score) overall and in patients with baseline MIDAS grades III and IV only (ITT population)

Parameter	Stratified (n=825)[a]		Standard (n=986)[a]		Stratified vs. standard		
	n/N	%[b]	n	%[b]	Odds ratio	95% CI	p-value
ITT population	366/778	47.04	355/949	37.41	1.496	1.232, 1.818	<0.0001
Baseline MIDAS grades III and IV only	334/675	49.48	324/831	38.99	1.531	1.245, 1.883	<0.0001

[a] Total number of patients in the ITT analysis set in each treatment group.
[b] Denominator is the number of patients in each treatment group with data reported.
Note: Odds ratio is ratio of the odds of MIDAS score improving ≥50% for stratified care versus standard care.

Table S3 Summary of key secondary variables in the overall population and in patients with baseline MIDAS grades III and IV (ITT population)

	Stratified (n=825)[a]	Standard (n=986)[a]			
Mean MIDAS score					
	LS mean change from baseline		**Difference in LS mean change Stratified minus standard**	**95% CI**	**p-value**
Overall ITT population					
	(n=781)[b]	(n=950)[b]			
	-14.60	-10.71	-3.89	-6.47, -1.31	0.0031
MIDAS grades III and IV only					
	(n=675)[b]	(n=831)[b]			
	-17.30	-12.35	-4.95	-7.86, -2.04	0.0009
Subject-rated global evaluation, n (%)			**p-value stratified vs. standard care overall**		
Overall ITT population					
	(n=806)[b]	(n=971)[b]	0.1568		
Excellent	227 (28.16%)	252 (25.95%)			
Good	319 (39.58%)	378 (38.93%)			
Satisfactory	155 (19.23%)	216 (22.25%)			

Table S3 Summary of key secondary variables in the overall population and in patients with baseline MIDAS grades III and IV (ITT population)

	Stratified (n=825)[a]	Standard (n=986)[a]			
Poor	105 (13.03%)	125 (12.87%)			
MIDAS grades III and IV only					
	(n=698)[b]	(n=847)[b]	0.0496		
Excellent	205 (29.37%)	222 (26.21%)			
Good	271 (38.83%)	320 (37.78%)			
Satisfactory	132 (18.91%)	192 (22.67%)			
Poor	90 (12.89%)	113 (13.34%)			
SF-36 score for mental and physical component[c]					
	LS mean change from baseline		**Difference in LS mean change Stratified minus standard**	**95% CI**	**p-value**
Overall ITT population					
Mental score	(n=772)[b]	(n=940)[b]			
	2.26	1.91	0.34	-0.52, 1.20	0.4351
Physical score	(n=772)[b]	(n=940)[b]			
	3.08	1.84	1.23	0.52, 1.95	0.0007
MIDAS grades III and IV only					
Mental score	(n=666)[b]	(n=820)[b]			
	2.55	1.84	0.71	-0.24, 1.66	0.1429
Physical	(n=666)[b]	(n=820)[b]			
	3.55	2.01	1.55	0.77, 2.32	<0.0001

[a] Number of patients in the overall ITT population.
[b] Number of patients in indicated categories with data reported.
[c] A positive mean change from baseline indicates an improvement from baseline at the final visit.
LS Least squares.

- A statistically significantly higher percentage of patients in the overall ITT population and patients with baseline MIDAS grades III and IV receiving stratified care were classified as MIDAS score improvers (≥50% improvement from baseline in MIDAS score) compared with those receiving standard care (47% vs. 37%, respectively, p<0.0001 for the ITT population; 49% vs. 39%, p<0.0001, respectively, for patients with baseline MIDAS grades III and IV only).

- Mean change from baseline in MIDAS score at the final visit was statistically significantly better in patients in the overall ITT population and patients with baseline MIDAS grades III and IV only who received stratified care compared with the respective populations receiving standard care (the estimated treatment difference was -3.89, 95% CI -6.47, -1.31, p=0.0031 for the overall ITT population;

-4.95, 95% CI -7.86, -2.04, p=0.0009 for patients with baseline MIDAS grades III and IV only).

- Subject-rated global evaluation scores were statistically significantly higher in patients with baseline MIDAS grades III and IV only receiving stratified care compared with those receiving standard care (approximately 29% and 39% patients receiving stratified care vs. approximately 26% and 38% of patients receiving standard care had ratings of excellent or good at the final visit, p=0.0496).

- SF-36 physical component scale scores were statistically significantly more improved in patients in the overall ITT population and patients with baseline MIDAS grades III and IV at baseline only who received stratified care compared with those receiving standard care (p=0.0007 and p<0.0001, respectively).

- Escape medication and time to escape medication use were similar between the stratified and standard care treatment groups.

- The ability to function after treatment was similar between the stratified and standard care treatment groups.

- There were no apparent differences between patients receiving stratified and standard care treatment with regard to any pharmacoeconomic parameters.

Safety results

There were a total of 6 SAEs reported for patients receiving zolmitriptan during this study, all of which occurred in patients receiving stratified care. Two of these SAEs, chest pain and asthma, were considered by the investigator to be related to study treatment, and led to discontinuation from the study.

There were a total of 17 discontinuations due to AEs (DAEs) during this study (including all ITT patients, those who took zolmitriptan, as well as those who did not) (12 [1.48%] patients receiving stratified care and 5 [0.51%] patients receiving standard care): 13 patients discontinued the study due to treatment-related AEs (as considered by the investigator) and an additional 4 patients who discontinued the study due to non-treatment-related AEs (as considered by the investigator).

Conclusions

- Stratified care based on MIDAS grade for the acute treatment of migraine headache was statistically significantly superior to standard care for the primary and most secondary endpoints for the overall population (all MIDAS grades) and especially for patients with baseline MIDAS grades III and IV only.

- Both stratified and standard care regimens that included zolmitriptan treatment were well tolerated with regard to the incidence of DAEs and the incidence, nature, and severity of SAEs reported.

- These results suggest that the use of stratified care based on baseline MIDAS score as part of a prescribed treatment regimen is superior to standard care.

Date of the report

22 June 2006