SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: ZOMIG™ 2.5 mg tablet

ACTIVE INGREDIENT: Zolmitriptan

Trial title (number): DISC Trial. An Open, Randomised, Parallel-Group, Multicentre Trial to Compare the Efficacy of a Stratified Treatment Regimen for Acute Migraine Attacks, in which Patients Receive Therapy According to the Grade of their Migraine Disability at Baseline, Assessed by the MIDAS Questionnaire, with that of 2 Other Treatment Regimens, in which Patients Receive Standard Therapy that may be altered after 3 Attacks (Stepped Care) or within Individual Attacks (Staged Care) (311CIL/0081)

Clinical phase: IIIb

First subject recruited: 16 December 1997
Last subject completed: 10 March 1999
Zeneca approval date: 18 August 1999

Publications: No publications based on this trial to date.

OBJECTIVES

The primary objective of this trial was to compare the efficacy of a stratified care treatment regimen with stepped care and staged care regimens in the acute treatment of migraine by assessing: the disability time per attack (defined as the product of the level and duration of disability in the period between 0 and 4 hours after dosing); the attack response rate over 6 treated migraine headaches, as assessed at 2 hours after dosing (a positive response is defined as a reduction in headache intensity from severe or moderate to mild or no pain or from mild to no pain).

The secondary objective of this trial was to compare the efficacy of a stratified care treatment regimen with stepped and staged care regimens in the acute treatment of migraine by assessing: attack response rate with regard to headache intensity assessed at 1 and 4 hours after dosing; proportion of attacks pain-free 2 hours after dosing over 6 attacks; area under the pain relief versus time curve (0 to 4 hours after dosing) per attack; proportion of attacks with meaningful migraine relief (MMR) by 1, 2 and 4 hours after dosing, duration of disability per attack; lost work time per attack occurring during work time; proportion of patients withdrawing from each treatment regimen from the point of randomisation; proportion of patients with good or excellent rating of overall patient satisfaction.

METHODS

Design: This was a randomised, open, parallel-group, international, multicentre trial.

Population: The trial had a projected inclusion figure of 900 patients and a total of 1109 patients were screened. A total of 1062 patients were randomised to one of three treatment arms for a maximum of 6 attacks or until the date of close of recruitment, whichever was the earlier. Altogether, 354 patients were randomised to receive stratified care (treatment with acetylsalicylic acid plus metoclopramide for patients with migraine disability assessment [MIDAS] grade II at baseline and treatment with zolmitriptan for patients with MIDAS grades III or IV at baseline), 352 were randomised to receive stepped care (treatment with acetylsalicylic acid plus metoclopramide with assessment for step-up to zolmitriptan after 3 attacks, depending on attack response) and 356 were randomised to receive staged care (treatment with acetylsalicylic acid plus metoclopramide with the opportunity, after 2 hours, to use zolmitriptan if the headache was moderate or severe). The safety population comprised 930 patients who treated at least one migraine attack. A total of 835 patients were included in the intention-to-treat (ITT) population which excluded patients who did not complete any diary cards and those who were affected by a MIDAS grade change protocol amendment which resulted in the misgrading of 98 patients. Treatment regimens were balanced according to MIDAS grades.

Key inclusion criteria: Established diagnosis of migraine; 1 migraine headache per month in the 3 months before the trial; no 5-hydroxytryptamine $(HT)_{1B/1D}$ receptor agonists taken in the 3 months before the trial; non-migraine headaches on <10 days per month in the 6 months before the trial; migraine-related disability of MIDAS grades II, III or IV (assessed by completion of the MIDAS questionnaire).

Key exclusion criteria: History of basilar, ophthalmoplegic or hemiplegic migraine headache; history or symptoms suggestive of ischaemic heart disease or other vascular disease; previous cerebral vascular accident or transient ischaemic attacks; systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg; unacceptable adverse experience following previous use of trial medication (or other 5-$HT_{1B/1D}$ receptor agonists); current or anticipated use of methysergide or methylergonovine in the 2 weeks before, or during, the trial.

Dosage: In all regimens, the treatments and doses used were oral acetylsalicylic acid 800 to 1000 mg and metoclopramide 10 mg (as free or fixed combination), and oral zolmitriptan 2.5 mg.

Key assessments: Patients used diary cards to record data on their migraine headache before and at 1, 2 and 4 hours after taking treatment. Details of concomitant medication and patient overall satisfaction with the treatment regimen were also recorded. The primary analysis was carried

out on an ITT basis. Misgraded patients were analysed as a subgroup using the same assumptions as for the ITT population. In addition to the ITT analysis, per-protocol and all-randomised analyses were carried out on the primary endpoints.
The primary endpoints for analysis were: disability time per attack and attack response rate over 6 treated migraine headaches, as assessed at 2 hours after dosing;. The secondary endpoints were: attack response rate with regard to headache intensity assessed at 1 and 4 hours after dosing; proportion of attacks pain-free 2 hours after dosing over 6 attacks; area under the pain relief versus time curve (0 to 4 hours after dosing) per attack; proportion of attacks with MMR by 1, 2 and 4 hours after dosing; duration of disability per attack; lost work time per attack occurring during work time; proportion of patients withdrawing from each treatment regimen from the point of randomisation; and the proportion of patients with good or excellent rating of overall satisfaction.
The safety of the treatment regimens was assessed by recording the incidence and severity of any adverse events occurring during the trial.
To allow for the repeated observations per patient, continuous data were analysed using a random effects analysis of variance and discrete data were analysed using a generalised linear mixed model using the SAS macro GLIMMIX. Both approaches adjusted for the effects of baseline covariates (eg pre-dose headache intensity or disability), country, MIDAS grade, attack number and patient. Treatment effects were found to differ between attacks 1 to 3 and attacks 4 to 6, mainly due to differences in the stratified versus stepped comparison across these two attack groups. Results were presented separately for these groups of attacks together with an average of these two results (overall, attacks 1 to 6).

RESULTS
Demography: The demography of the ITT population was well balanced across all treatment arms.
Efficacy: Both primary endpoints, disability time and attack response rate, were significantly better in the stratified care regimen averaged over all attacks compared with the stepped care ($p<0.001$) and the staged care ($p<0.001$) regimens (Tables I-IV). The majority of any advantage of stratified care over stepped care was due to the difference in outcome over the first 3 attacks. While the majority of the advantage over staged care was due to differences in outcomes over the first 2 hours of each attack. There was a trend for patients with higher MIDAS scores to treat attacks when ‘severe’ rather than ‘moderate’ and this was reflected across all the treatment arms. Results from secondary endpoints supported findings for the primary endpoints.

Table I Mean AUC for disability[a] per patient: ITT population

Attacks Treatment regimen	MIDAS grade							
	All grades		II		III		IV	
	N	Mean (mm.h)	N	Mean (mm.h)	N	Mean (mm.h)	N	Mean (mm.h)
Overall								
Stratified care	276	185.0	67	166.6	102	177.7	107	203.4
Stepped care	271	209.4	64	193.2	97	202.9	110	224.6
Staged care	285	199.7	76	198.6	105	190.3	104	210.0
Attacks 1 to 3								
Stratified care	275	176.0	67	154.4	102	169.9	106	195.7
Stepped care	271	218.5	64	200.1	97	210.2	110	236.4
Staged care	284	196.1	76	196.8	104	186.8	104	204.9
Attacks 4 to 6								
Stratified care	216	188.3	54	184.8	74	178.3	88	198.9
Stepped care	218	196.8	49	176.7	81	195.8	88	208.9
Staged care	211	202.7	55	205.6	80	186.9	76	217.1

[a]Defined as the product of the level and duration of disability in the period between 0 and 4 hours after dosing.
N Number of patients per treatment arm and MIDAS grade.
ITT Intention-to-treat.
AUC Area under the curve.
MIDAS Migraine disability assessment.

Table II Statistical analysis of mean AUC for disability[a] per patient: ITT population

Comparison	Actual mean	Least squares mean	Treatment effect[b]	95% CI	p-Value
Overall					
Stratified vs	185.0	184.0	-21.25	(-31.44, -11.07)	<0.001
stepped care	209.4	205.2			
Stratified vs	185.0	184.0	-19.43	(-29.73, -9.14)	<0.001
staged care	199.7	203.4			
Attacks 1 to 3					
Stratified vs	176.0	180.4	-42.61	(-54.01, -31.21)	<0.001
stepped care	218.5	223.0			
Stratified vs	176.0	180.4	-20.79	(-31.93, -9.65)	<0.001
staged care	196.1	201.2			
Attacks 4 to 6					
Stratified vs	188.3	187.5	0.10	(-13.27, 13.48)	0.988
stepped care	196.8	187.4			
Stratified vs	188.3	187.5	-18.08	(-30.38, -5.78)	0.004
staged care	202.7	205.6			

[a]Defined as the product of the level and duration of disability in the period between 0 and 4 hours after dosing.
[b]Difference in least squares means.
CI Confidence interval.

Table III Attack response rate[a] over 6 treated migraine headaches, as assessed at 2 hours after dosing: ITT population

Attacks	Treatment regimen	Proportion of attacks responding[a] (%[b])							
		MIDAS grade							
		All grades		II		III		IV	
Overall	Stratified care	731/1388	(52.7)	171/324	(52.8)	282/492	(57.3)	278/572	(48.6)
	Stepped care	553/1363	(40.6)	147/312	(47.1)	213/492	(43.3)	193/559	(34.5)
	Staged care	498/1368	(36.4)	135/356	(37.9)	209/508	(41.1)	154/504	(30.6)
1 to 3	Stratified care	421/770	(54.7)	97/176	(55.1)	168/281	(59.8)	156/313	(49.8)
	Stepped care	247/758	(32.6)	73/179	(40.8)	97/270	(35.9)	77/309	(24.9)
	Staged care	299/768	(38.9)	80/206	(38.8)	125/284	(44.0)	94/278	(33.8)
4 to 6	Stratified care	310/618	(50.2)	74/148	(50.0)	114/211	(54.0)	122/259	(47.1)
	Stepped care	306/605	(50.6)	74/133	(55.6)	116/222	(52.3)	116/250	(46.4)
	Staged care	199/600	(33.2)	55/150	(36.7)	84/224	(37.5)	60/226	(26.5)

[a]A positive response was defined as a reduction in headache intensity from severe or moderate to mild or no headache pain or from mild to no pain.

[b]Percentage of ITT attacks with data.

2 hours represents the period 91 to 180 minutes after dosing.

ITT Intention-to-treat.

MIDAS Migraine disability assessment.

Table IV Statistical analysis of attack response rate[a] over 6 treated migraine headaches, as assessed at 2 hours after dosing: ITT population

Comparison	Actual response rate	Estimated response rate	Odds ratio	95% CI	p-Value
Overall					
Stratified vs	0.527	0.492	1.67	(1.31, 2.12)	<0.001
stepped care	0.406	0.367			
Stratified vs	0.527	0.492	2.14	(1.66, 2.77)	<0.001
staged care	0.364	0.311			
Attacks 1 to 3					
Stratified vs	0.547	0.512	2.91	(2.18, 3.87)	<0.001
stepped care	0.326	0.265			
Stratified vs	0.547	0.512	2.05	(1.55, 2.72)	<0.001
staged care	0.389	0.338			
Attacks 4 to 6					
Stratified vs	0.502	0.473	0.96	(0.71, 1.30)	0.793
stepped care	0.506	0.483			
Stratified vs	0.502	0.473	2.24	(1.64, 3.07)	<0.001
staged care	0.332	0.286			

[a]A positive response was defined as a reduction in headache intensity from severe or moderate to mild or no headache pain or from mild to no pain.
2 hours represents the period 91 to 180 minutes after dosing.
ITT Intention-to-treat.
CI Confidence interval.

Safety: All randomised patients who received at least one dose of study medication for an attack were included in the safety analysis (N = 930).
1. Overall safety: The number of adverse events reported across all attacks was higher in the stratified care regimen (19.5%) compared with the stepped care (9.7%) and staged care (13.1%) regimens. This trend was reflected in the number of drug-related adverse events; stratified care (16.8%), stepped care (6.4%) and staged care (11.0%) but not in the number of attacks leading to withdrawal due to an adverse event; stratified care (3.3%), stepped care (2.9%) and staged care (3.8%). In the stratified regimen, more adverse events were reported during attacks by the MIDAS grade III and IV patients (23.0%) compared with the grade II patients (6.7%). The most common adverse events reported (frequency >2%) were those usually seen following treatment with 5-$HT_{1B/1D}$ receptor agonists, with nausea being the highest at 2.6%. There were no unexpected adverse events reported at a frequency of >2%.
2. Serious adverse events: 8 patients reported serious adverse events after having taken at least one dose of trial medication (however, any temporal relationship for patient 311CIL/0081/0152/0001 cannot be confirmed). The incidence of serious adverse events in the stratified care regimen (0.1%) was similar to that reported in the stepped care (0.2%) and staged care (0.2%) regimens.

3. Withdrawals due to adverse events: The proportion of patients withdrawn due to adverse events was similar in the 3 arms: stratified care (3.3%), stepped care (2.9%) and staged care (3.8%).