CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-231

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA:	21-231 JAN 24 2001
Drug Name:	[redacted] (zolmitriptan)
Indication:	[redacted]
Sponsor:	AstraZeneca
Clinical Reviewer:	Armando Oliva, M.D.
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1. Introduction

ZOMIG® is currently marketed for the acute treatment of migraine with or without aura in adults. The original ZIMIG® Tablets NDA (NDA 20-768) was approved on November 26, 1997. The current submission provides application of supporting the use of [redacted] for the acute treatment of migraine with or without aura in adults. In this review, Study 311CIL/0107 will be discussed.

> **Study 311CIL/0107** was a randomized, double-blind, placebo-controlled, parallel group, multi-center trial comparing zolmitriptan 2.5 mg with placebo in the treatment of a single migraine attack conducted in Canada, South Africa, and the UK.

2. Study 311 CIL/0107

2.1. Objective

The primary objective was to evaluate the efficacy of zolmitriptan (2.5 mg orally disintegrating tablet) in the acute treatment of migraine.

2.2. Efficacy Measures

The efficacy measure was headache rating scale, which was defined as severe, moderate, mild, or none. The primary endpoint was headache response 2 hours after dosing. Headache response was defined as an improvement of migraine headache from severe or moderate pain to mild or no pain.

Secondary endpoints include headache response at 0.5, 1, and 4 hours after the first dosing; pain-free at 1, 2, and 4 hours after dosing; one rank decrease on the migraine headache rating scale at 0.5 and 1 hour after dosing; patient preference, defined as whether the patient preferred the orally disintegrating tablet taken in this trial to normal tablets; and adverse events.

2.3. Study Design

This was a randomized, double blind, placebo-controlled trial. After an initial screening visit, each patient treated a single migraine of moderate or severe headache pain with double-blind medication (typically within 6 weeks of randomization), completed a diary card, and revisited the investigation site within 2 weeks after treatment. Double-blind trial medication was either orally disintegrating zolmitriptan (up to two 2.5 tablets separated by at least 2 hours) or orally disintegrating placebo tablets. If sufficient relief was not obtained within 2 hours of administration of the first dose, a second dose or escape medication, as predetermined by consultation with each patient's investigator, was taken at the patient's discretion.

Patients who did not contact the trial center within 6 weeks of randomization were contacted to determine whether they treated a migraine or to reconfirm their willingness to continue in the trial. Those who did not treat a migraine within 6 weeks after reconfirming their participation were withdrawn from the trial.

2.4. Statistical Analysis Plan

The primary efficacy parameter was the proportion of patients in each treatment group with a headache response 2 hours after the first dosing if no further treatments were administered before assessment. The primary efficacy analysis was a logistic regression using PROC LOGISTIC in SAS performed on the intention-to-treat (ITT) population. The analysis model will include the effects of treatment, center and treatment-by-center interaction.

Secondary efficacy parameters include the proportion of patients with a headache response at 0.5, 1, and 4 hours after the first dosing if no further treatments were administered before assessment; the proportion of patients in each treatment group who were pain-free at 1, 2, and 4 hours after the first dosing if no further treatments were administered before assessment; the proportion of patients with a decrease in headache pain of at least one rank from the time of first dosing to 0.5 and 1 hour; the proportion of patients who preferred trial medication over the migraine medication normally taken; and incidence, intensity, seriousness, and relationship of adverse events. Secondary analyses, except the incidence, intensity, seriousness, and relationship of AEs, were logistic regression analyses performed on the ITT population.

2.5. Patient Population

2.5.1. Demographic

A total of 573 patients were randomized, 291 to zolmitriptan 2.5 mg (orally disintegrating tablet) and 282 to placebo. Of these, 102 patients did not treat an attack, 60 patients were randomized to zolmitriptan 2.5 mg, and 42 patients were randomized to placebo. Therefore, a total of 471 patients

treated an attack. The safety population included 471 patients, 231 patients in the zolmitriptan 2.5 mg group and 240 patients in the placebo group. One patient randomized to placebo withdrew consent after treating a migraine and did not have any post dose efficacy assessments; therefore, this patient was excluded from the intention–to–treat (ITT) population. The ITT population included 470 patients, 231 patients in the zolmitriptan 2.5 mg group and 239 patients in the placebo group. The per–protocol (PP) population included 450 patients, 219 patients in the zolmitriptan 2.5 mg group and 231 patients in the placebo group. No patients were misrandomized.

Demographic characteristics of patients enrolled in this trial are summarized in Table 2.5.1.1; migraine histories and baseline characteristics are summarized in Table 2.5.1.2. There were no appreciable differences in demography, migraine histories, or baseline characteristics between treatment groups. More patients in both treatment groups treated migraines with moderate headache pain (zolmitriptan 72%, placebo 70%) than severe headache pain (zolmitriptan 27%, placebo 30%).

Nausea, photophobia, and phonophobia historically accompanied migraine attacks in patients in both treatment groups, and a majority of patients always or sometimes experienced aura with migraines. At baseline in this study, nausea was experienced by approximately half the patients in both treatment groups; photophobia and phonophobia were each experienced by a majority of patients in both treatment groups; auras were experienced by less than 25% of patients in both treatment groups.

Table 2.5.1.1. Demographic Configuration for All Patients (ITT Population)

Characteristic	Treatment group	
	Zolmitriptan	Placebo
Number of patients exposed	231	240
Age (y)		
Number of patients	231	239
Mean	41	42
SD	9.9	10.2
Range	18 - 62	18 - 62
Age distribution; number (%)[a] of patients		
18 to 39 y	98 (42)	90 (38)
40 to 65 y	133 (58)	149 (62)
Sex; number (%)[a] of patients		
Male	27 (12)	33 (14)
Female	204 (88)	206 (86)
Weight (kg)		
Number of patients	231	239
Mean	70	70
SD	15.1	16.0
Range	41 - 125	42 - 164
Height (cm)		

Number of patients	231	239
Mean	165	165
SD	8.9	8.4
Range	142 - 192	145 – 189
Race; number (%) of patients		
Caucasian	223 (97)	231 (97)
Other[b]	8 (3)	8 (3)

SD standard deviation.

[a] Percentages are based upon the number of patients in the ITT population

[b] Other includes Afro-Caribbean, Asian, Oriental, Mixed, and not otherwise classified.

Table 2.5.1.2. Migraine History and Baseline Characteristics (ITT Population)

Characteristic	Treatment group	
	Zolmitriptan	Placebo
Age at onset of migraine attacks (y)		
Number of patients	231	239
Mean	20	20
SD	9.4	10.3
Median	18	17
Range	3 - 49	4 - 46
Number of attacks per month in last 3 months		
Number of patients	231	239
Mean	8	8
SD	4.8	5.2
Median	6	6
Range	3 - 36	3 - 36
Average number of days of non-migraine headaches per month		
Number of patients	231	239
Mean	2	2
SD	1.8	1.8
Median	2	1
Range	0 - 6	0 - 6
Patients always experiencing aura; number (%) of patients	48 (21)	43 (18)
Patients never experiencing aura; number (%) of patients	105 (45)	114 (48)
Patients sometimes experiencing aura; number (%) of patients	78 (34)	82 (34)
Patients usually experiencing nausea; number (%) of patients		
Yes	202 (87)	203 (85)
No	29 (13)	36 (15)
Patients usually experiencing vomiting; number (%) of patients		
Yes	87 (38)	92 (38)
No	144 (62)	147 (62)
Patients usually experiencing photophobia; number (%) of patients		

Yes	202 (87)	217 (91)
No	29 (13)	22 (9)
Patients usually experiencing phonophobia; number (%) of patients		
Yes	191 (83)	190 (79)
No	40 (17)	49 (21)
Patients usually experiencing somnolence; number (%) of patients		
Yes	115 (50)	136 (57)
No	116 (50)	103 (43)
Patients usually experiencing dizziness; number (%) of patients		
Yes	77 (33)	83 (35)
No	154 (67)	156 (65)
Patients usually experiencing other symptoms; number (%) of patients		
Yes	67 (29)	83 (35)
No	164 (71)	156 (65)
Average duration of a typical migraine; number (%) of patients		
4 - 12 hours	27 (12)	39 (16)
>12 - 24 hours	70 (30)	82 (34)
>24 - 48 hours	78 (34)	61 (26)
>48 hours	56 (24)	57 (24)
Patients usually suffering recurrent attacks		
Yes	90 (39)	95 (40)
No	141 (61)	144 (60)
Headache pain at baseline		
Mild	1 (<1)	0 (0)
Moderate	167 (72)	168 (70)
Severe	63 (27)	71 (30)
Aura at baseline; number (%) of patients[a]		
Yes	52 (23)	56 (24)
No	172 (77)	180 (76)
Nausea at baseline; number (%) of patients[a]		
Yes	128 (56)	130 (54)
No	100 (44)	109 (46)
Photophobia at baseline; number (%) of patients[a]		
Yes	179 (78)	195 (82)
No	51 (22)	44 (18)
Phonophobia at baseline; number (%) of patients[a]		
Yes	143 (62)	167 (70)
No	88 (38)	70 (30)

[a] Number of patients with response may be less than total number of randomized patients.

2.5.2. Patient Disposition

One hundred and two patients withdrew from the trial before treating a migraine; 60 in the zolmitriptan treatment group and 42 in the placebo treatment group (Table 2.5.2). Table 2.5.2 presents the patients disposition.

Table 2.5.2. Patients Disposition (All Patients)

Reason for withdrawal	Number of patients (%)[a]					
	Zolmitriptan			Placebo	Total	
	N = 291			N = 282	N = 573	
	n	%	n	%	n	%
Patient lost to follow-up	6	2	8	3	14	2
Protocol non-compliance[b]	47	16	31	11	78	14
Withdrawal of consent	6	2	2	1	8	1
Other	1	<1	1	<1	2	<1
Total	60	21	42	15	102	18

[a] Percentages based upon the total number of patients randomized to each treatment group, N.
[b] Protocol non-compliance included patients who were withdrawn because they did not treat a migraine
attack within 12 weeks of receiving trial medication.

2.6. Sponsor's Analyses

Only patients who treated a migraine with severe or moderate headache pain and who received at least one efficacy assessment were included in ITT analyses. Patients with mild headaches were included in the analyses of pain-free and one point drop.

There were 573 randomized with 231 in zolmitriptan group and 240 in placebo group, respectively. There were 231 in zolmitriptan group and 239 in placebo in the ITT population.

2.6.1. Sponsor's Primary Analysis

The proportion of patients with headache response in the zolmitriptan treatment group exceeded the proportion of patients with headache response in the placebo treatment group by a statistically significant amount, 63% to 22% (odds ratio 6.1, 95% CI 4.0 to 9.3, $p<0.0001$) (Table 2.6.1).

Table 2.6.1. Headache Response at 2 Hours by Treatment Group (ITT Population)

Zolmitriptan treatment group N = 231		Placebo treatment group N=239		Statistical comparison of zolmitriptan versus placebo		
N	Headache Response n (%)a	N	Headache Response n (%)a	Odds ratio	95% CI	p-value
220	138 (63)	236	53 (22)	6.1	4.0, 9.3	<0.0001

a Percentages are based upon the total number of patients in the ITT reporting at 2 hours.
CI : Confidence interval.
Headache response is the diminution of headache pain from moderate or severe at the time of treatment to mild or none at the assessment.

Patients experienced a headache response if their assessment of headache pain was reduced from moderate or severe at the time of treatment to mild or none at assessment. The odds of experiencing a headache response 2 hours after treatment were 6.1 times more likely for patients treating with zolmitriptan relative to placebo. No appreciable differences in headache response among the per protocol population relative to the ITT population were observed.

2.6.2. Sponsor's Analyses on Secondary Endpoints

Headache response at 0.5, 1, and 4 hours after first dosing: the proportions of patients who responded at 0.5, 1, and 4 hours after first dosing are summarized in Table 2.6.2. Patients who administered a second treatment were treatment failures and were included in analyses at subsequent assessments as patients who did not experience a headache response. The odds of experiencing a headache response 0.5 hours after treatment were 1.7 times more likely for patients treating with zolmitriptan relative to placebo, 3.5 times more likely at 1 hour, and 6.3 times more likely at 4 hours. More patients in the zolmitriptan treatment group (40%) experienced a headache response through 24 hours after treatment with a single dose of trial medication when compared with patients in the placebo group (12%).

Pain-free at 0.5, 1, 2, and 4 hours after first dosing: The proportions of patients who were pain-free at 0.5, 1, 2, and 4 hours after first dosing irrespective of baseline intensity are summarized in Table 2.6.2. Patients administering a second treatment were counted as treatment failures for assessments subsequent to the second treatment. The odds of being free from headache pain after treating a moderate or severe migraine were 3.1 times more likely at 1 hour for patients treating with zolmitriptan relative to placebo, 4.7 times more likely at 2 hours, and 4.9 times more likely at 4 hours. More patients treating with zolmitriptan (23%) were pain-free through 24 hours after treatment with a single dose of trial medication than patients treating with placebo (7%).

One point decrease on the migraine headache rating scale: The proportions of patients with improved headache pain at 0.5, 1, 2, and 4 hours after first dosing are summarized in Table 2.6.2. Patients who administered a second treatment were treatment failures and were included in analyses at subsequent

assessments as patients who did not experience a headache response. The odds of an improvement in headache pain were 1.7 times more likely at 0.5 hour after treatment with zolmitriptan relative to placebo, 2.7 times more likely at 1 hour.

Table 2.6.2. Summary of Secondary Efficacy Parameters (ITT Population)

Time h	Zolmitriptan treatment group N = 231		Placebo treatment group N=239		Statistical comparison of zolmitriptan versus placebo		
	N	Headache Response n (%)a	N	Headache Response n (%)a	Odds ratio	95% CI	p-value
Headache response							
0.5	227	36 (16)	237	23 (10)	1.7	1.0, 3.1	.0538
1	224	101 (45)	232	45 (19)	3.5	2.3, 5.3	<0.0001
4	226	115 (51)	239	34 (14)	6.3	4.0, 9.8	<0.0001
Pain-free rate							
0.5	228	3 (1)	237	1 (<1)	NC	NC	NC
1	225	17 (8)	232	6 (3)	3.1	1.2, 7.9	0.0207
2	221	59 (27)	236	17 (7)	4.7	2.6, 8.4	<0.0001
4	227	84 (37)	239	26 (11)	4.9	3.0, 8.0	<0.0001
Improved headache pain rate							
0.5	228	51 (22)	237	36 (15)	1.7	1.0, 2.7	0.0385
1	225	115 (51)	232	67 (29)	2.7	1.8, 3.9	0.0001
2	221	146 (66)	236	70 (30)	NC	NC	NC
4	227	117 (52)	239	40 (17)	NC	NC	NC

a Percentages are based upon the total number of patients in the ITT reporting at each time interval.
CI Confidence interval.
Headache response is the diminution of headache pain from moderate or severe at the time of treatment to mild or none at the assessment.

Patients in the zolmitriptan group had a greater probability of achieving initial headache response within 4 hours than those in placebo group. For those patients who treated a migraine, the median time to second treatment (second dose or escape medication) was more than twice as long in the zolmitriptan group relative to placebo, 5 hours and 45 minutes versus 2 hours and 10 minutes.

2.6.3 Summaries of headache response at 2 hours by subgroup

Headache response at 2 hours was summarized by age group, gender, menses, weight group, intensity of headache pain at baseline, pretreatment headache duration, migraine onset while waking or sleeping, baseline aura, baseline nausea, baseline photophobia, and baseline phonophobia. No clinically significant differences in headache response between subgroups were observed except for baseline intensity and baseline photophobia.

Table 2.6.3. Headache Response at 2 Hours by Baseline Characteristics

Baseline characteristic	Zolmitriptan	Placebo
	% patients with headache response	% patients with headache response
Age group		
18-39 y	59	24
40-65 y	65	21
Sex		
Male	70	18
Female	62	23
Menses		
With	57	21
Without	62	23
Weight group		
50-80 kg	62	20
>80 kg	66	31
Baseline intensity		
Moderate	68	25
Severe	48	16
Migraine duration		
0-30 min	54	23
30-60 min	57	34
1-2 hr	60	19
2-4 hr	69	20
>4 hr	78	17
Onset		
On waking	62	22
Female	64	23
Baseline aura		
With	63	29
Without	63	21
Baseline nausea		
With	59	18
Without	67	28
Baseline photophobia		
With	59	23
Without	77	21
Baseline phonophobia		
With	59	19
Without	68	31

2.7. Reviewer's Analyses

2.7.1. Analyses on Headache Response, Pain-free, and One Point Decrease

The sponsor reported the results using logistic regression with terms for baseline intensity, treatment, and country. This reviewer reproduced the sponsor's results.

The protocol specified analysis is logistic regression with terms for treatment and center. One patient in zolmitriptan group whose headache pain at baseline is mild is included in the analysis. Table 2.7.1 presents p-values of the protocol specified analysis using logistic regression with terms for treatment and center.

Table 2.7.1. P-value for the Protocol Specified Analysis

Variables	Time	P-value
Headache response	0.5	.0429
	1	.0001
	2	.0001
	4	.0001
Pain-free	1	.0183
	2	.0001
	4	.0001
One Point Decrease	0.5	**.0576**
	1	.0001

Comparing to Table 2.6.1 and 2.6.2, we see that the sponsor's analysis and the protocol specified analysis are consistent except for one point decrease at 0.5 hour in which the protocol specified analysis gives a non-significant p-value.

This reviewer also checked the center effect for headache response at 2 hours. Among 45 centers, there are 38, 4, and 3 centers in which the headache responses at 2 hours in zolmitriptan group are greater, equal, and smaller than that in placebo group, respectively.

2.7.2. Analyses on Nausea, Photophobia, and Phonophobia

The sponsor didn't analyze the migraine associated symptoms: nausea, photophobia, and phonophobia. According to Guidance for Industry: General Considerations for the Clinical Evaluation of Drugs for the Acute Treatment of Migraine, "in order to establish efficacy as a migraine treatment, the study should also provide evidence of efficacy against the three most common migraine associated symptoms", analyses of these three migraine associated symptoms will

be performed in this section.

Chi-square test is used in testing the proportion of nausea, photophobia, and phonophobia comparing two treatment groups. Table 2.7.2, and 2.7.3 present the results at baseline, and at 2 hours, respectively.

Table 2.7.2. Chi-square Test for Nausea, Photophobia, and Phonophobia at Baseline

Symptom	Zolmitriptan	Placebo	p-value
Nausea	128/228 (56%)	130/239 (54%)	.704
Photophobia	179/230 (78%)	195/239 (82%)	.311
Phonophobia	143/231 (62%)	167/237 (70%)	.050

Table 2.7.3. Chi-square Test for Nausea, Photophobia, and Phonophobia at 2 Hours

Symptom	Zolmitriptan	Placebo	p-value
Nausea	69/221 (31%)	103/236 (44%)	.006
Photophobia	97/221 (44%)	152/236 (64%)	.001
Phonophobia	68/221 (30%)	132/236 (56%)	.001

3. Conclusion

The analysis based on the current submission provides statistically significant evidence that zolmitripatn-treated patients had greater headache response at 2 hours than that placebo-treated patients had.

/S/

Kun He, Statistical Reviewer

Concurrence:

/S/

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APPEARS THIS WAY
ON ORIGINAL