U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-450 / S-005
Drug Name:	Zomig® (Zolmitriptan Nasal Spray)
Indication(s):	Migraine
Applicant:	AstraZeneca
Date(s):	Date of Submission: December 14, 2007
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Keywords:

Crossover design, imputation, enriched enrollment, generalized estimation equation, logistic regression, placebo challenge, sensitivity analysis, worst case analysis.

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1. EXECUTIVE SUMMARY

The submission of this Supplemental NDA included one efficacy study D1221C00005 of Zomig® (zolmitriptan) Nasal Spray for the treatment of Migraine in pediatric patient population. The study is intended to fulfill the pediatric commitment for Zomig® Nasal Spray.

1.1 Conclusions and Recommendations

The study D1221C00005 failed to demonstrate that zolmitriptan is effective as a treatment of acute migraine headache in the adolescent patient population. Neither one-hour headache response nor two-hour sustained headache response showed treatment effect that reached statistical significance regardless of what data set was used.

1.2 Brief Overview of Clinical Studies

The efficacy study D1221C00005 included in the submission was a multicenter, double-blind, randomized, placebo-controlled, 2-way crossover study with a single-blind, placebo challenge (enriched enrollment) for each attack. Eligible subjects were randomized into one of the two crossover sequences to treat 2 moderate or severe migraine headaches.

For each migraine attack, when migraine pain reached moderate-to-severe intensity, all subjects were initially challenged with a placebo nasal spray. Subjects who achieved reduction in headache pain to mild or none within 15 minutes were defined as early placebo responders and did not use randomized treatment for that attack. Subjects who did not respond within 15 minutes used randomized treatment with either zolmitriptan 5-mg nasal spray or placebo.

The co-primary efficacy variables were 1-hour headache response and 2-hour sustained headache response.

A total of 248 adolescent subjects were enrolled at 17 investigative sites in the United States.

1.3 Statistical Issues and Findings

The original protocol for this study intended that the primary endpoint would be the 1-hour headache response as assessed in an enriched population using a novel crossover study design. However, FDA comments on the protocol arrived after initiation of the study. FDA required the co-primary endpoints of 1-hour headache response and sustained headache response to 2 hours for those patients responding at 1 hour. FDA was also concerned with dropping the placebo responders after randomization, noting that it may be difficult to interpret such an analysis using the enriched population. Additionally, there was a concern of possible imbalance between treatment groups due to dropping placebo responders post-randomization. FDA and AstraZeneca acknowledged that the acceptability and interpretability of the data would be discussed when the results were available, and the trial was continued.

Given the FDA's concerns, AstraZeneca submitted a SAP to FDA, proposing a sensitivity analysis treating those with an initial placebo response as responders to randomized treatment, irrespective of which treatment group they were assigned to for that attack. This SAP initiated further dialogue with the FDA, which continued beyond the completion of the study.

The FDA requested a worst-case scenario analysis after enrollment was completed, but prior to unblinding. AstraZeneca agreed, since the FDA recognized the extreme improbability of achieving a positive result with the requested analysis. However, AstraZeneca was confident the data would confirm the appropriateness of the originally intended analysis.

With the above issues in mind, the reviewer performed primary analysis on data sets of all randomized and treated (ART), intend-to-treat (ITT), and observed cases (OC). None of analyses indicated treatment effect that reached statistical significance. The sponsor presented results with significant treatment effect from analyses that were not planned.

The reviewer has experienced extreme difficulties in analyzing the data due to poor data quality, missing information (information not entered in the data by the sponsor), poor organization of the data, and various errors. Numerous efficacy values appeared to be imputed appeared deviating from the rules set by SAP.

The reviewer has requested the sponsor to submit listings of subjects with their assessment values, imputed or observed, that used in the sponsor's analysis together with the SAS programs.

2. INTRODUCTION

Zomig® (zolmitriptan) is indicated for the acute treatment of migraine, with or without aura, in adults. In US, Zomig's approvals were granted November 25, 1997 (tablet), February 13, 2001 (ZMT 2.5mg), September 17, 2001 (ZMT 5mg) and September 30, 2003 (nasal spray).

The NDA submission included a PK study in adolescents (study D1221C00004) and an acute efficacy and safety study in adolescents (study D1221C00005). This document contains the statistical evaluation of study D1221C00005.

2.1 Overview

The efficacy study included in the submission was a multicenter, double-blind, randomized, placebo-controlled, 2-way crossover study with a single-blind, placebo challenge (enriched enrollment) for each attack. Eligible subjects were randomized into one of the two crossover sequences to treat 2 moderate or severe migraine headaches.

For each migraine attack, when migraine pain reached moderate-to-severe intensity, all subjects were initially challenged with a placebo nasal spray. Subjects who achieved reduction in headache pain to mild or none within 15 minutes were defined as early placebo responders and

did not use randomized treatment for that attack. Subjects who did not respond within 15 minutes used randomized treatment with either zolmitriptan 5-mg nasal spray or placebo.

The 2nd migraine attack was handled in a similar manner with crossover-randomized treatment. Subjects had 12 weeks to complete the study.

The co-primary efficacy variables were 1-hour headache response and 2-hour sustained headache response.

A total of 248 adolescent subjects were enrolled at 17 investigative sites in the United States.

2.2 Data Sources

All document reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for the submission is listed below:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Primary objective

The primary objective of the study was to evaluate the efficacy of zolmitriptan 5-mg nasal spray, as compared to placebo, for the acute treatment of migraine headache in adolescent subjects (aged 12 to17 years).

3.1.2 Study design

This was a multicenter, double-blind, randomized, placebo-controlled, 2-way crossover study with a single-blind, placebo challenge (enriched enrollment) for each attack. A total of 248 adolescent subjects were enrolled at 17 investigative sites in the United States.

Subjects were screened for eligibility during Visit 1. At Visit 2, eligible subjects were randomized into one of the two crossover sequences to treat 2 moderate or severe migraine headaches. For each headache, subjects had access to 3 nasal spray devices (here after referred to as the 1st, 2nd, and 3rd devices). For each migraine attack, when migraine pain reached moderate-to-severe intensity, all subjects were initially challenged with a placebo nasal spray (i.e., 1st device). Subjects who achieved reduction in headache pain to mild or none within 15

minutes were defined as early placebo responders and did not use randomized treatment for that attack. Subjects who did not respond within 15 minutes used randomized treatment (2^{nd} device) with either zolmitriptan 5-mg nasal spray or placebo. If headache pain persisted at 2 hours after using the 2^{nd} device, a 3rd device (same randomized treatment) or approved escape medication was permitted. Pain intensity was assessed at 15 minutes after the 1^{st} device and at 15, 30, 45, 60, 90, and 120 minutes after the 2^{nd} device.

The 2nd migraine attack was handled in a similar manner with crossover-randomized treatment. Subjects had 12 weeks to complete the study. An electronic logpad device was assigned to all subjects to record and report the information.

A total of 248 adolescent subjects were enrolled at 17 investigative sites in the United States.

3.1.3 Efficacy Evaluation

The primary analyses were based on the 1-hour headache response rate and 2-hour sustained headache response for the 1^{st} headache attack. The co-primary variables were:

1. Headache response at 1 hour after randomized treatment (2^{nd} device). Headache response was defined as an improvement in migraine headache intensity from severe or moderate to mild or none. This was performed using the 1st attack data (per original study design) based on the ART population (per FDA request) and using a worst-case scenario methodology (per FDA request).

2. Two-hour sustained headache response defined as headache response at 1 hour post randomized dose, without return to moderate or severe pain, and with no use of rescue medication through 2 hours (per FDA request). This was also performed using the 1st attack data based on the ART population (per FDA request) and using a worst-case scenario methodology (per FDA request).

3.1.4 Statistical methods

Analyses of the co-primary efficacy endpoints were based on the all randomized and treated (ART) population, which included all subjects who were randomized and treated. This set of subjects included subjects only if they treated with either the 1^{st}, 2^{nd}, or 3^{rd} device for either attack. Subjects were classified according to the original randomized treatment sequence. The primary analysis for the co-primary endpoints was the logistic regression analysis through GEE model using the 1^{st} attack data. The factors in the models were treatment and region (Middle, South, and West). Nominal p-values were reported for all the secondary analyses, and no adjustments were made to the reported p-values.

Analyses were performed using the ART population and using a worst-case scenario methodology (FDA required). The worst-case scenario defined special handling for subjects whose headache response was missing at the 1-hour time point and for those who responded to

placebo prior to using the randomized treatment. If migraine headache response was missing at the 1-hour time point, the response was set to Yes for subjects assigned to placebo for that attack, but was imputed to No for those assigned to zolmitriptan. Similarly, if subjects respond to placebo (1st device), the 1- hour headache response for those assigned to placebo was set to Yes, but was imputed to No for those assigned to zolmitriptan.

Co-primary endpoint of 2-hour sustained headache response was also based on FDA requested ART population and a worst-case scenario methodology using the 1st attack data. If a subject responded to the placebo challenge (enriched enrollment), this worst-case scenario for 2-hour sustained headache response would be set to responder if this subject was assigned to placebo treatment for that attack and would be set to non-responder if this subject was assigned to zolmitriptan treatment for that attack.

Last observation carried forward (LOCF) was utilized to impute missing data within an attack. If a certain time point for an efficacy measure (pain intensity, presence of symptom, interference with normal activity) is missing, the closest non-missing efficacy measure documented prior to the missing time point was carried on through the rest of the missing efficacy measure time points.

3.1.5 Subject population

A total of 248 subjects were enrolled and randomized to either zolmitriptan/placebo (n=128) or placebo/zolmitriptan (n=120) at 17 centers in the US. Similar proportions of subjects were discontinued in both treatment sequence groups (19.5% in the zolmitriptan/placebo group and 20.0% in the placebo/zolmitriptan group), and 103 and 96 subjects in the zolmitriptan/placebo and placebo/zolmitriptan groups, respectively, completed the study. The most common reasons for discontinuation in both treatment sequences were protocol noncompliance (8.6% and 10.8% in the zolmitriptan/placebo and placebo/zolmitriptan groups, respectively) and loss to follow-up (7.8% and 7.5% in the zolmitriptan/placebo and placebo/zolmitriptan groups, respectively).

Subjects were similar between the 2 treatment sequence groups. In general, the overall study population was primarily female (57%) and Caucasian (80%). Mean age was 14 years, with 61% of subjects from 12 to 14 years of age. In both treatment sequence groups, approximately 10% of subjects were Black, 9% Hispanic, and <1% were Asian. Table 1 presents the subject disposition and demographic characteristics.

Table 1 Subject population and disposition (Source: Table S1 of sponsor's study report)

		Zolmitriptan/Placebo		Placebo/Zolmitriptan		Total	
Population (ART)							
N randomized (N planned)		128	(136)	120	(136)	248	(272)
Disposition (ART)							
N (%) of subjects who completed[a]		103	(80.5)	96	(80.0)	199	(80.2)
N (%) of subjects who discontinued		25	(19.5)	24	(20.0)	49	(19.8)
N analyzed for safety[b]		114		100		214	
N analyzed for efficacy (ART)		112		102		214	
N analyzed for efficacy (ITT)		91		80		171	
N analyzed for efficacy (PP)		83		72		155	
Demographic characteristics (ITT)							
Sex [n (%)]	Male	39	(42.9)	34	(42.5)	73	(42.7)
	Female	52	(57.1)	46	(57.5)	98	(57.3)
Age [yr]	Mean (SD)	14.2	(1.6)	14.1	(1.5)	14.2	(1.5)
	Range	12 to 17		12 to 17		12 to 17	
Age group [n (%)]	12 to 14 y	55	(60.4)	49	(61.8)	104	(60.8)
	15 to 17 y	36	(39.6)	31	(38.8)	67	(39.2)
Race [n (%]	Caucasian	71	(78.0)	66	(82.5)	137	(80.1)
	Black	9	(9.9)	8	(10.0)	17	(9.9)
	Hispanic	11	(12.1)	5	(6.3)	16	(9.4)
	Asian	0		1	(1.3)	1	(0.6)

3.1.6 Subjects' History of Migraine Attacks

The history of migraine attacks was also similar between groups (Table 2). In the overall ITT population, migraine attacks were experienced a mean of 4.6 times/month, were without aura in 63% of subjects, and were accompanied by nausea, photophobia, phonophobia, and vomiting in 84%, 97%, 91%, and 43% of subjects, respectively. The baseline characteristics of the ITT population were similar to that of the ART population.

Table 2 Migraine headache history for the ITT efficacy population (Source: Table 13 of sponsor's study report)

Migraine characteristics	Treatment sequence: Zolmitriptan/ Placebo (N=91)		Placebo/ Zolmitriptan (N=80)		Total (N=171)	
Age at onset of migraine attacks (y)						
Mean (SD)	9.4 (3.3)		10.0 (3.1)		9.7 (3.2)	
Minimum, maximum	2.0, 16.0		2.0, 15.0		2.0, 16.0	
Average number of attacks/month[a]						
Mean (SD)	4.6 (2.6)		4.6 (2.8)		4.6 (2.7)	
Minimum, maximum	2.0, 12.0		2.0, 16.0		2.0, 16.0	
Average number of days with nonmigraine headaches/month[b]						
Mean (SD)	4.3 (4.2)		3.6 (4.1)		4.0 (4.1)	
Minimum, maximum	0.0, 13.0		0.0, 13.0		0.0, 13.0	
	n	(%)	n	(%)	n	(%)
Type of migraine						
With aura	14	(15.4)	14	(17.5)	28	(16.4)
Without aura	60	(65.9)	47	(58.8)	107	(62.6)
Both with and without aura	17	(18.7)	19	(23.8)	36	(21.1)
Duration of untreated migraine						
> 2 to 4 hours	6	(6.6)	4	(5.0)	10	(5.8)
> 4 to 6 hours	14	(15.4)	15	(18.8)	29	(17.0)
> 6 to 8 hours	15	(16.5)	11	(13.8)	26	(15.2)
> 8 hours	56	(61.5)	50	(62.5)	106	(62.0)
Subjects with migraine and associated:						
Nausea	77	(84.6)	66	(82.5)	143	(83.6)
Photophobia	88	(96.7)	77	(96.3)	165	(96.5)
Phonophobia	84	(92.3)	71	(88.8)	155	(90.6)
Vomiting	37	(40.7)	37	(46.3)	74	(43.3)

[a] Minimum of 2 per month during the school year.
[b] For the past 3 months (must be less than 14).
ITT, Intention to treat; N, number (total population); n, number (subpopulation); SD, standard deviation.
Data derived from Tables 11.1.4.3 and 11.1.4.4 in Section 11.

3.1.7 Efficacy results Reported by the Sponsor

Summary of Placebo Challenge Results

The results of placebo challenge (enriched enrollment) for the ART population are summarized in Table 3 by treatment sequence.

Table 3 Summary results of placebo challenge by treatment sequence, ART population (Source: Table 15 of sponsor's study report)

Attack	Zolmitriptan/Placebo (N=112)				Placebo/Zolmitriptan (N=102)			
	Responder	Non-responder	Missing	Total	Responder	Non-responder	Missing	Total
First attack	23	84	5[a]	112	29	68	5	102
Second attack	14	60	38[b]	112	15	66	21[c]	102

[a] Two because treated 2nd attack.
[b] Twenty-eight because treated only 1st attack.
[c] Seventeen because treated only 1st attack.
ART, all randomized; N, number (total population); n, number (subpopulation).
Data derived from Table 11.2.20.3 in Section 11.

Efficacy Results

The co-primary efficacy endpoint for this trial was the 1-hour headache response and the 2-hour sustained headache response after the randomized dose the trial medication. This was performed using FDA requested worst-case scenario methodology for the ART population. Results are summarized in Table 4 and Table 5.

Table 4 Headache response rate at 1 hour post dosing for the 1st attack, worst-case scenario and ART population (Source: Table 21 of sponsor's study report)

	Zolmitriptan			Placebo			Statistical comparison (logistic regression) of zolmitriptan vs placebo[a]		
		Headache response			Headache response				
Population	Number assessed	n	(%)	Number assessed	n	(%)	Odds ratio	95% confidence interval (L,U)	p-value
ART	112	52	(46.4)	102	61	(59.8)	0.582	(0.338, 1.002)	0.051

ART, all randomized treated; (L,U) lower and upper 95% confidence limits of odds ratio of rates for subjects treated with zolmitriptan versus subjects treated with placebo; N, number (total population); n, number (subpopulation).
Data derived from Tables 11.2.4.3.3 and 11.2.4.8.1 in Section 11.

Table 5 Two-hour sustained headache response rate for the 1st attack, worst-case scenario, ART population (source: Table 22 of sponsor's study report)

	Zolmitriptan			Placebo			Statistical comparison (logistic regression) of zolmitriptan vs placebo		
		Headache response			Headache response				
Population	Number assessed	n	(%)	Number assessed	n	(%)	Odds ratio	95% confidence interval (L,U)	p-value
ART	112	47	(42.0)	102	51	(50.0)	0.720	(0.418, 1.240)	0.236

ART, all randomized treated; (L,U) lower and upper 95% confidence limits of odds ratio of rates for subjects treated with zolmitriptan versus subjects treated with placebo; N, number (total population); n, number (subpopulation).
Data derived from Tables 11.2.11.2.3 and 11.2.11.5.3 in Section 11.

The sponsor reported that for the ART population, the results show that placebo response was slightly superior, but not significantly different, from zolmitriptan for headache response at 1 hour (p=0.051) or 2-hour sustained headache response (p=0.236) using 1st attack data.

The sponsor argued, however, that for the ITT population, the analysis showed that subjects treated with zolmitriptan 5-mg nasal spray had a 1.827 times greater odds of having a headache response at 1 hour compared with placebo, which was statistically significant (p=0.013). Actual response rates for 1 hour were 58.1% for the zolmitriptan-treated group and 43.3% for the placebo group.

The results of the analyses for headache response for both attacks at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1.5 hours, and 2 hours post dosing were secondary variables, and results of the ITT and PP populations, are summarized in Table 6 by treatment.

Table 6 Headache response rate for both attacks at 15 minutes, 30 minutes, 45 minuts, 1 hour, 1.5 hour, and 2 hours post dosing (Source: Table 23 of sponsor's study report)

	Zolmitriptan ITT (N=162), PP (N=146)			Placebo ITT (N=148), PP (N=136)			Statistical comparison (GEE analyses) of zolmitriptan vs placebo		
		Headache response			Headache response				
Timepoint Population	Number assessed	n	(%)	Number assessed	n	(%)	Odds ratio	95% confidence interval (L,U)	p-value
At 15 min									
ITT	148	55	(37.2)	127	29	(22.8)	2.020	(1.162, 3.510)	0.013
PP	134	51	(38.1)	120	27	(22.5)	2.145	(1.201, 3.831)	0.010
At 30 min									
ITT	148	64	(43.2)	127	35	(27.6)	2.057	(1.235, 3.424)	0.006
PP	134	60	(44.8)	120	32	(26.7)	2.326	(1.359, 3.981)	0.002
At 45 min									
ITT	148	69	(46.6)	127	45	(35.4)	1.595	(0.969, 2.624)	0.066
PP	134	64	(47.8)	120	41	(34.2)	1.775	(1.057, 2.979)	0.030
At 1 hour									
ITT*	**148**	**86**	**(58.1)**	**127**	**55**	**(43.3)**	**1.827**	**(1.137, 2.936)**	**0.013**
PP	134	77	(57.5)	120	52	(43.3)	1.777	(1.076, 2.934)	0.025
At 1.5 hours									
ITT	148	89	(60.1)	127	62	(48.8)	1.590	(0.980, 2.577)	0.060
PP	134	82	(61.2)	120	59	(49.2)	1.643	(0.991, 2.722)	0.054
At 2 hours									
ITT	148	97	(65.5)	127	69	(54.3)	1.633	(0.978, 2.726)	0.061
PP	134	88	(65.7)	120	66	(55.0)	1.589	(0.932, 2.709)	0.089

*Originally intended primary endpoint.
(L,U), Lower and upper 95% confidence limits of odds ratio of rates for subjects treated with zolmitriptan versus subjects treated with placebo; GEE, generalized estimated equations; ITT, intention to treat; N, number (total population); n, number (subpopulation); PP, per-protocol.
Data derived from Tables 11.2.4.3.1, 11.2.5.2, 11.2.4.6.1, and 11.2.5.3.1 in Section 11.

The results of placebo challenge (enriched enrollment) for the ART population are summarized in Table 15 by treatment sequence.

3.1.8 Efficacy Results from Reviewer's Analysis

The sponsor reported that the FDA-requested co-primary endpoints showed that placebo response was slightly superior to, but not significantly different, from zolmitriptan for headache response at 1 hour (p=0.051) or 2-hour sustained headache response (p=0.236) using 1st attack data in the worst-case analysis.

Because the worst case analysis is considered conservative, and usually used as the last resort, the reviewer performed analyses on observed cases (OC) and with last observation carry forward (LOCF), which included most patients. Including a subject with missing data, especially those placebo responders, involve a substantial amount of imputation in a complex scheme. Rules of imputation proposed by the sponsor and specified in SAP were followed. However, large discrepancies between the sponsor and the reviewer in imputed data have occurred.

The following discrepancies were identified by the reviewer.

1. Four subjects (subjects 0002/012, 0003/025, 0018/002, 0018/004) did not receive any treatment were included in the sponsor's ART analysis as non-responders.

2. Eleven subjects did not record their assessments for placebo challenge. Eight of them should be considered as responders in the LOCF analysis based on the rules set in the SAP. However, all of them were considered as non-responders in the sponsor's analysis.
3. At least two subjects (subjects 0005/018 and 0006/009) were entered as non-responders in the data for placebo challenge although they should be responders based on rules set by SAP.
4. At least one subject had recorded pain intensity value of 1 at 1-hour, 1.5-hour and 2-hour post 2nd device, but was coded as non-responder for 2-hour sustained headache response.

Other problems included subjects who were not placebo responders but did not take randomized treatment (at least 10 subjects), subjects did not take 2nd device but had post 2nd-device assessments (5 subjects), assessment outside the window (at least 20% of the subjects), or took 1st device twice (4 subjects).

About 20% of the subjects had missing assessment time or had assessment time outside the 22-minute window for placebo challenge. For the 1st attack, 16 of the subjects were assessed after one hour, 9 of them were assessed after 2 hours, and the largest time of assessment was 806 minutes. For the 2nd attack, 14 of the subjects were assessed after one hour, 6 of them were assessed after 2 hours, and the largest assessment time was 1119 minutes. It is not clear how late assessment of the placebo challenge had affected assessment for the randomized treatment. For example, a subject had 15-minute assessment of the placebo challenge completed at 60 minutes post 1st device with 2 points reduction in pain intensity. It is not clear whether the post-2nd-device assessments at 15 minutes, 30 minutes, and 45 minutes of this subject were true measures or were carried from the first one. It appeared to the reviewer that both could be true based on various individual data. There are multi-dimensional data that need to be cross checked in order to have a thorough understanding of how data were entered and imputed, and there are too many questions to be asked about data of individual subjects.

3.1.8.1 Headache Response of Placebo Challenge

Headache response for placebo challenge was measured at 15 minutes post 1st device. Analysis of response for placebo challenge used ART patient population, which included 208 subjects (100 in the Placebo/Zolmitriptan sequence and 108 in the Zolmitriptan/Placebo sequence). Subjects who recorded their pain intensity value outside the 22-minute window were considered as non-responders by the sponsor. A total of 11 subjects had missing assessment for placebo response, and their response values were imputed by the reviewer based on the rules set by SAP as follows:

1. If the 15-minute post 1st device assessment was missing, and the patient was not treated with the 2nd or 3rd device, the patient was considered a placebo responder.
2. If the 15-minute post 1st device assessment was missing, and the patient was treated with the 2nd or 3rd device, the patient was considered a non-responder.
3. If the 15-minute post 1st device assessment was missing, and whether or not the patient was treated with the 2nd or 3rd device was missing but efficacy evaluations after the 15-minute post 1st device were present, the patient was considered a non-responder.

Note that assessment values of the placebo challenge, imputed or observed, were carried forward in the ART analysis for 1-hour headache response if no post 2nd device assessments were available.

The following table presents the response rate for placebo challenge.

Table 7 Response rate for placebo challenge by treatment sequence (Source: Reviewer's analysis)

	Placebo/Zolmitriptan # of responders/N (%)	Zolmitriptan/Placebo Number of responders/N (%)
1st Attack	31/100 (31.00%)	25/108 (23.15%)
2nd Attack	17/83 (20.48%)	18/78 (23.08%)

3.1.8.2 Efficacy Results from 1st Headache Attack

The primary efficacy endpoints of one-hour headache response and two-hour sustained headache response were based on 1st headache attack data. The following analyses were performed for one hour headache response for the 1st attack.

Analysis 1: this analysis was performed based on ART patient population using LOCF. All 208 treated patients were included. Subjects without assessment post 2nd device carried forward their assessment value of placebo challenge, which could be imputed as well.

Among the 100 subjects who took placebo, 62 (62%) of were responders at one hour, and 77 (71%) of the 108 subjects who were treated with zolmitriptan were responders. The logistic regression test yielded a p-value of 0.1538.

Analysis 2: this analysis was a LOCF analysis that only carried forward values after the 2nd device. This is the analysis that was originally intended for the study. A total of 142 subjects were included, among them 5 subjects did not take 2nd device but had assessments post 2nd device. A total of 31 (51%) of the 61 placebo-treated subjects and 52 (64%) of 81 zolmitriptan-treated subjected were responders at one hour. The p-value was 0.1254 from the logistic regression model.

Analysis 3: this is an analysis on observed cases (OC). A total of 131 subjects who had assessed value at 1 hour after 2nd dose were included, among them 28 (50%) of the 56 subjects treated with placebo and 49 (65%) of 75 subjects treated with zolmitriptan were responders at one hour. The p-value was 0.0866 from the test.

Details of the above results are presented in Table 8.

Table 8 Analysis of 1-hour headache response (Source: Reviewer's analysis)

Analysis	Included (N)		LOCF from P-Challenge (N)		LOCF Post-2nd device		Observed		Responder (n, %)		p-value
	Placebo	Zomig	Placebo	Zomig	Placebo	Zomig	Placebo	Zomig	Placebo	Zomig	
1. ART	100	108	39	27	5	6	56	75	62 (62%)	77 (71%)	0.1538
2. ITT	61	81	0	0	5	6	56	75	31 (51%)	52 (64%)	0.1254
3. OC	56	75	0	0	0	0	56	75	28 (50%)	49 (65%)	0.0866

Since none of the above analyses yielded significant treatment difference, the worst scenario analysis was not performed.

A total of 115 subjects had values for 2 hour sustained headache response. Imputation was difficult because of different situations of missing values. The reviewer found no imputation method is reasonable, and only observed data could be considered reliable. Therefore, only observed data of 2-hour response were included in the analysis.

A total of 17 (34.0%) among the 50 placebo-treated subjects and 34 (52.3%) among the zolmitriptan-treated subjects were responders for 2-hour sustained headache relief. The analysis yielded a p-value of 0.0696 for the treatment difference.

3.1.8.3 Efficacy Results from 2nd Attack

A total of 161 subjects took placebo challenge for the 2nd headache attack, 83 in the placebo/zolmitriptan sequence and 78 in the zolmitriptan/placebo sequence. Among the subjects, 17 (20%) of the 83 in placebo/zolmitriptan sequence and 18 (23%) of the 78 in the zolmitriptan/placebo sequence were responders. The counts included six subjects with missing values imputed as responders based on rules set in SAP.

Analyses based on patient data of ART, ITT, and OC were performed in the same manner as for the 1st attack. None of the analyses produced statistically significant treatment difference. The results are presented in Table 9.

Table 9 Analysis of 2-hour sustained headache response (Source: Reviewer's analysis)

Analysis	Included (N)		LOCF from P-Challenge (N)		LOCF Post-2nd device		Observed		Responder (n, %)		p-value
	Placebo	Zomig	Placebo	Zomig	Placebo	Zomig	Placebo	Zomig	Placebo	Zomig	
1. ART	78	83	23	21	4	7	51	55	42 (54%)	51 (61%)	0.3153
2. ITT	55	62	0	0	4	7	51	55	24 (44%)	34 (55%)	0.2259
3. OC	51	55	0	0	0	0	51	55	24 (47%)	32 (58%)	0.2780

A total of 97 subjects were included in the analysis of 2-hour sustained headache response; among them 13 (27.1%) of the 48 placebo-treated subjects and 19 (38.8%) of the 49 zolmitriptan-treated subjects were responders for 2-hour sustained headache relief. The analysis yielded a p-value of 0.2786 for the treatment difference.

3.1.8.4 Analysis Combining the Data of Both Headache Attacks

In analyses that combining the both attacks, only subjects who contributed to both attacks are included. A total of 159 subjects were included in the analysis for 1-hour headache response. The analysis resulted in a p-value of 0.0312 for the treatment difference in favor of zolmitriptan. A total of 71 subjects were included in the analysis of 2-hour sustained headache response. A p-value of 0.1383 was obtained for the treatment difference in favor of zolmitriptan.

3.2 Evaluation of Safety

Refer to Clinical Review by Dr. Teresa Podruchny for Evaluation of Safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table presents descriptive statistics of 1-hour headache response from subgroups by gender and age group. The ITT patient population was used; i.e., only patients with post-2nd-device assessments were included. Data from both headache attacks were included; 142 subjects for the 1st attack and 117 subjects for the 2nd attack. Analysis by race was not performed since the majority of patients were white.

Table 10 Subgroup analysis by gender and age group for the 1-hour headache response

Number (%) of Responders	Placebo	Zomig
Gender		
Male	21/49 (42.86%)	36/62 (58.06%)
Female	34/67 (50.75%)	50/81 (61.73%)
Age (years)		
12-14	37/75 (49.33%)	54/88 (61.35%)
15-17	18/41 (43.90%)	32/55 (58.18%)

4.2 Other Special/Subgroup Populations

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The original design of the study intended to use 1-hour headache response as the primary endpoint in an enriched population of subjects, which would exclude subjects who responded to placebo challenge. The Agency requires co-primary endpoints of 1-hour headache response and 2-hour sustained headache response as a standard for acute migraine treatment. The Agency was also concerned with dropping the placebo responders after randomization, noting that it may be difficult to interpret such an analysis using the enriched population. However, the Agency's comments arrived after the initiation of the study.

The placebo responders, although stayed in the study for the treatment of 2 headache attacks, were not allowed to record assessment beyond 15-minute assessment post 1st dose, resulted a large number of various imputations in order to include these subjects in analyses. Efficacy analyses based on observed data or imputed data were performed. None of the analyses for the 1st attack produced results that indicated significant treatment effect.

The large scale of imputation is not limited to the cause of excluding placebo responders. It was evident that the study had poor patient compliance and the data were lack of quality. It appears that numerous imputation schemes were not planned and were arbitrary.

5.2 Conclusions and Recommendations

The study D1221C00005 failed to demonstrate that zolmitriptan is effective as a treatment of acute migraine headache in the adolescent patient population. Neither one-hour headache response nor two-hour sustained headache response reached statistical significance in treatment difference regardless of the data set used.

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